Enantioselective synthesis using bromoacetals.

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ENANTIOSELECTIVE SYNTHESIS USING BROMOACETALS

By

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Enantioselective synthesis using bromoacetals

S. A. Boyes

Abstract

A brief overview of why it is important to prepare a chiral compound as a specific enantiomer rather than as a racemate is discussed along with several general strategies on how they maybe prepared.

The area of research into the preparation of racemic and enantiomerically pure arylpropanoic acids is briefly reviewed by reference to some of the more important synthons. Some of the more general procedures that have been developed for the construction of arylpropanoic acids are discussed.

The preparation of substituted alkyl aryl ketones and their subsequent two step conversion into diastereomerically enriched dimethyl tartrate (*S*)-bromoalkyl aryl acetals is described. An investigation into the effects of solvent, source of anhydrous acid, work-up procedure, source of bromine and temperature upon the bromination of these dimethyl tartrate acetals is discussed.

Direct conversion of these diastereomerically enriched dimethyl tartrate (*S*)-bromoalkyl aryl acetals into enantiomerically pure (*S*)-bromoalkyl aryl ketones and their subsequent conversion into (*S*)-bromoalkyl aryl esters *via* a Baeyer-Villiger reaction is described. Hydrolysis of these (*S*)-bromoalkyl aryl esters followed by treatment with diazomethane afforded the corresponding methyl (*S*)-bromoalkyl esters with minimal racemisation, while treatment of these (*S*)-bromoalkyl aryl esters with an amine gave the corresponding amide with minimal racemisation.

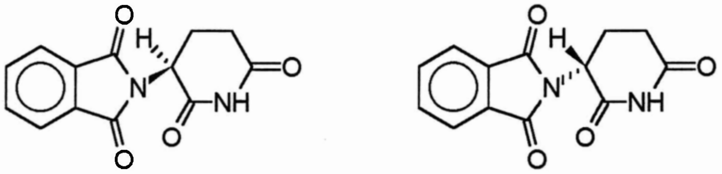
Reduction with sodium borohydride at low temperature of a (*S*)-bromoalkyl aryl ketone afforded exclusively the corresponding (1*S*,2*S*) alkyl aryl bromohydrin as predicted using the Felkin-Anh model.

Stereospecific conversion of our diastereomerically enriched dimethyl tartrate (*S*)-bromoalkyl aryl acetals into (*S*)-arylcarboxylic acids using a silver promoted or solvent promoted rearrangement is discussed. Subsequent conversion of these (*S*)-arylcarboxylic acids into the corresponding Boc amide *via* a modified Curtius rearrangement is described.

Possible further uses of dimethyl tartrate bromoacetals leading to the synthesis of highly functionalised lactones, lactols, epoxides, chiral diacids, diamines, chiral ligands, resolving agents etc are also discussed.

Introduction

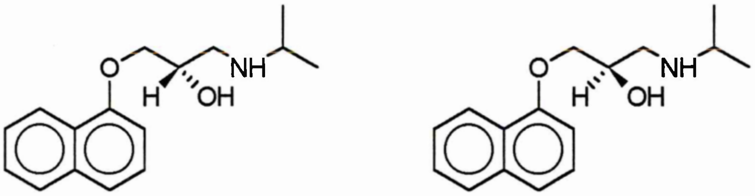
The synthesis of a specific enantiomer rather than a mixture of stereoisomers has become increasingly important in organic synthesis. A particular enantiomer maybe biologically active while the other may have no activity or indeed be harmful, the 'textbook' example of this being Thalidomide **1** where both had the required sedative effect but the (-)-enantiomer caused foetal deformities (see Figure 1).[1]



1 (+)-(*S*)-Thalidomide **1** (-)-(*R*)-Thalidomide

Figure 1

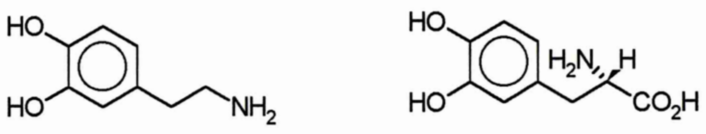
For many other biologically active compounds the two enantiomers have very different properties and so the required enantiomer must be present exclusively. A good example of this is Propranolol **2** where the (*S*)-enantiomer is a β blocker, used in the treatment of heart disease, while the (*R*)-enantiomer acts as a contraceptive (see Figure 2).



2 (*S*)-Propranolol **2** (*R*)-Propranolol

Figure 2

Alternatively the administration of a single enantiomer may be important because the way the body's enzymes interact with each enantiomer maybe different. This is clearly illustrated in the treatment of Parkinson's disease, where the active compound is dopamine **3** which is produced from the prodrug DOPA **4** (see Figure 3). A prodrug is used because dopamine cannot cross the 'blood-brain barrier'.



3 dopamine **4** (*S*)-DOPA

Figure 3

Once in the brain, the enzyme dopamine decarboxylase converts this enantiomer into the achiral dopamine, but the enzyme only works on the (*S*)-enantiomer shown.

Many classical methods of synthesis give a racemate from which the required isomer is usually difficult (expensive) to separate and purify. It would therefore be advantageous to be able to synthesise the required isomer exclusively.

Methods of preparing enantiomerically enriched compounds

There are essentially four basic methods of preparing enantiomerically enriched compounds:-

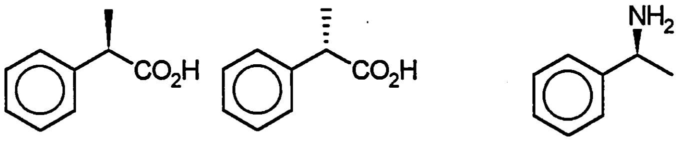
1) Resolution.
2) Asymmetric synthesis using a chiral template.
3) Asymmetric synthesis using a chiral auxiliary.
4) Asymmetric synthesis using a chiral reagent or enzymes.

Each of these has its advantages and disadvantages in terms of cost and practicality.

Resolution

This 'classical' approach is where the compound is produced as a racemate which is then separated. The two isomers have identical physical properties, except for the direction in which they rotate plane polarised light, and so a physical difference has to be induced.

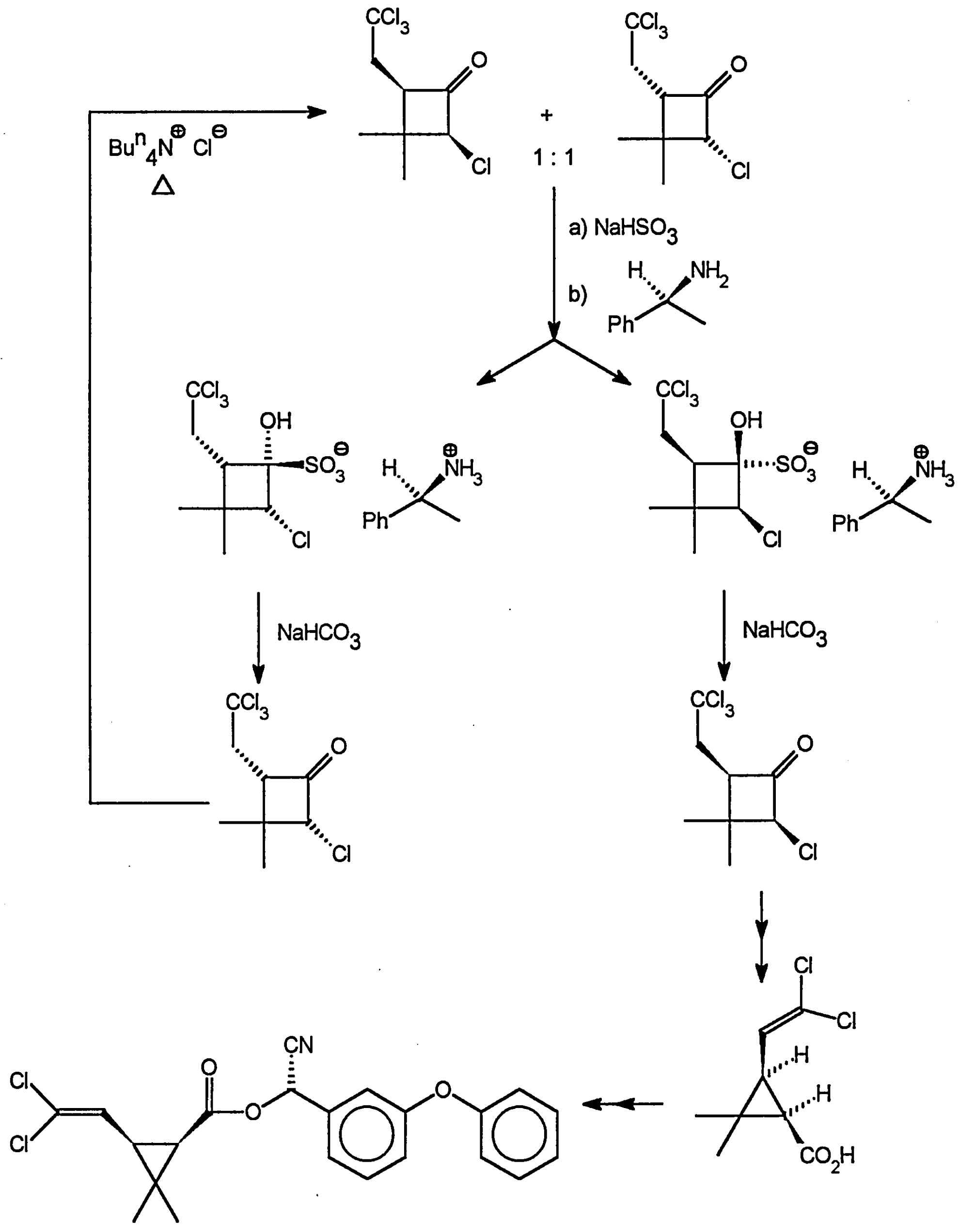
For example a racemic mixture of carboxylic acids can be resolved by the addition of an appropriate optically pure amine,[2] such as α-methylbenzylamine **5** which is available in both enantiomeric forms (see Figure 4).



5 α-methylbenzylamine

Figure 4

The amine will form a salt with each of the carboxylic acids and since the two salts are diastereoisomeric they will have different physical properties thus allowing for separation (e.g. by fractional crystallisation). Fractional crystallisation in this case is where one salt is less soluble in a given solvent than the other and thereby preferentially crystallises out, although more than one fractional crystallisation maybe needed in order to obtain optically pure material. The product is then isolated by treatment of the salt with dilute hydrochloric acid. This is a relatively cheap method of purification but depends on the functionalities present. But it can never give more than 50% yield unless recycling of the 'non-required isomer' is incorporated into the process e.g. Cypermethrin **6** where a cyclobutanone intermediate is resolved and the non-required isomer is racemised and recycled (see Scheme 1).[3]



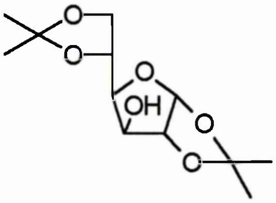
6 Cypermethrin

Scheme 1

Chiral template

The use of a chiral template to prepare enantiomerically pure compounds involves starting with a chiral compound and converting it into the required product by reactions which retain the stereo-integrity. A key feature of this approach, is that some or all of the atoms in the starting material can be found in the final product, with the starting material usually being an amino acid or carbohydrate.

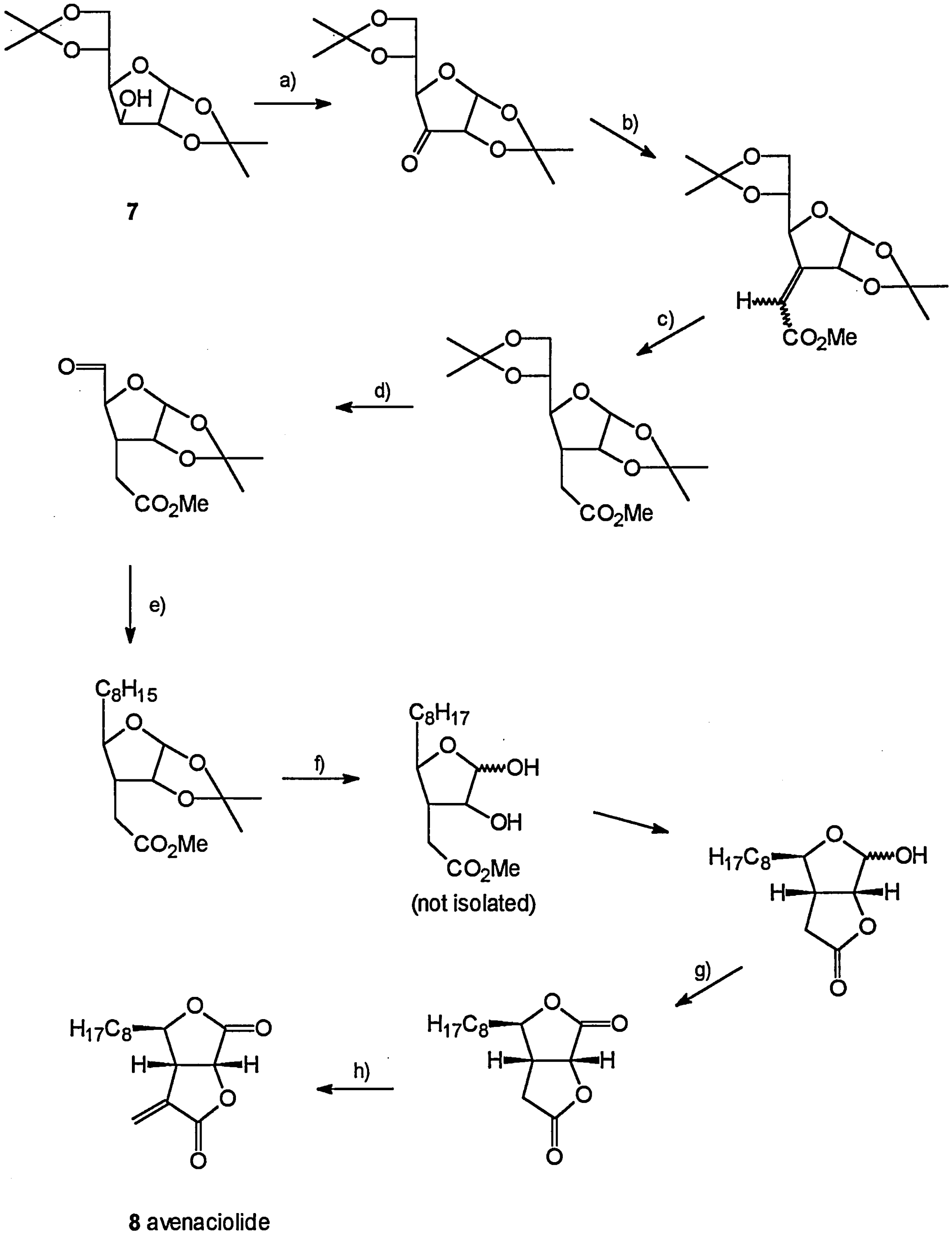
For example, D-glucose can be protected as the di-acetonide acetal **7** (see Figure 5).[4]



7

Figure 5

This leaves one free hydroxyl on the β face upon which manipulation can take place. Attack can only take place on the β face due to the steric hindrance in the rigid trioxabicyclo[3.3.0]octane system. This is illustrated in the synthesis of the anti-fungal agent avenaciolide **8** (see Scheme 2).[4] Oxidation with chromium trioxide gives the ketone which can undergo a Wittig reaction to give a mixture of *E*- and *Z*- alkenes. Catalytic hydrogenation gives the substituent exclusively on the α face due to steric hindrance. Controlled mild acid hydrolysis removes the least stable acetal revealing a diol which can undergo further transformations, while strongly acidic conditions hydrolyse the bicyclic acetal.



a) CrO$_3$ b) Ph$_3$P=CHCO$_2$Me c) H$_2$ / Pd d) (i) CH$_3$COOH (ii) NaIO$_4$

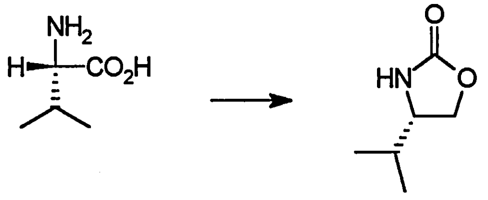
e) (i) Ph$_3$P=CHC$_6$H$_{13}$ (ii) H$_2$/Pd f) HCl$_{(aq)}$ g) Pyridine / CrO$_3$ h) CH$_2$O / base

Scheme 2

Reactions such as these rely on the ready availability of chiral starting materials, but unfortunately there are relatively few which are synthetically useful.

Chiral auxiliary

This method of asymmetric synthesis involves 'tagging' a chiral group onto the substrate and using it to direct the formation of one or more neighbouring chiral centres (i.e. diastereoselectivity).[5] One of the most useful examples has been shown to involve chiral oxazolidinones (see Scheme 3).

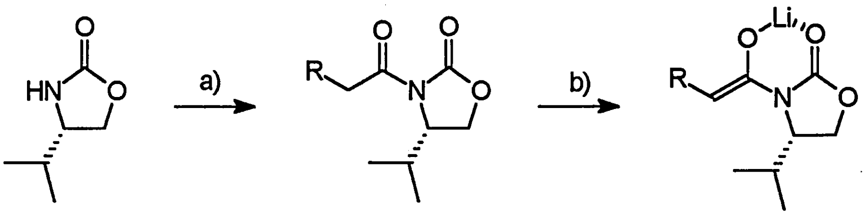


9 (S)-valine **10**

i) B_2H_6 ii) H_2O iii) $(EtO)_2CO$ / K_2CO_3

Scheme 3

This oxazolidinone **10** is derived from S-valine **9**, but others can be used.[6] A key feature is the relatively large isopropyl group next to the carboximide nitrogen, where the substrate is to be subsequently attached (see Scheme 4).



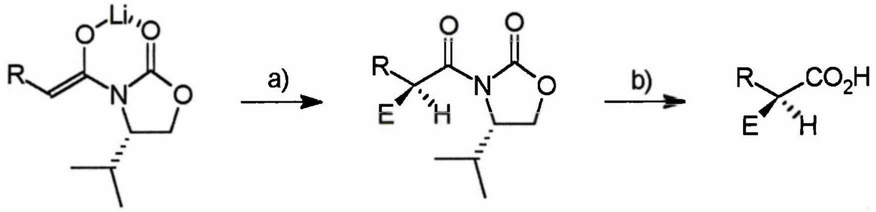
10

a) i) LDA ii) RCH_2COCl b) LDA

Scheme 4

The enolate generated has a fixed conformation due to the dipolar interaction between the lactam carbonyl and the enolate lithium with the *Z*-isomer predominating due to the minimal steric hindrance compared to the *E*-isomer.

This *Z*-enolate can then undergo reaction with various electrophiles, with the isopropyl group largely preventing attack from the lower face (see Scheme 5).

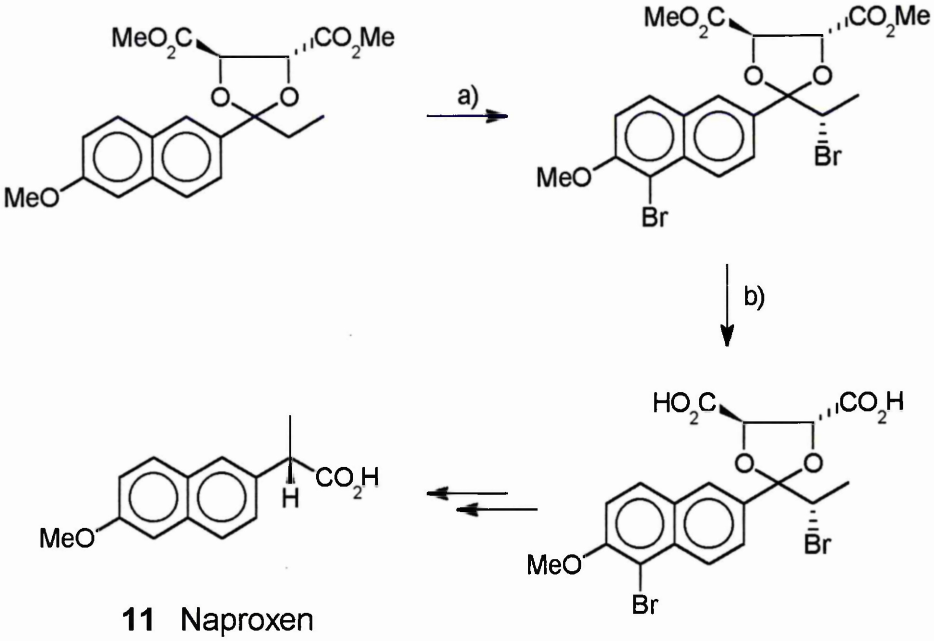


a) E-Hal b) OH^- / H_2O

Scheme 5

The substituted imide thus produced, can then be hydrolysed to give the free acid and the oxazolidinone can be re-used.

An example where a chiral auxiliary is used on an industrial scale is in the synthesis of Naproxen **11**(*S*) (see Scheme 6) where the chiral auxiliary (dimethyl tartrate) is first used to direct the stereochemistry of the bromination reaction, and then provides the optimum transition state for aryl migration.[7]



11 Naproxen

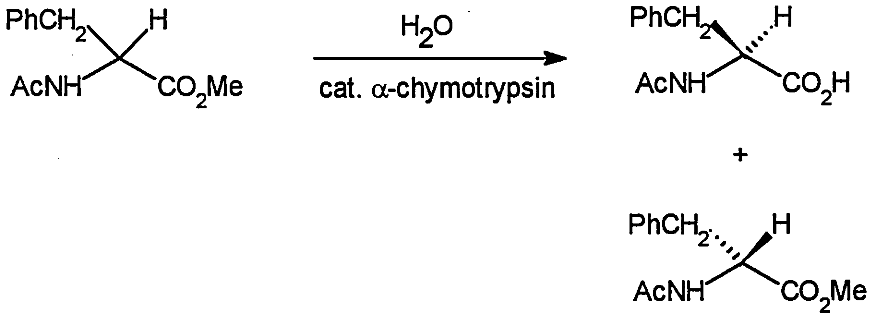
a) H^+ / Br_2 b) OH^- / H_2O

Scheme 6

The bromination and aryl migration reactions are discussed in more detail in a later section and provide the basis for the chemistry described in this thesis.

Enzymes and Chiral Reagents

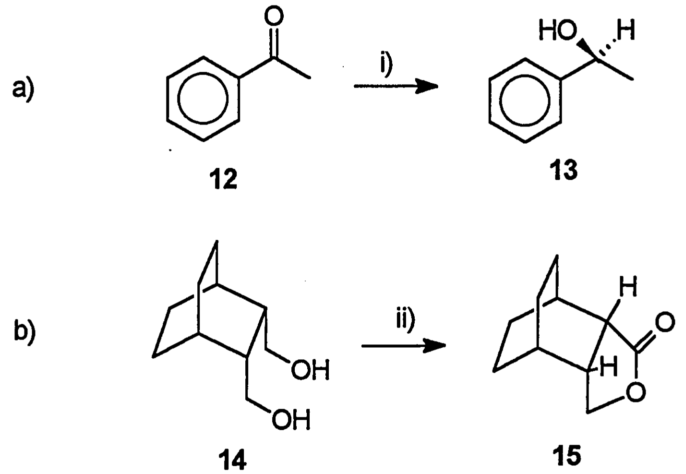
The use of enzymes and chiral reagents in organic synthesis has the possibility of producing enantiomerically pure compounds. Enzymes are usually cheap to obtain as whole cells but maybe more expensive when the pure enzyme is required. The enzyme chymotrypsin can be used to resolve a racemic mixture of esters by preferentially hydrolysing one of the enantiomers (see Scheme 7).[8]



Scheme 7

This ability to differentiate between enantiomers relies on the different way each enantiomer binds to the active site of the enzyme, giving a faster rate for one enantiomer compared to the other.

The way a molecule binds to the active site of the enzyme affects the final stereochemistry of the product (see Scheme 8a). The reduction of a prochiral ketone **12** with an enzyme found in baker's yeast gives an enantiomerically enriched product **13**.[9]



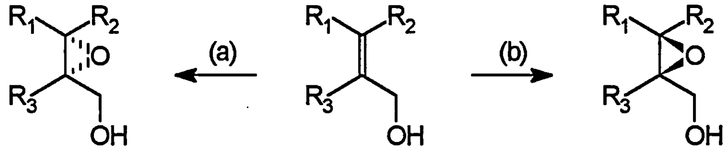
i) Baker's yeast.

ii) Horse liver alcohol dehydrogenase / flavin mononucleotide / nicotinamide adenine dinucleotide.

Scheme 8

Another example where the differentiation in the way a molecule binds to an enzyme is not restricted to prochiral molecules. In Scheme 8b a meso diol **14** is converted into an enantiomerically enriched lactone **15**;[10] here one of the hydroxy groups undergoes oxidation when it binds to the active site, while the other remains unbound.

Many important non-enzymatic asymmetric synthetic methods have been developed in recent years, the Katsuki-Sharpless epoxidation probably being one of the most significant.[11] It allows either enantiomer to be synthesised from the same starting material in high yield and high enantiomeric excess (see Scheme 9).



a) 2*R*,3*R*-Diethyl tartrate / ^{t}BuOOH / Ti(O^{i}Pr)$_4$

b) 2*S*,3*S*-Diethyl tartrate / ^{t}BuOOH / Ti(O^{i}Pr)$_4$

Scheme 9

The enantiomer formed depends upon the chiral component, either (2*R*,3*R*)-diethyl tartrate or (2*S*,3*S*)-diethyl tartrate, both of which are commercially available. The reaction requires only a catalytic amount of the chiral component and must be carried out at a low temperature with total exclusion of water.[11]

More recent work has produced a further method for the asymmetric epoxidation of alkenes using a stoichiometric amount of NaOCl as oxidant and a catalytic amount of a chiral manganese (III) complex (see Figure 6).[12]

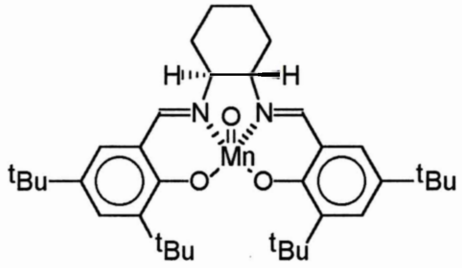
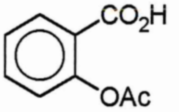


Figure 6

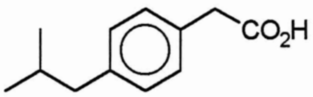
The advantage of these chiral manganese complexes is that the alkene to be epoxidised does not have to contain an allylic hydroxyl group.

Arylpropanoic acids: a brief history and background

Since the early 1970's a considerable amount of work has been carried out into the synthesis of 2-arylpropanoic acids as non-steroidal anti-inflammatory agents.[13] This interest originally stems from the development of benzoic acid derivatives such as Aspirin **16**, which has a wide therapeutic use, and gave rise to the development of arylacetic acids such as Ibufenac **17** (see Figure 7).



16 Aspirin

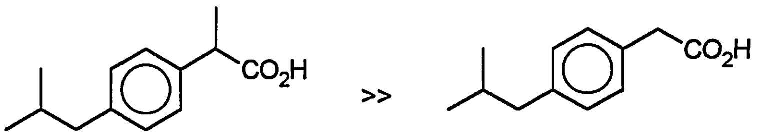


17 Ibufenac

Figure 7

These compounds are believed to have a similar mode of action: by cyclooxygenase inhibition they stop the arachidonic acid cascade to prostaglandins and thromboxane A_2 which are responsible for the inflammation mechanism.[13]

The introduction of the methyl group into the aliphatic side chain of aryl-substituted acetic acids is beneficial since ibuprofen **18** (see Figure 8) is more active than Ibufenac.



18 Ibuprofen

17 Ibufenac

Figure 8

This has given rise to a wide variety of substituted arylpropanoic acids (for selected examples see Table 1) along with numerous methods for their synthesis.[13]

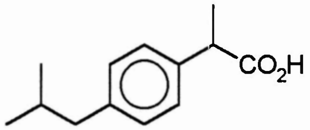
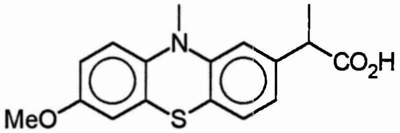
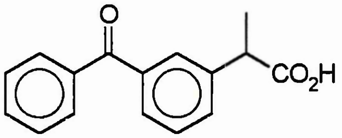
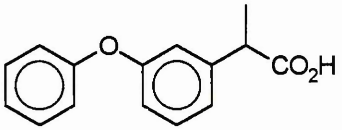
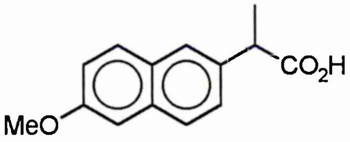
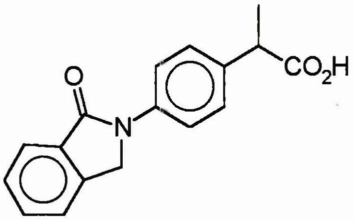
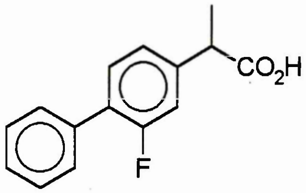
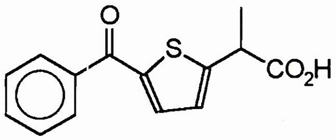
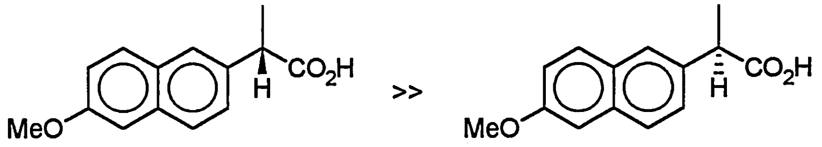
Structural Formula	**Trade Name (Common name)**	**Manufacturer**
	BRUFEN (Ibuprofen)	BOOTS
	PIROCRID (Protizinic acid)	THERAPLIX
	PROFENID (Ketoprofen)	SPECIA
	NALGESIC (Fenoprofen)	DISTA PRODUCTS (LILLY)
	NAPROZIN (Naproxen)	SYNTEX
	FLOSINT (Indoprofen)	CARLO ERBA
	FROBEN (Flurbiprofen)	BOOTS
	SURGAM (Tiaprofenic acid)	ROUSSEL

Table 1

The introduction of a methyl substituent also creates a chiral centre, and therefore the possibility that one enantiomer has the greater pharmacological activity. This is clearly demonstrated by Naproxen **11**(*S*) where the (*S*)-enantiomer is 28 times more active than the (*R*)-enantiomer (see Figure 9).[14-16]

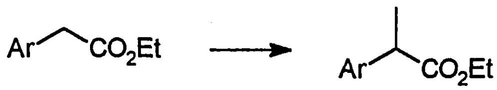


11 (*S*)-Naproxen **11** (*R*)-Naproxen

Figure 9

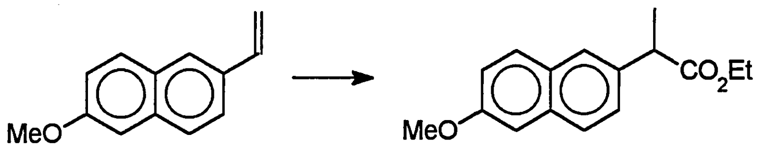
Numerous methods have been developed for the preparation of racemic arylpropanoic acids (see Scheme 10 for selected examples) while there are fewer asymmetric methods (see Scheme 11 for selected examples).

a) From arylacetic acids.[17]



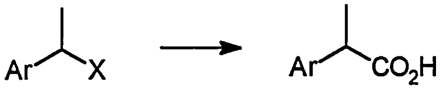
Reagents: NaH, MeI, $MeOCH_2CH_2OMe$

b) From aryl alkenes.[15]



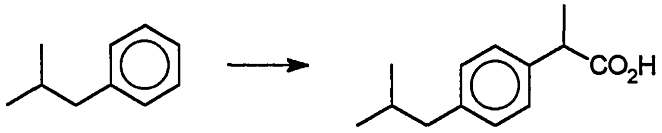
Conditions: CO / EtOH, $(Ph_3P)_2PdCl_2$, BF_3 / Et_2O, pressure, 120°C

c) Via organometallics.[18]



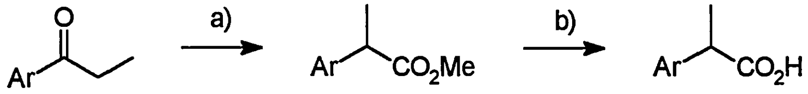
X= Cl or Br Reagents: Mg, Et_2O, CO_2, H_3O^+

d) Via lactic acid derivatives.[19]



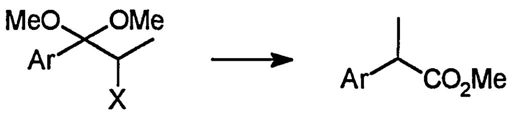
Reagents: 2,5-dioxo-3,6-dimethyl-1,4-dioxane, polyphosphoric acid

e) Rearrangement of propiophenones.[20]



Reagents: a) $Pb(OAc)_4$, 70% $HClO_4$, $HC(OMe)_3$ b) aq NaOH then H_3O^+

f) Rearrangement of α-substituted propiophenone acetals.[14, 16, 21-28]

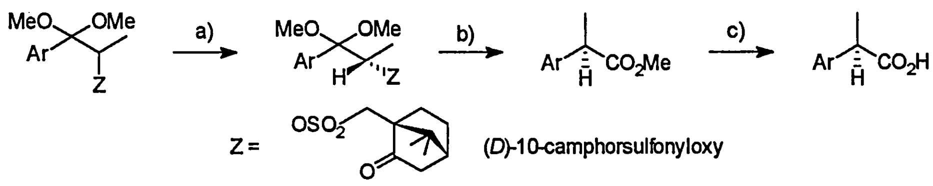


X = Br, Cl, OMs, OTosyl

Scheme 10

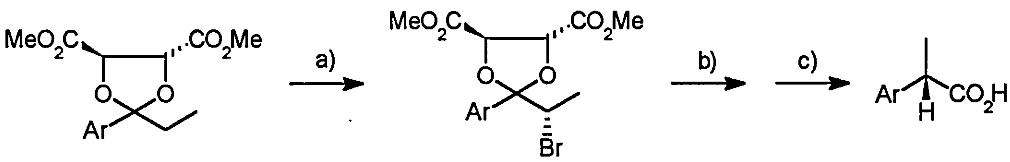
a) Chiral auxiliary and rearrangement.

i)[14]



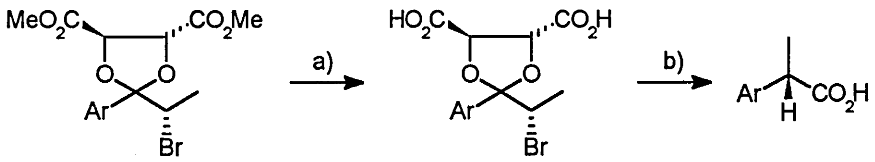
a) Recrystallisation b) $CaCO_3$, DMF / H_2O c) HCl, $MeOCH_2CH_2OMe$

ii)[7, 22]



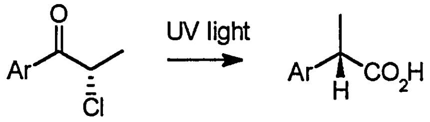
a) Br_2 b) $AgBF_4$ c) aq HCl

iii)[7, 29]

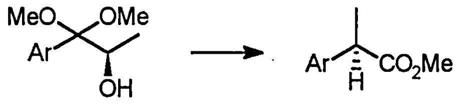


a) NaOH / MeOH then HCl b) K_2HPO_4 / KH_2PO_4 / H_2O

b) Photochemical rearrangement[28]

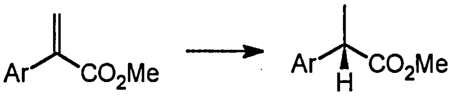


c) Rearrangement[25, 26]



Reagents: PPh_3, CCl_4, Pyridine, DCM

d) Chiral Hydrogenation[30]



H_2 / (*S*) BINAP Rh $(OAc)_2$ catalyst

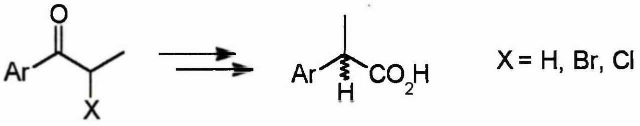
Scheme 11

It is clear that there are many methods for preparing racemic arylpropanoic acids of which only a few are highlighted in Scheme 10, but for the asymmetric preparation of arylpropanoic acids, the rearrangement of an α-substituted propiophenone derivative is a popular method.

Some recent developments in the preparation of enantiomerically pure arylpropanoic acids

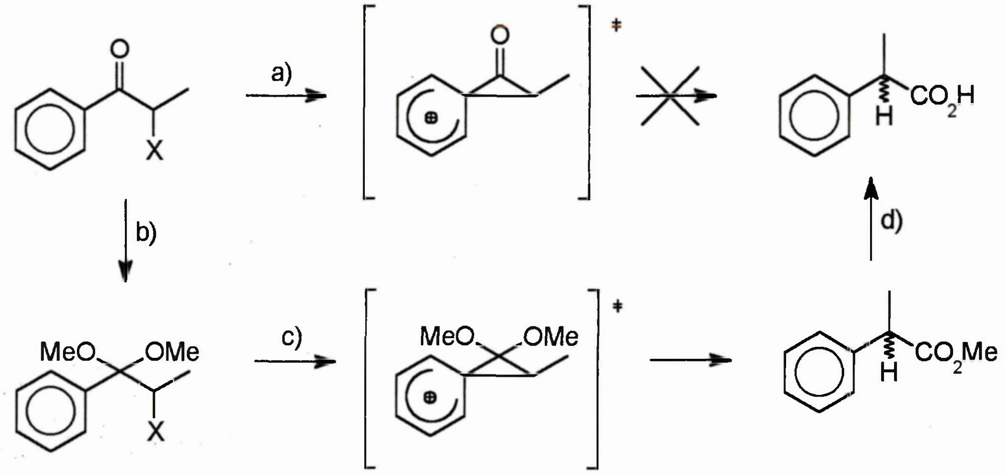
Aryl rearrangement

A considerable amount of work has been published by numerous people, especially by the 'Zambon Chimica S.p.A.' group,[7, 14, 16, 21-24, 27-29] relating to the 1,2 aryl rearrangement of propiophenone and α-substituted propiophenone derivatives (see Scheme 12).



Scheme 12

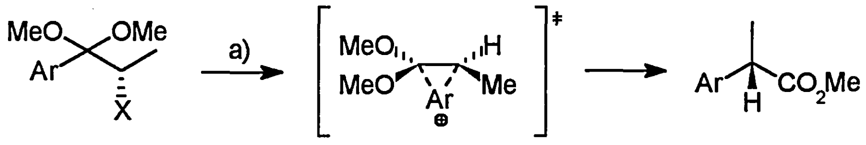
The methods that have been developed for this rearrangement involve the use of a Lewis acid catalyst and the masking of the sp^2 hybridised carbonyl as an sp^3 hybridised acetal to avoid geometrical constraints [28] (see Scheme 13).



X = Br, Cl a) Lewis acid b) MeOH / H^+ c) Lewis acid d) H_3O^+

Scheme 13

Castaldi *et al* suggested a mechanism where the role of the catalyst was to polarise the carbon-X bond with the associated shift of the aryl group.[22] Controlling the stereochemistry of the transition state is vital to controlling the stereochemistry of the product (see Scheme 14).[29, 7]



a) Lewis acid

Scheme 14

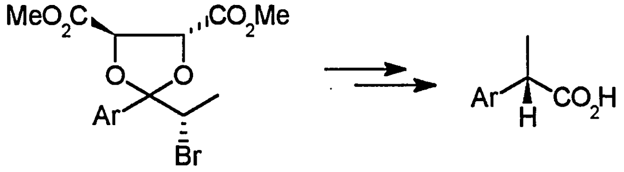
The choice of substituent X and the Lewis acid catalyst play an important role in the control of the stereochemistry. A wide number of Lewis acid catalysts are known to rearrange racemic haloalkyl aryl acetals to give arylcarboxylic acid esters [21, 22] in high yield (see Table 2).

Aryl	X	Catalyst	Solvent/ Temperature, °C	Reaction time, h	Yield, %
4-Methoxyphenyl	**Br**	**$ZnBr_2$**	**Toluene /115**	**0.5**	**98**
4-Methylphenyl	**Br**	**$ZnBr_2$**	**Toluene /115**	**1.5**	**96**
Phenyl	**Br**	**$ZnBr_2$**	**Toluene /115**	**5**	**80**
4-Chlorophenyl	**Br**	**$ZnBr_2$**	**Toluene /115**	**24**	**78**
6-Methoxy-2-naphthyl	**Br**	**$ZnBr_2$**	**Toluene /115**	**0.5**	**98**
4-Isobutylphenyl	**Cl**	**$ZnBr_2$**	**Toluene /115**	**4**	**94**
4-Methoxyphenyl	**Cl**	**$ZnCl_2$**	**Toluene /115**	**1**	**97**
4-Methoxyphenyl	**Br**	**$SnCl_2$**	**Toluene /115**	**1**	**94**
4-Methoxyphenyl	**Br**	**$CoCl_2$**	**TCE / 115**	**1**	**97**
4-Methoxyphenyl	**Br**	**Hg_2Cl_2**	**DCE /80**	**20**	**98**
4-Methoxyphenyl	**Br**	**$PdCl_2$**	**DCE /80**	**20**	**98**
4-Methoxyphenyl	**Br**	**Cu_2Br_2**	**TCE / 135**	**20**	**98**
4-Methoxyphenyl	**Br**	**$CaBr_2$**	**TCE / 146**	**3**	**25**
6-Methoxy-2-naphthyl	**Br**	**$AgBF_4$**	**Methanol / 40**	**1**	**98**
4-Isobutylphenyl	**Cl**	**$AgBF_4$**	**Methanol / 40**	**16**	**82**
4-Methoxylphenyl	**Br**	**$AgBF_4$**	**Methanol / 40**	**1.5**	**98**
6-Methoxy-2-naphthyl	**Br**	**$AgNO_3$**	**Methanol / 40**	**3**	**96**

DCE = 1,2 Dichloroethane, TCE = 1,1,2,2 Tetrachloroethane

Table 2

The results in Table 2 indicate that bromine is a better leaving group than chlorine, which has been attributed to the difference in relative energies of the carbon-halogen bonds.[21, 22] Table 2 also shows that $AgBF_4$ is a better Lewis acid catalyst than $ZnBr_2$ because it promotes the rearrangement at a lower temperature, while other Lewis acids require the use of high temperatures for longer periods of time than are required for $ZnBr_2$. It is also clear from the results in Table 2 that the nature of the aryl substituent has a considerable effect on the reaction time, with electron donating substituents such as methoxyl promoting rearrangement significantly more quickly than that with electron withdrawing substituent such as chlorine. Searching through the literature for references regarding the stereo-controlled rearrangement of aryl bromoacetals using Lewis acid catalysis showed that predominantly silver tetrafluoroborate had been used [7, 29] (see Scheme 15 and Table 3).



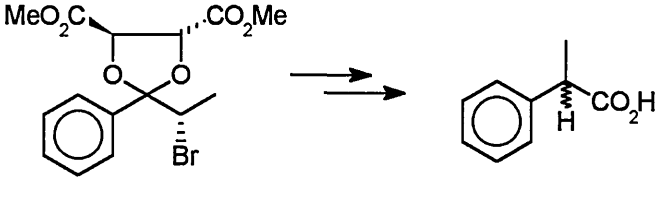
Reagents: $AgBF_4$ then H_3O^+

Scheme 15

Aryl	d.e	Temperature, °C / time, h	e.e	Yield, %
4-Methoxyphenyl	**90**	**15 / 4.5**	**90**	**90**
Phenyl	**90**	**35 / 28**	**90**	**90**
4-Chlorophenyl	**88**	**50 / 8**	**86**	**90**
6-Methoxy-2-naphthyl	**82**	**15 / 18**	**82**	**94**
6-Methoxy-2-naphthyl	**98**	**15 / 18**	**98**	**97**

Table 3

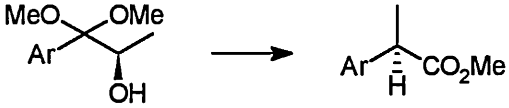
Comparing the results in Tables 2 and 3 indicates that the best method for rearranging aryl bromoacetals is to use silver tetrafluoroborate which gives a product with almost no racemisation of the new chiral centre. Surprisingly, no reference regarding the use of $ZnBr_2$ for the 1,2 aryl rearrangement of enantiomerically enriched aryl bromoacetals was found. As will be mentioned later, when we attempted such a rearrangement the product obtained was racemic (see Scheme 16).



Conditions: $ZnBr_2$ / toluene / reflux then H_3O^+

Scheme 16

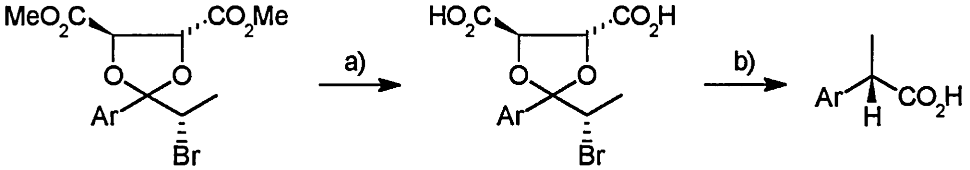
Other methods that do not use silver or zinc salts for the 1,2 aryl rearrangement of α-substituted aryl acetals have been developed which use either triphenylphosphine, carbon tetrachloride and pyridine (see Scheme 17) [16, 26] or aqueous phosphate buffer at reflux (see Scheme 18).[7]



Reagents: PPh_3, CCl_4, Pyridine, DCM

Scheme 17

The method in Scheme 17 is, according to the authors, stereospecific and has a 70-80% yield, but it does depend on the installation of the stereocentre prior to the preparation of the acetal.



a) NaOH / MeOH then HCl b) K_2HPO_4 / KH_2PO_4 / H_2O

Scheme 18

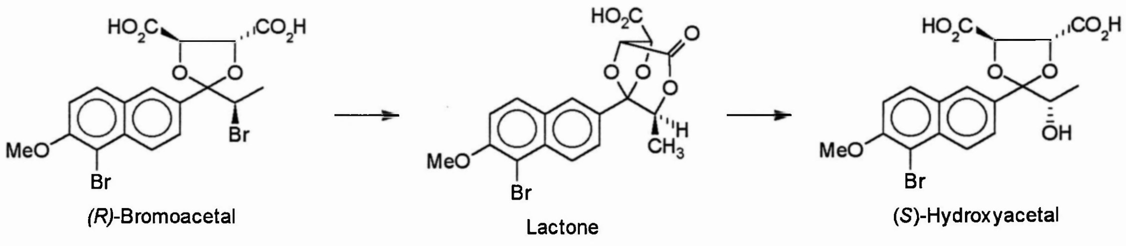
The method used in Scheme 18 makes use of the dimethyl tartrate chiral auxiliary for directing the diasteroselective bromination of the aryl acetal and after modification provides the functionality required for the aryl rearrangement. A surprising feature of the reaction is that it is possible for the arylpropanoic acid product to have a higher enantiomeric excess than the diastereoisomeric excess of the starting bromoacetal (see Table 4).[7]

Entry	Bromoacetal Ratio (*S*:*R*)*	Yield, %	Product Ratio (*S*:*R*)
1	**100:0**	**80**	**>99:1**
2	**94:6**	**74**	**99:1**
3	**92:8**	**72**	**98.5:1.5**
4	**50:50**	**45**	**84:16**
5	**1:99**	**12**	**7:93**

* configuration at the C-Br centre

Table 4

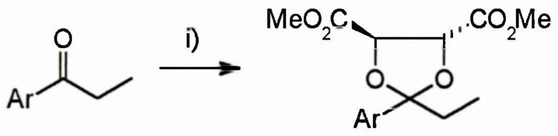
The increase in the optical purity is clearly shown in entry 4 of Table 4 where the starting material has a 50:50 ratio of diastereoisomers, but the product has a 84:16 mixture of enantiomers, though the yield is only modest. This increase in the optical purity is due to the (*R*)-diastereoisomer (configuration at the C-Br centre) of the bromoacetal preferring to convert to the (*S*)-hydroxyacetal via a lactone (see Scheme 19) rather than rearrange in the same way as the (*S*)-diastereoisomer (configuration at the C-Br centre).[7]



Scheme 19

Preparation of dimethyl tartrate acetals

As mentioned before, the ideal starting material for the 1,2 aryl rearrangement is an α-bromoacetal with the carbon bearing the bromine having the (*S*)-stereochemistry. In order to prepare these '(*S*)-bromoacetals' (configuration at the C-Br centre) the use of dimethyl tartrate as a chiral auxiliary has been well documented in the literature.[7, 29, 31-33] The dimethyl tartrate acetals are prepared in high yield from the corresponding aryl alkyl ketone (see Scheme 20).



i) (2*R*,3*R*) Dimethyl tartrate, $MeSO_3H$, $HC(OMe)_3$

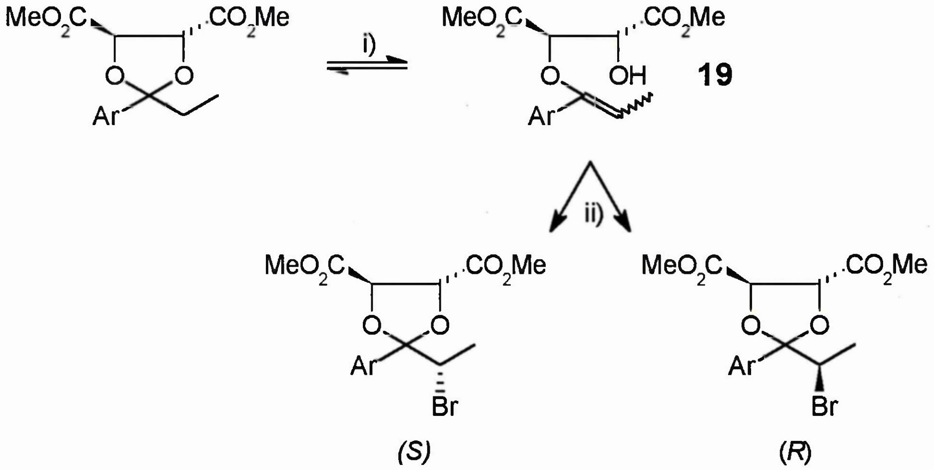
Scheme 20

Other more conventional methods for the preparation of acetals have not been successfully applied to the preparation of dimethyl tartrate acetals, but this will be discussed later in Section 1 of the discussion.

Bromination of dimethyl tartrate acetals.

Once the acetals have been prepared they are reacted with a source of bromine to give the corresponding bromoacetals, with the choice of solvent and brominating agent being crucial to the diastereomeric purity of the bromoacetal produced. A considerable amount of work has been done by the 'Zambon' group into the acid catalysed bromination of dimethyl tartrate derived acetals.[29, 31] The effects of temperature, solvent, brominating agent, acid catalyst and the chiral auxiliary will be described in depth later in the Section 2 of the discussion.

In summary, the bromination of dimethyl tartrate acetals is achieved in the presence of anhydrous acid to give a mixture of diastereoisomers. An investigation to determine the stereoselection has been attempted by the 'Zambon' group using a conformationally restricted substrate, but at present the stereoselectivity of the bromination is not understood.[31] The mechanism involves the acid catalysed generation of an enol ether **19** by the opening of the 1,3-dioxolane, followed by reaction with bromine to give the bromoacetal (see Scheme 21).

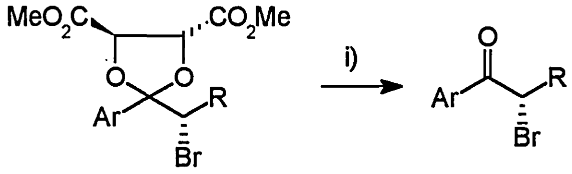


i) Anhydrous H$^+$ ii) Br$_2$

Scheme 21

The preparation of enantiomerically pure bromoketones.

The 'Zambon' group also published a paper on the preparation of enantiomerically pure bromoketones from dimethyl tartrate bromoacetals (see Scheme 22).[33]



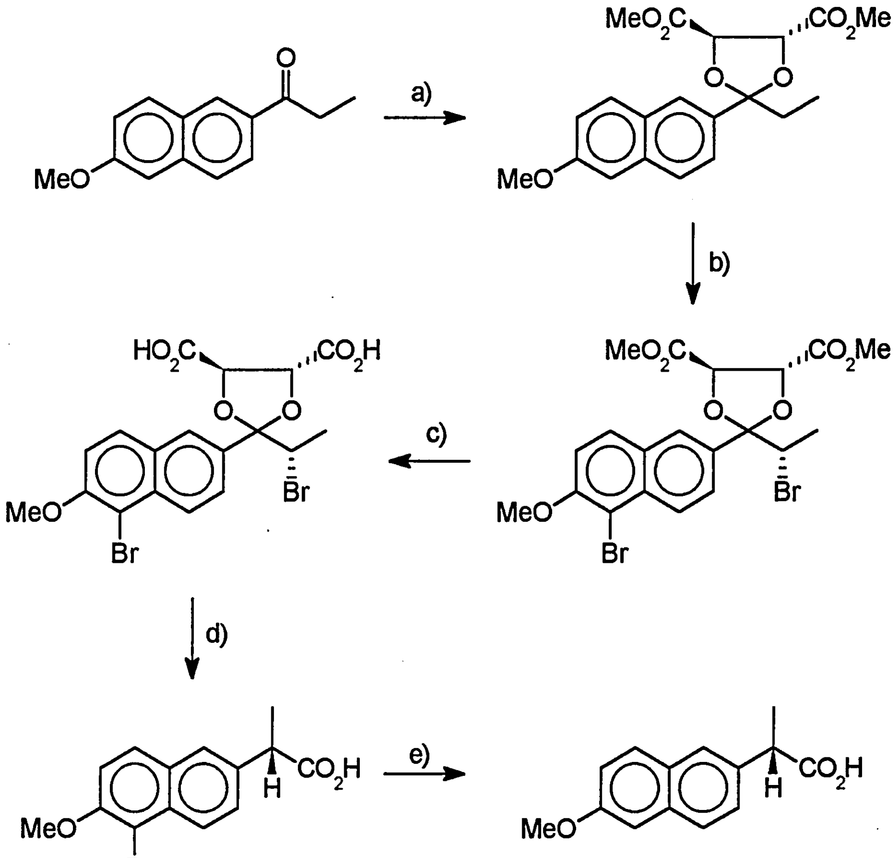
i) $MeSO_3H$, H_2O

Scheme 22

Under aqueous acidic conditions a bromoacetal will hydrolyse back to the bromoketone and racemise the stereocentre bearing the bromine, but under the conditions described, where the amount of water is kept to a minimum, the stereocentre is retained with minimal racemisation. When a diastereomerically enriched bromoacetal is hydrolysed to give an enantiomerically enriched mixture of bromoketones, the bromoketone can sometimes be recrystallised to give a single enantiomer. This will be discussed in more detail in Section 2 of the discussion.

Summary

Combining all the published work by the 'Zambon' group it is possible to describe a commercial method for the preparation of enantiomerically pure Naproxen **11**(*S*) (see Scheme 23).[7]



11 Naproxen

a) Dimethyl tartrate, $MeSO_3H$, $HC(OMe)_3$ b) H^+, Br_2, CCl_4

c) NaOH, H_2O then HCl d) Phosphate buffer e) H_2, Pd / C

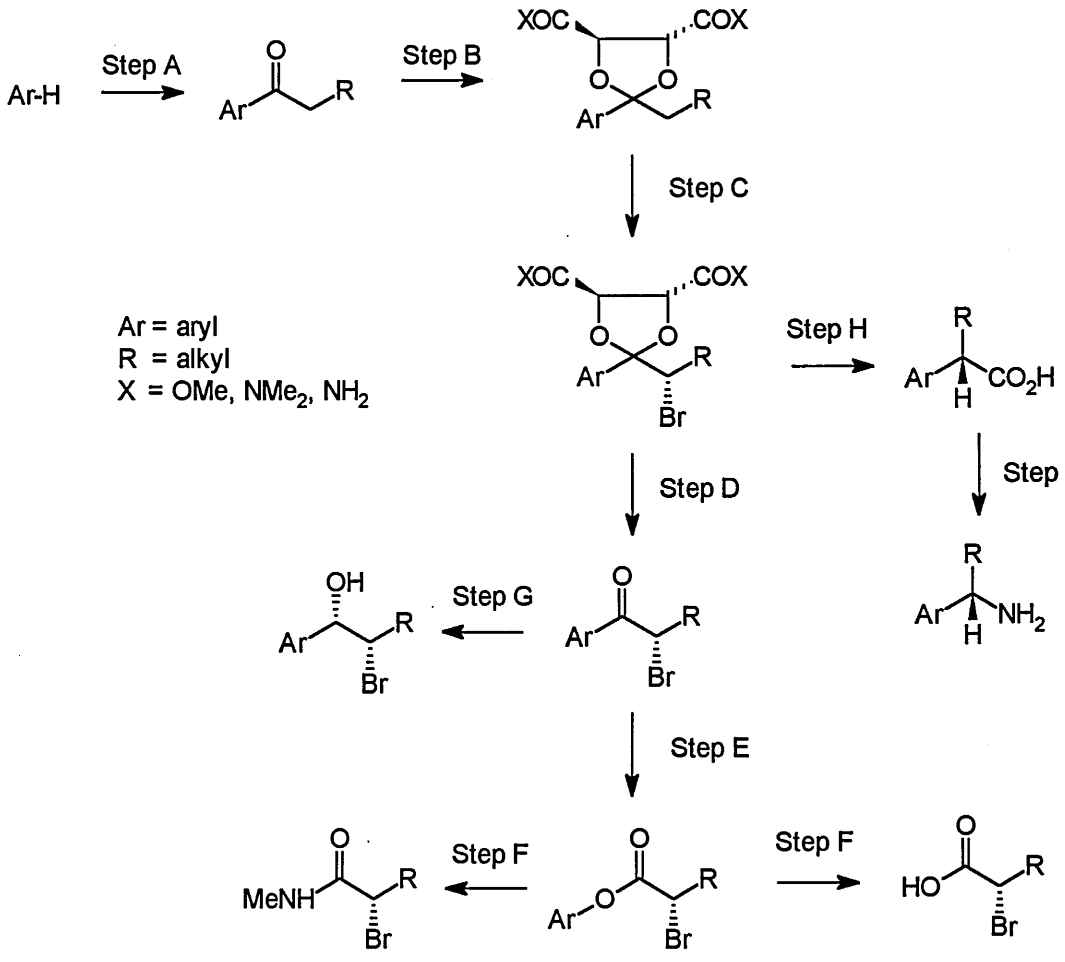
Scheme 23

The following sections, will describe how the chemistry developed for the commercial synthesis of arylpropanoic acids can be applied to the synthesis of other enantiomerically enriched compounds.

Discussion

The diagram below (Scheme 24) details a general summary of the chemistry described in this thesis. Section 1 outlines the preparation of dimethyl tartrate acetals from the corresponding ketones and their subsequent bromination. Section 2 describes how these bromoacetals were used in the preparation of aryl bromoketones, bromoamides, bromoesters and bromohydrins, while Section 3 describes the rearrangement of bromoacetals to 2-arylcarboxylic acids and their subsequent conversion to aryl alkyl amines. In the diagram the major isomer is shown when there is more than one isomer present (see Scheme 24).

Overall Reaction Scheme



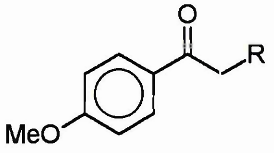
Scheme 24

Section 1 of this discussion will detail the preparation of the ketones **21-26**, **40-44** and **46-49** by Friedel-Crafts acylation (step A) and how they were converted into the corresponding acetals **91-96**, **98-103** (step B) by reaction with the chiral auxiliary dimethyl tartrate. Once the acetals had been purified they were then brominated (step C) using liquid bromine to give a mixture of diastereoisomers **108-121**. Section 2 will discuss how these bromoacetals were hydrolysed to the corresponding bromoketones (step D), and how the bromoketones **78-85** and **87** which were (re)crystallised to give single enantiomers. Reduction of the bromoketone **81** at low temperature using sodium borohydride (step G) gave the bromohydrin **149**(1*S*,2*S*) as a single diastereoisomer. Alternatively Baeyer-Villiger oxidation (step E) of the bromoketones **80**, **81** and **83-85** gave the corresponding aryl bromoesters **128-132** without racemisation of the chiral centre. These aryl bromoesters **128-132** could be converted in to chiral bromoacids **133-137** and bromoamides **145-148** respectively by reaction with aqueous lithium hydroxide or an amine (step F). Section 3 will detail the conversion of aryl bromoacetals into 2-arylcarboxylic acids **151-153** and **162** (step H) by rearrangement with inversion of the stereogenic centre. Preliminary work into the conversion by a modified Curtius rearrangement (step I) of 2-arylcarboxylic acids to give the corresponding 1-aryl alkyl (Boc protected) amines **166, 168** and **169** was started. Each of these steps will now be discussed in more detail.

Section 1

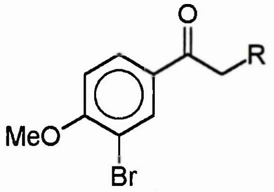
Preparation of ketones 21-26, 40-44, 46-49, 59-62, 64 and 69

Initial work was with propiophenone **82** which is a cheap commercially available compound, but as the project developed it became necessary to prepare the aryl alkyl ketones **21-26, 40-44, 46-49, 59-62, 64** and **69** given in Figure 10.



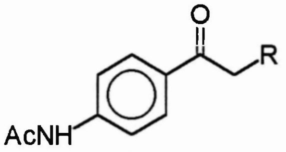
4-Methoxyphenyl

21 R = CH_3
22 R = CH_2CH_3
23 R = $CH(CH_3)_2$
24 R = $(CH_2)_3CH_3$
25 R = $(CH_2)_7CH_3$
26 R = CH_2Ph



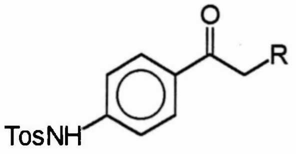
3-Bromo-4-methoxyphenyl

40 R = CH_2CH_3
41 R = $CH(CH_3)_2$
42 R = $(CH_2)_3CH_3$
43 R = $(CH_2)_7CH_3$
44 R = Ph



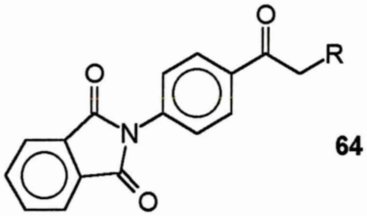
4-Acetamidophenyl

46 R = CH_3
47 R = CH_2CH_3
48 R = $CH(CH_3)_2$
49 R = $(CH_2)_3CH_3$



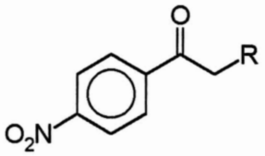
4-(*p*-Toluenesulphonamido)phenyl

59 R = CH_3
60 R = CH_2CH_3
61 R = $CH(CH_3)_2$
62 R = $(CH_2)_3CH_3$



64 R = CH_3

4-Phthalimidophenyl



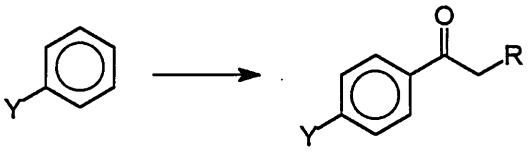
69 R = CH_3

4-Nitrophenyl

Figure 10

Generally compounds containing *para*-substituted aromatic rings are more crystalline than those with an *ortho*- or *meta*-substituted aromatic ring (cf. *o*-, *m*-, *p*-xylenes). The amide, *p*-toluenesulphonamido and phthalimido groups are highly polar and therefore induce hydrogen bonding between neighbouring molecules. These intermolecular interactions increase the probability of the formation of crystalline solids. It was hoped that the introduction of these substituents would eventually give crystalline bromoacetals that might be recrystallised to a single diastereoisomer. The literature states that propiophenone dimethyl tartrate bromoacetals containing a 4-methoxy are liquid,[29] but they would be useful in that they could provide a direct comparison between our results and the literature. Compounds that contained a 4-nitro group were thought to be synthetically useful because it was anticipated that the nitro would provide a handle through which further modification could be achieved. The compounds containing 3-bromo-4-methoxyphenyl were originally side products from the bromination of 4-methoxyphenyl substituted acetals (discussed later in Section 1), but it was noted that they increased the crystallinity of the bromoacetals and so became very useful as well as making synthesis easier.

As these ketones are *para*-substituted aryl alkyl ketones the obvious method of synthesis was by Friedel-Crafts acylation (see Scheme 25) except for 4-nitrophenyl where alternative methods were attempted.



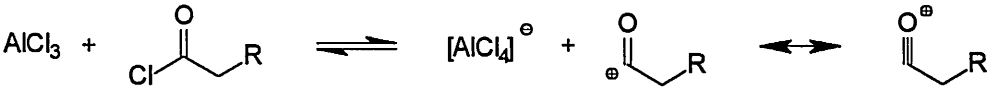
Reagents: $AlCl_3$, RCH_2COCl

R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $(CH_2)_3CH_3$, $(CH_2)_7CH_3$, Ph

Y = AcNH, TosNH, MeO

Scheme 25

Anhydrous aluminium chloride and the acid halide (bromide or chloride) form a complex in which the carbonyl is electron deficient (see Scheme 26). Substitution on the aromatic ring occurs at the least sterically hindered positions that have a high electron density.



Scheme 26

When substituent Y donates electrons into the aromatic ring the *ortho-* and *para-*positions are activated, but if Y is physically large the *ortho*-positions are sterically hindered and reaction only takes place at the *para*-position (see Figure 11).

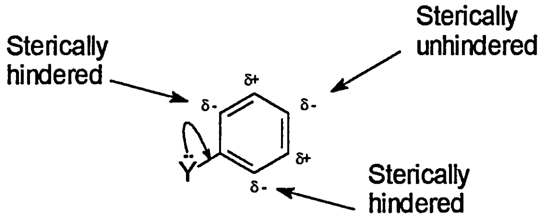
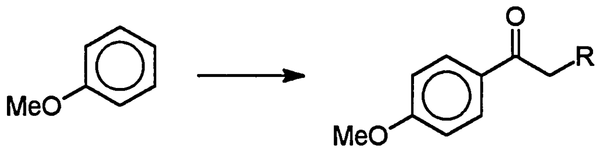


Figure 11

4-Methoxyphenyl and 3-bromo-4-methoxyphenyl substituted ketones (**21-26** and **40-44**)

Preparation of ketones with a methoxy substituent in the *para*-position of the aromatic ring is readily achieved by Friedel-Crafts acylation on anisole **20** (see Scheme 27).



20

21 R = CH_3, 92%
22 R = CH_2CH_3, 94%
23 R = $CH(CH_3)_2$, 95%
24 R = $(CH_2)_3CH_3$, 94%
25 R = $(CH_2)_7CH_3$, 99%
26 R = Ph, 86%

Reagents: $AlCl_3$, RCH_2COCl

Scheme 27

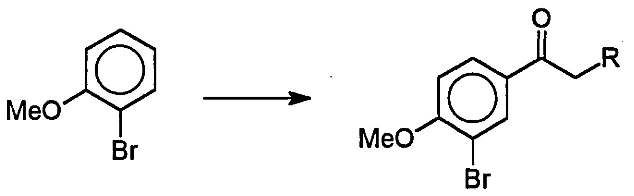
Anhydrous aluminium chloride (1.5 equivalents) and the acid chloride (1.4 equivalents) were stirred at room temperature in dry dichloromethane (DCM), to which anisole **20** was added dropwise. Upon complete conversion as indicated by thin layer chromatography (TLC) the reaction mixture was poured onto ice / conc. HCl to decompose the aluminium chloride / ketone complex. Characterisation of the products by ^1H NMR spectroscopy showed the typical doublet of doublets at 6.9ppm and 7.9ppm in the aromatic region of the spectrum, while infrared spectroscopy (IR) showed the typical ketone carbonyl stretch around 1680cm^{-1}. The products were obtained in excellent yields although large scale reactions also produced small amounts of impurities **27-38** (see Figure 12).

27	**33**	R = CH_3
28	**34**	R = CH_2CH_3
29	**35**	R = $CH(CH_3)_2$
30	**36**	R = $(CH_2)_3CH_3$
31	**37**	R = $(CH_2)_7CH_3$
32	**38**	R = Ph

Figure 12

These impurities were first noticed when the progress of the reaction was followed by gas chromatography (GC). Further investigation using GC mass spectroscopy (GC-MS) allowed them to be characterised, from which their method of formation was deduced. The by-products **27-38** are produced when aluminium chloride acts as a Lewis acid and cleaves the C-O ether bond to give the products **27-38** with a free hydroxyl. This can then react with a molecule of the acid chloride to give the esters **33-38**. The production of **27-38** was minimised by slower addition of anisole and faster agitation of the reaction mixture.

In order to prepare the ketones **40-44**, which contain a *para*-methoxy and a *meta*-bromo substituent, 2-bromoanisole **39** was used instead of anisole **20** (see Scheme 28). The inductive effect of the bromo substituent slightly decreases the electron density in the aromatic ring, but the mesomeric effect allows the unpaired electrons of bromine to resonate around the aromatic ring. The overall effect is to slightly activate the *ortho-* and *para-* positions relative to itself (*meta-* relative to the methoxyl), but this effect is very small when compared to that caused by the methoxyl, so in this competing process the effect of the methoxy dominates and only one product is observed.



39

40 R = CH_2CH_3, 87%

41 R = $CH(CH_3)_2$, 85%

42 R = $(CH_2)_3CH_3$, 79%

43 R = $(CH_2)_7CH_3$, 84%

44 R = Ph, 78%

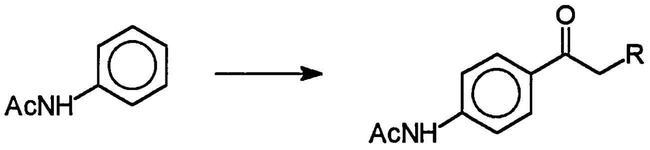
Reagents: $AlCl_3$, RCH_2COCl

Scheme 28

The reaction was done under the same conditions as when anisole **20** was used as the starting material.

Acetamido substituted ketones (46-49)

Preparation of *para*-substituted aromatic ketones with the acetamido functionality was by Friedel-Crafts acylation using acetanilide **45** (see Scheme 29).



45

46 R = CH_3, 99%

47 R = CH_2CH_3, 90%

48 R = $CH(CH_3)_2$, 95%

49 R = $(CH_2)_3CH_3$, 95%

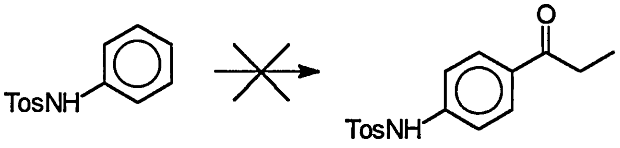
Conditions: $AlCl_3$, RCH_2COCl, Δ (CS_2 or DCM)

Scheme 29

When acetanilide **45** (1.0 equivalent), anhydrous aluminium chloride (3.0 equivalents) and the acid chloride (1.5 equivalents) were heated to reflux in DCM the required product was obtained in good yield when the reaction was done on a small scale. The extra aluminium chloride needed when compared to the analogous reaction with anisole has been generally attributed to the fact that acetanilide **45** can itself complex with the aluminium chloride thereby hindering the acylation reaction. Larger scale preparations (>5g) gave significant amounts of 'polymerisation', possibly due to cross linking by a Friedel-Crafts alkylation with the DCM solvent. One reaction 'polymerised' to form a amorphous solid which was almost insoluble in solvents such as acetone, ethyl acetate or DCM. The material was so inert that the use of chromic acid failed to remove material attached to the glassware. Further investigation led to changing the solvent from DCM to carbon disulphide. This prevented the cross linking whilst making the work-up a little more convoluted due to the excess carbon disulphide having to be decanted off, prior to dilution of the reaction mixture with DCM and pouring it onto ice / conc. HCl. The use of carbon disulphide as the solvent gave excellent results but had the problems of flammability and odour.

p-Toluenesulphonamide substituted ketones **59-62**

It was anticipated that, under either of the conditions used for acylation of acetanilide **45**, the corresponding acylation of *N*-tosylaniline **50** would take place (see Scheme 30).



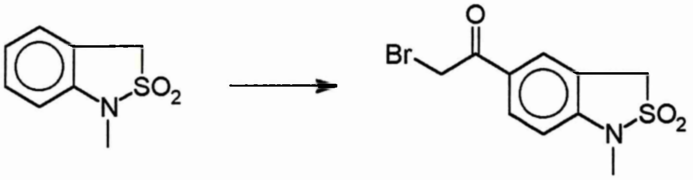
50 **59**

Conditions: $AlCl_3$, CH_3CH_2COCl, Δ (CS_2 or DCM)

Scheme 30

Refluxing *N*-tosylaniline **50**, aluminium chloride and propionyl chloride in DCM or carbon disulphide showed no sign of the required product but gave some 'polymerisation / decomposition' of the starting materials. Prolonged heating increased the amount of 'polymerisation / decomposition' but none of the required product was observed by TLC. This could be due to the fact that the sulphonamide substituent was not sufficiently activating the aromatic ring when compared to the acetamido group. Evidence to support this can be found by comparing the pKa of the sulphonamide group with that of acetamide and indicated that the sulphonamide group was slightly electron withdrawing, while the acetamide group was activating.

This is in contrast to a method published by Skorcz in which it is reported that acylation of a sulphonamide substituted compound **51** was done in an excellent yield using bromoacetyl bromide to give **52** (see Scheme 31).[34]



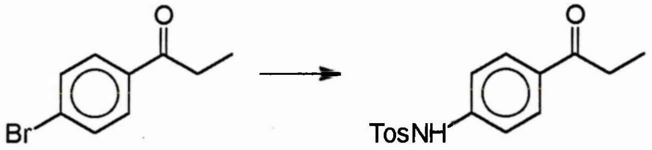
51 **52**

Reagents: $AlCl_3$, $BrCH_2COBr$

Scheme 31

It must be noted that when preparing the corresponding acetyl compound these authors use phosphoric acid and acetic anhydride rather than acetyl chloride and aluminium chloride.

Whilst searching through the literature, a reaction involving the copper promoted nucleophilic substitution of bromine by the *p*-toluenesulphonamido group came to our attention (see Scheme 32).[35]



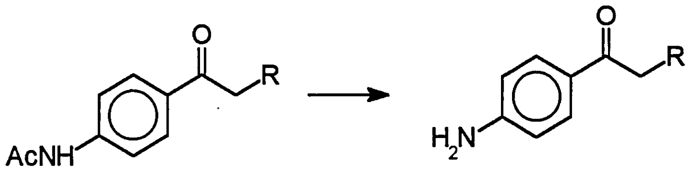
53 **59**

Reagents: K_2CO_3, $Cu(OAc)_2$, *p*-toluenesulphonamide

Scheme 32

When we repeated this substitution reaction, 4-bromopropiophenone **53** was heated to reflux in dry DMF with anhydrous potassium carbonate (1.5 equivalents), *p*-toluenesulphonamide (2.0 equivalents) and copper acetate (~0.1 equivalents). After 24 hours reflux the reaction was worked up and the product purified by flash chromatography. The product **59** was obtained in very good yield (97%) when the reaction was done on a small scale. Larger scale reactions showed complete conversion of the 4-bromopropiophenone **53**, but the product could not be isolated from the excess of *p*-toluenesulphonamide and reducing the amount of *p*-toluenesulphonamide used in the reaction to one equivalent resulted in incomplete conversion of 4-bromopropiophenone **53**. When 4-chloropropiophenone **54** was substituted for 4-bromopropiophenone **53** no reaction was observed at all. Obviously under these reaction conditions there is not sufficient energy to break the carbon chlorine bond.

Since direct preparation of the *p*-toluenesulphonamido ketones **59-62** was not straight forward, an alternative was to take the acetamido ketones **46-49** and hydrolyse the amide to give the corresponding aminoketones **55-58** (see Scheme 33). These aminoketones **55-58** could then be converted to the *p*-toluenesulphonamido ketones **59-62** by reaction with *p*-toluenesulphonyl chloride in pyridine.

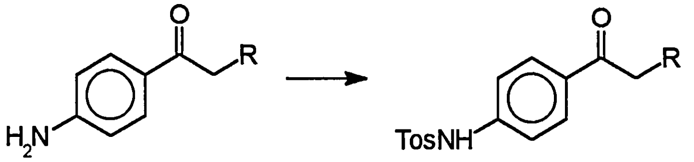


46	**55**	R = CH_3,89%
47	**56**	R = CH_2CH_3,88%
48	**57**	R = $CH(CH_3)_2$,70%
49	**58**	R = $(CH_2)_3CH_3$, 94%

Conditions: $HCl_{(aq)}$, Δ or $HCl_{(aq)}$, ethanol, Δ

Scheme 33

Hydrolysis of the acetamido group by refluxing in aqueous hydrochloric acid gave the corresponding the amino ketones in good yields, but the acetamido ketones **46-49** had a low solubility until the reaction was at reflux. When the solvent was changed to 50 / 50 aqueous hydrochloric acid / ethanol the solubility of the acetamido ketones **46-49** was increased, but the isolation of the product was hindered. Therefore the most convenient method of hydrolysis was using aqueous hydrochloric acid at reflux. Conversion of amino ketones **55-58** to the corresponding *p*-toluenesulphonamido ketone **59-62** was achieved in high yields by stirring the amino ketone **55-58** with *p*-toluenesulphonyl chloride (1.05 equivalents) in pyridine at room temperature for 24 hours (see Scheme 34).



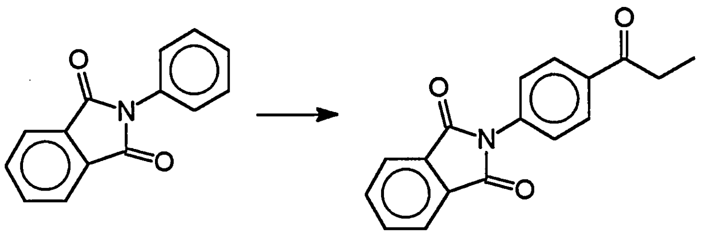
55	**59**	R = CH_3,98%
56	**60**	R = CH_2CH_3, 91%
57	**61**	R = $CH(CH_3)_2$, 94%
58	**62**	R = $(CH_2)_3CH_3$, 90%

Reagents: *p*-toluenesulphonyl chloride, pyridine

Scheme 34

Phthalimido ketones

It was anticipated that Friedel-Crafts acylation on *N*-phenylphthalimide **63** would be a relatively straight forward reaction (see Scheme 35).



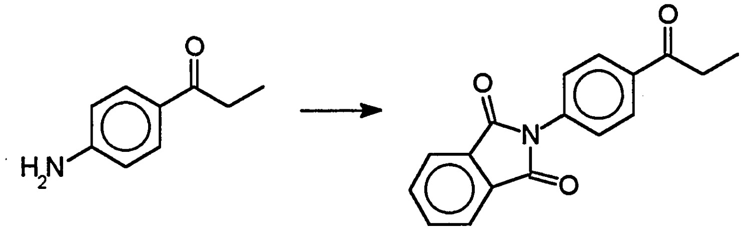
63 **64**

Conditions: $AlCl_3$, CH_3CH_2COCl, Δ, (DCM or CS_2)

Scheme 35

Anhydrous aluminium chloride (3.0 equivalents), propionyl chloride (3.0 equivalents) and *N*-phenylphthalimide **63** were dissolved in DCM and heated at reflux for 48 hours during which no reaction was observed. Increasing the amounts of aluminium chloride and propionyl chloride had no effect on the reaction. Surprisingly little or no decomposition of the starting material was noted, as the starting material **63** could be recovered. This lack of reactivity could possibly be due to the phthalimide substituent sufficiently deactivating the aromatic ring preventing reaction as observed with the tosyl substituent, or possibly that the phthalimide co-ordinates with the aluminium chloride.

An alternative method of synthesis was by reaction of the amino ketone **55** with phthalic anhydride in glacial acetic acid at reflux for 24 hours (see Scheme 36).



55 **64**

Reagents: phthalic anhydride, glacial acetic acid

Scheme 36

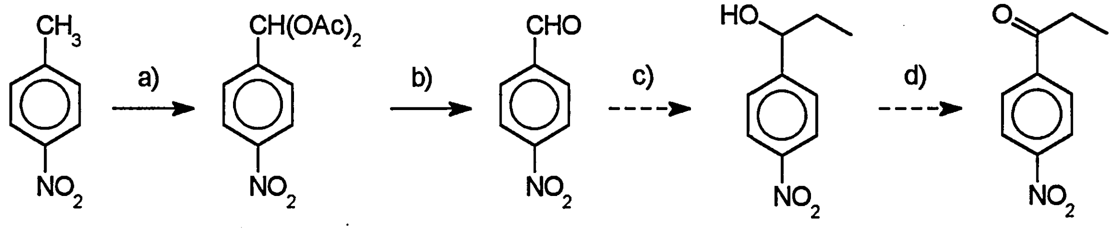
This gave the required product **64** in good yield (75%) as a pale grey crystalline solid.

Preparation of 4-nitropropiophenone

At first glance the preparation of 4-nitro substituted aryl alkyl ketones might seem to be relatively straight forward, but we found this not to be so.

Method 1 (Oxidation of 4-nitrotoluene followed by Grignard)

Our first attempt at preparing 4-nitropropiophenone (see Scheme 37) was to prepare 4-nitrobenzaldehyde **67** *via* its diacetate **66** from 4-nitrotoluene **65** by oxidation with chromium trioxide in acetic anhydride. It was anticipated that this 4-nitrobenzaldehyde **67** would then undergo Grignard reaction with ethyl magnesium bromide to give the alcohol **68** which could be oxidised to give 4-nitropropiophenone **69**.

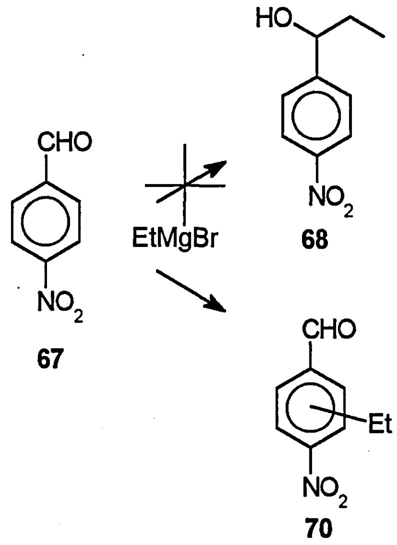


65 **66** **67** **68** **69**

Reagents: a)CrO_3, Ac_2O b) H_3O^+ c) EtMgBr d) [O]

Scheme 37

The preparation of 4-nitrobenzaldehyde **67** was achieved in 74% overall yield according to the method outlined in Vogel.[36] Ethyl magnesium bromide was prepared in dry THF to which 4-nitrobenzaldehyde (dissolved in dry THF) was added at such a rate as to maintain a steady reflux. We were surprised to find that a black discolouration developed throughout the reaction mixture. We analysed a small sample by TLC, and this showed that there was only one product present. A small sample was worked up and analysed by ^{1}H NMR which showed that the aldehyde was still present and that the Grignard reagent had substituted onto the aromatic ring under the influence of the nitro group to give **70** (see Scheme 38).

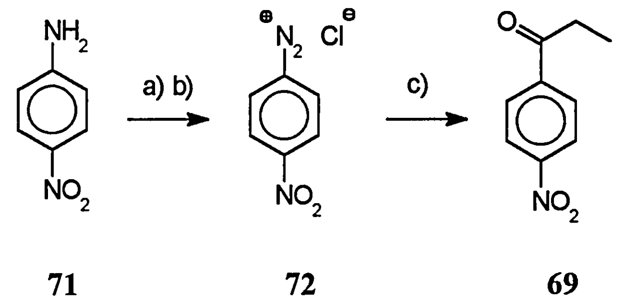


Scheme 38

We were very surprised at this, but it has been documented in the literature before.[37] After our first attempt at preparing 4-nitropropiophenone had failed we investigated several alternative methods.

Method 2 (Diazonium from 4-nitroaniline)

The ability to substitute various functional groups for a diazonium group has been well documented in the literature; usually the reaction is carried out in aqueous solution using a copper salt as a catalyst to introduce substituents like fluorine. It has been reported that under similar conditions it is possible to introduce the acyl functionality (see Scheme 39).[38]



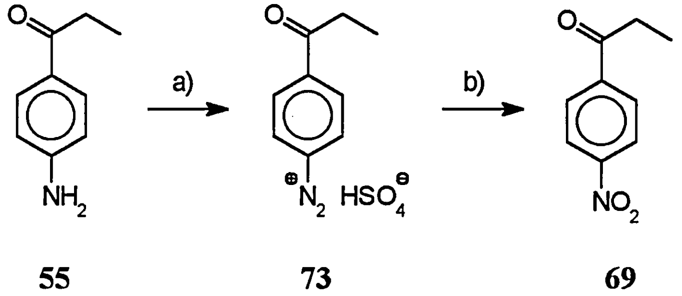
Reagents: a) $NaNO_2$, HCl b) NaOAc c) propanaldoxime, $CuSO_4$, NaOAc

Scheme 39

The procedure involved the generation of the diazonium salt **72** of 4-nitroaniline **71** using conc. HCl and sodium nitrite at 0 °C, after which the reaction mixture was neutralised with sodium acetate. A solution of propanaldoxime, sodium acetate, copper sulphate and sodium sulphite in water was added to the diazonium salt. After a period of being stirred, followed by standing, the pH was adjusted to pH 3 before being filtered and the liquors refluxed with 2N HCl. The crude material isolated at the end of the reaction showed numerous spots by TLC. None of the products showed a reaction with 2,4-DNP (2,4-dinitrophenylhydrazine), so we investigated other alternative methods for preparing 4-nitropropiophenone.

<u>Method 3</u> (Diazonium from 4-amino propiophenone)

As mentioned above the use of the diazonium functional group is a well documented handle for the introduction of other functional groups. Our attempt to introduce the acyl group onto 4-nitroaniline failed, but we decided to attempt to introduce the nitro group onto the diazonium salt of 4-aminopropiophenone **55** (see Scheme 40).



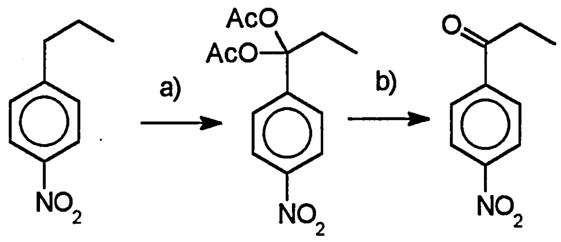
Reagents: a) $NaNO_2$, H_2SO_4 b) $NaNO_2$, H_2SO_4, glacial acetic acid

Scheme 40

The diazonium salt **73** was prepared in a slightly different manner to method 1 in that we used conc. sulphuric acid rather than conc. HCl.[39] After isolation of the diazonium salt further portions of conc. sulphuric acid and sodium nitrite were added. Next day TLC analysis showed mainly starting material amongst several other minor products.

Method 4 (Oxidation of 4-nitropropylbenzene)

The oxidation of 4-nitrotoluene using chromium trioxide dissolved in acetic anhydride was relatively straight forward and gave high yields and so it was decided to attempt a similar reaction using 4-nitropropylbenzene **74** (see Scheme 41).



74 **75** **69**

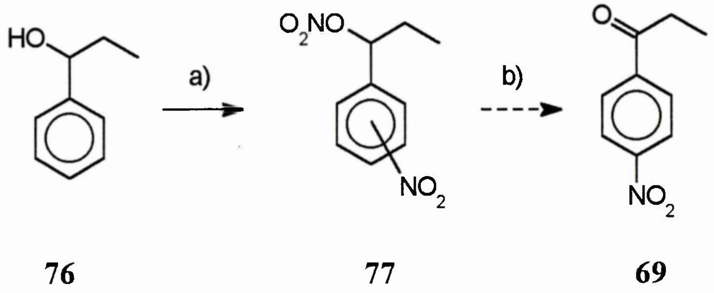
Reagents: a) CrO_3, Ac_2O b) H_3O^+

Scheme 41

When analysis of the reaction mixture by TLC showed no starting material remained, the crude material was isolated. TLC analysis showed two spots which were separated by flash chromatography, but ^1H NMR analysis of these fractions indicated that neither was the required product.

Method 5 (Nitration of 1-phenyl-1-propanol)

Our final attempt to prepare 4-nitropropiophenone was by nitration of 1-phenyl-1-propanol **76** to give the nitrate ester **77**.[40] The mixture of o- and *p*-isomers according to the literature could be separated by crystallisation. The nitrate ester would then be converted to the 4-nitropropiophenone **69** (see Scheme 42).



Reagents: a) urea, HNO_3, H_2SO_4 b) EtO^-

Scheme 42

Urea was dissolved in 96% nitric acid / conc. sulphuric acid before the addition of 1-phenyl-1-propanol and after 2 hours stirring TLC analysis showed complete conversion of starting material. The crude product was isolated after neutralisation and extraction. Several unsuccessful attempts were made to isolate the required nitrate ester.

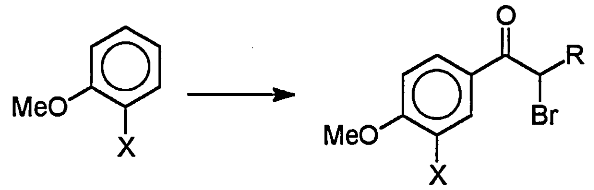
After these unsuccessful attempts at preparing 4-nitropropiophenone we decided to concentrate our efforts on other more promising areas of research.

Preparation of racemic bromoketones

We had a requirement for several racemic α-bromoketones since, when following other people's work or developing new methods of preparing enantiomerically pure compounds, it would be very useful to have the corresponding racemic compounds for comparison. Two different methods were used to prepare the racemic bromoketones; our first method was a Friedel-Crafts acylation similar to that used to prepare ketones **21-26**, while the second method used copper (II) bromide to convert ketones to α-bromoketones.

Method 1

Using similar conditions to those outlined in Scheme 27 used to prepare ketones **21-26** we prepared the bromoketones **78-81** by the same Friedel-Crafts acylation method except that an α-bromoacid halide was used instead of a simple acid halide (see Scheme 43). As before 2-bromoanisole **39** or anisole **20** was used in order to prepare compounds with or without a *m*-bromo substituent.



20 X = H	**78**	R = CH_3, 62%
20 X = H	**79**	R = CH_2CH_3, 84%
39 X = Br	**80**	R = CH_3, 76%
39 X = Br	**81**	R = CH_2CH_3, 72%

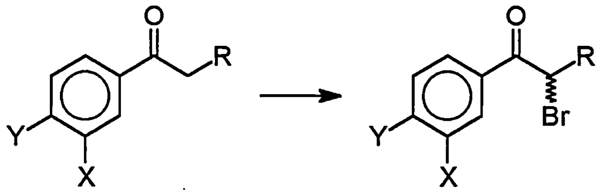
Reagents: $AlCl_3$, RCHBrCOBr

Scheme 43

Since the variety of commercially available α-bromoacid halides is relatively small, very little synthetic use was made of this reaction other than when R was methyl or ethyl.

Method 2

A convenient method of preparing racemic bromoketones with longer alkyl chains or other substituents is to react the ketone with copper (II) bromide (see Scheme 44).



22 X = H, Y = MeO	**79**	R = CH_2CH_3, 80%
26 X = H, Y = MeO	**87**	R = Ph, 82%
40 X = Br, Y = MeO	**81**	R = CH_2CH_3, 92%
41 X = Br, Y = MeO	**83**	R = $CH(CH_3)_2$, 82%
42 X = Br, Y = MeO	**84**	R = $(CH_2)_3CH_3$, 87%
43 X = Br, Y = MeO	**85**	R = $(CH_2)_7CH_3$, 86%
44 X = Br, Y = MeO	**86**	R = Ph, 81%
59 X = H, Y = TosNH	**88**	R = CH_3, 54%
82 X = H, Y = H	**89**	R = CH_3, 94%

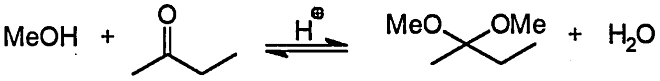
Conditions: $CuBr_2$, $CHCl_3$, EtOAc, N_2

Scheme 44

The starting ketone was dissolved in dry chloroform / ethyl acetate, through which nitrogen was bubbled for 5 minutes prior to the addition of copper (II) bromide. The reaction mixture was refluxed for 4 hours until TLC analysis showed no starting material (the starting material reacts with 2,4-DNP while the product does not).

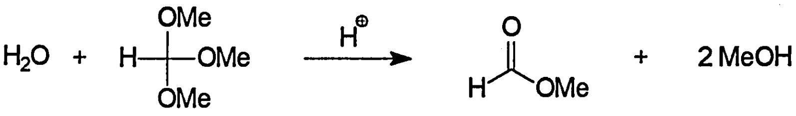
Preparation of acetals

There are many literature methods for the preparation of acetals from ketones or aldehydes,[41] but these generally apply to simple alcohols / diols such as methanol or ethylene glycol. Typically reaction conditions involve the use of anhydrous acid catalysis and removal of water either physically (azeotropically) or chemically. Removal of water is vital in order to drive the equilibrium to favour the product (see Scheme 45).



Scheme 45

In the literature relating to the synthesis of dimethyl tartrate acetals removal of water is usually achieved chemically by reaction with trimethyl orthoformate, the methyl formate and methanol produced being distilled off (see Scheme 46).[7, 29, 31, 32]

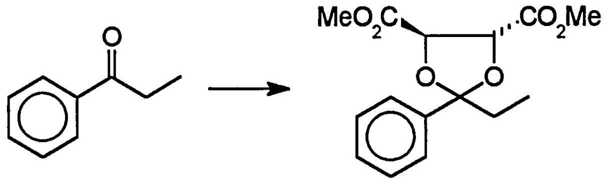


Trimethyl orthoformate

Scheme 46

Propiophenone acetals

To gain familiarity with the chemistry involved we repeated the literature method for the preparation of propiophenone dimethyl tartrate acetal **90** (see Scheme 47).[29] This method describes how propiophenone **82** was heated with trimethyl orthoformate (2.0 equivalents), dimethyl tartrate (2.0 equivalents) and methanesulphonic acid (0.1 equivalents), the methanol and methyl formate being distilled off during the reaction. We found that this method gave the required acetal **90** cleanly and efficiently in 99% yield.



82 **90**

Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

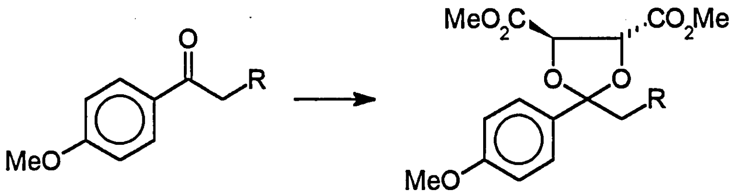
Scheme 47

Modification of the literature conditions showed that the amount of dimethyl tartrate could be reduced to 1.1 equivalents without a measurable effect on the yield and purity of the product. The ^{1}H NMR spectrum of the crude acetal **90** clearly showed the presence of the two methyl ester groups at 3.50ppm and 3.80ppm, while the methylene at 2.85ppm in propiophenone **82** moved upfield to 1.95ppm in the acetal **90**. For comparison we looked at a standard literature method for the preparation of acetals.[41] Propiophenone, dimethyl tartrate and methanesulphonic acid were refluxed with benzene or toluene and the water produced was removed azeotropically and collected in a Dean Stark trap. The reaction produced significant amounts of polymerisation / transesterification of dimethyl tartrate while only a small amount of the propiophenone was converted into the required product **90**, a possible explanation for this being the low solubility of dimethyl tartrate in toluene or benzene. Further additions of dimethyl tartrate and methanesulphonic acid during the reaction or increasing the initial amount of dimethyl tartrate and methanesulphonic acid in the reaction showed no increase in the amount of product to starting material.

It was clear that the optimum method for the preparation of propiophenone dimethyl tartrate acetal **90** was by reaction of propiophenone, dimethyl tartrate and trimethyl orthoformate in the presence of methanesulphonic acid.

4-Methoxyphenyl substituted acetals

Once a suitable method for the preparation of propiophenone dimethyl tartrate acetal **90** had been developed it was applied to ketones containing a 4-methoxy substituent **21-26** (see Scheme 48).

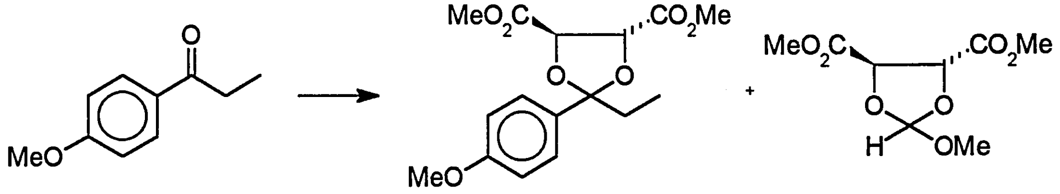


21	**91**	R = CH_3, 82%
22	**92**	R = CH_2CH_3, 69%
23	**93**	R = $CH(CH_3)_2$, 68%
24	**94**	R = $(CH_2)_3CH_3$, 69%
25	**95**	R = $(CH_2)_7CH_3$, 84%
26	**96**	R = Ph, 81%

Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 48

The 4-methoxypropiophenone dimethyl tartrate acetal **91** was initially prepared from 4-methoxypropiophenone **21** as outlined in the literature by Castaldi *et al.*[29] The conditions specified used the same conditions as for the preparation of propiophenone dimethyl tartrate acetal **90** (2.0 equivalents of dimethyl tartrate, 2.0 equivalents of trimethyl orthoformate and 0.1 equivalents of methanesulphonic acid). However, under these conditions a much longer reaction time was required (7 days) and another acetal **97** was also produced which was derived from dimethyl tartrate and methyl formate or trimethyl orthoformate (see Scheme 49).



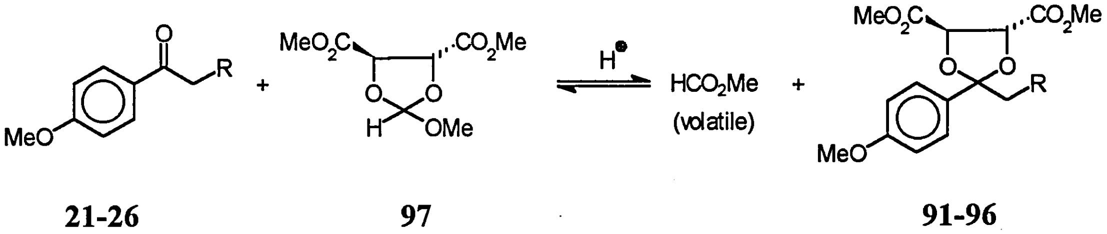
21 **91** **97**

Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 49

This orthoacetal **97** was difficult to separate from the required acetal by flash chromatography but could be separated by careful vacuum distillation.

The optimum conditions for minimising the formation of **97** were using 1.05 equivalents of dimethyl tartrate, 2.0 equivalents of trimethyl orthoformate and 0.1 equivalents of methanesulphonic acid. A possible scheme for the formation of the acetals **91-96** (see Scheme 50) is that the trimethyl orthoformate initially reacts with the dimethyl tartrate to give the orthoacetal **97**, which then itself reacts with the ketone to give the acetals **91-96.** The methyl formate produced is distilled off and drives the equilibrium towards the formation of the required acetal.



Scheme 50

This longer reaction time compared to that used for the preparation of propiophenone dimethyl tartrate acetal **90** could be explained by the methoxy substituent reducing the reactivity of the carbonyl carbon. The methoxy increases the electron density in the aromatic ring thereby reducing the electron deficiency of the carbonyl carbon (see Figure 13).

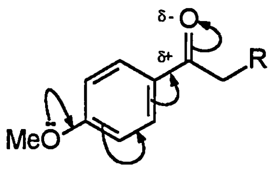
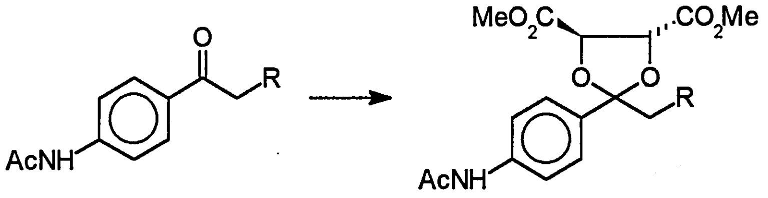


Figure 13

The crude acetals **91-95** still needed to be vacuum distilled because any contamination from the orthoacetal had a detrimental affect on the subsequent bromination reaction. There was an exception when R = Ph **96**, where purification by crystallisation from methanol was possible, which was fortunate because vacuum distillation required a very high temperature (which caused partial pyrolysis of the product) or extremely good vacuum (<0.1mm Hg).

4-Acetamido and 4-p-toluenesulphonamido substituted acetals

Using the same optimised conditions developed for the preparation of 4-methoxyphenyl substituted acetals **91-96**, 4-acetamidophenyl substituted acetals **98-99** (Scheme 51) and 4-(p-toluenesulphonamido)phenyl substituted acetals **100-103** were prepared (see Scheme 52).

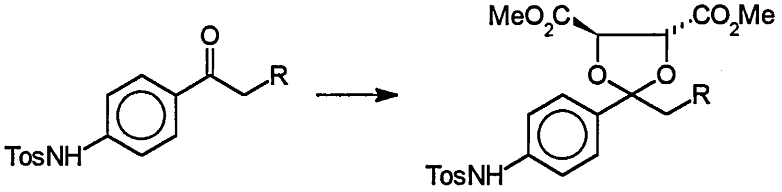


46 **98** R = CH_3, 46%

49 **99** R = $(CH_2)_3CH_3$, 44%

Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 51



59 **100** R = CH_3, 83%

60 **101** R = CH_2CH_3, 90%

61 **102** R = $CH(CH_3)_2$, 88%

62 **103** R = $(CH_2)_3CH_3$, 70%

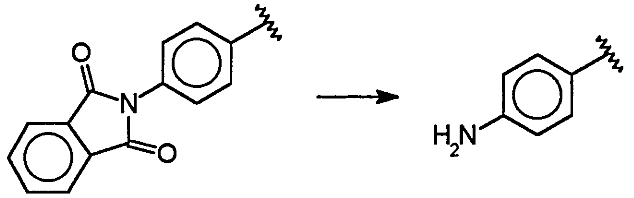
Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 52

Using these optimised conditions a small amount of the orthoacetal **97** was produced, but purification by flash chromatography was the only way as the product was insufficiently volatile for vacuum distillation. Flash chromatography was done in the presence of triethylamine in order to minimise degradation of the product on the silica. The 4-acetamidophenyl substituted acetals when pure were viscous liquids which partially crystallised though the modest yields reflect the difficulty in purification, while the crude 4-(p-toluenesulphonamido)phenyl substituted acetals **100-103** obtained were all straw coloured viscous liquids or solids, which were (re)crystallised from dry methanol to give white or pale brown crystalline solids.

4-Phthalimido substituted acetal

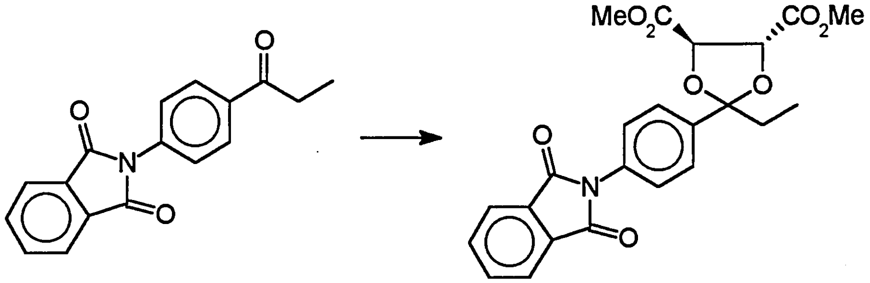
The preparation of other *para*-substituted acetals was attempted. The phthalimide group is known to induce crystallinity into the compounds containing it. It was hoped that the phthalimide group would protect the amine and could possibly be removed at a later time by reaction with hydrazine (see Scheme 53).



Reagents: N_2H_4

Scheme 53

We attempted to prepare the 4-phthalimidophenyl substituted acetal **174** using the same procedure outlined for the preparation of 4-methoxy, 4-acetamido and 4-(*p*-toluenesulphonamido)phenyl substituted acetals (see Scheme 54).



64 **174**

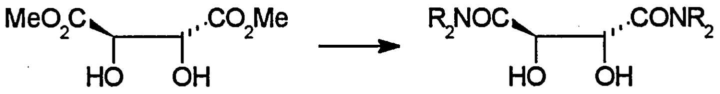
Reagents: (2*R*,3*R*) dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 54

When we attempted to purify the product **174** by flash chromatography, we were unable to separate the product from the starting material because they had similar R_f values. This was clearly shown in the ^1H NMR spectrum of the purest fractions where signals at 1.25ppm and 3.05ppm were observed which belonged to the alkyl chain of the starting material, while signals at 0.85ppm and 1.95ppm belonged to the alkyl chain of the product. These problems in purification and the promising results obtained for the preparation of other acetals suggested that our efforts were best concentrated in other areas, so work on this acetal was suspended.

Other chiral auxiliaries

The preparation of crystalline acetals detailed above had focused on the use of polar substituents on the aromatic ring; the alternative approach to induce crystallinity is to modify the chiral auxiliary. It has been mentioned earlier that the amide functional group is relatively polar and often induces crystallinity into a molecule and since dimethyl tartrate has two ester groups which can be readily converted into amides **104-105** by reaction with an amine, this approach was explored (see Scheme 55).



Dimethyl tartrate

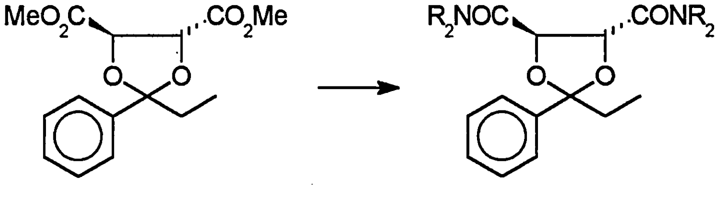
104 R = H

105 R = CH_3

Reagent: HNR_2

Scheme 55

These modifications to the chiral auxiliary could be introduced into the molecule by substitution at the carbonyl of dimethyl tartrate prior to acetal formation as in **104-105** or with the ester groups of the product acetal to give **106-107** (see Scheme 56).



90

106 R = H

107 R = CH_3

Reagent: HNR_2

Scheme 56

Preparation of Tartramides **104-105**

The preparation of the tartramide **104** was achieved by reaction of dimethyl tartrate with concentrated aqueous ammonia (see Scheme 57).

Dimethyl tartrate **104**

Reagent: conc. aqueous ammonia

Scheme 57

The crude product was isolated by removal of water, methanol and excess ammonia under reduced pressure to give a white crystalline solid in excellent yield (99%). The ^1H NMR spectrum showed the disappearance of the 2 peaks corresponding to the methoxy groups, while 2 peaks integrating for 4H appeared at 7.25ppm and 7.30ppm which corresponded to the amide protons. The appearance of 2 peaks is due to the restricted rotation about the carbonyl C-N bond (see Figure 14) making the amide protons non-equivalent.

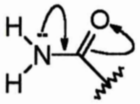
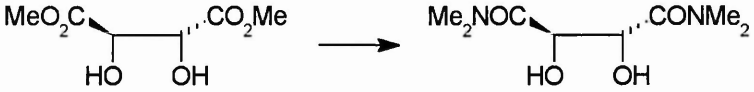


Figure 14

To prepare the tartramide **105** dimethylamine was stirred with dimethyl tartrate (see Scheme 58).



Dimethyl tartrate **105**

Reagent: $HNMe_2$

Scheme 58

Initially using a 40% w/v aqueous solution of dimethyl amine resulted in a poor yield and incomplete conversion. An improved method was found which used an excess of neat dimethylamine, obtained by distillation from 40% w/v aqueous solution, dried over KOH and collected at -78 °C.[42] Dimethyl tartrate was dissolved in anhydrous methanol and cooled to -78 °C prior to the addition of dimethylamine and the reaction was allowed to proceed at -5 °C in a freezer for 3 days. The reaction was allowed to warm to room temperature prior to removal of a small sample for crystallisation on a watch glass. Concentration of the remaining reaction mixture under reduced pressure was carried out before it was seeded and allowed to crystallise as a white crystalline material in 64% yield. The ^{1}H NMR spectrum showed 2 singlets at 2.95ppm and 3.05ppm each corresponding to 6 hydrogens and is due to π bonding between the nitrogen atom and the carbonyl carbon restricting the rotation about this bond. This restricted rotation makes the methyl groups non-equivalent (see Figure 15).

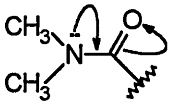
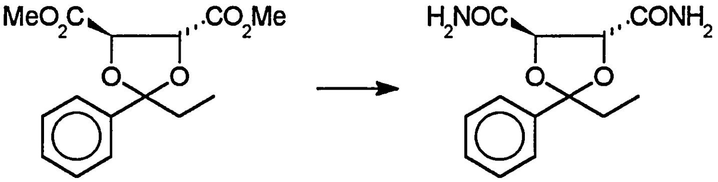


Figure 15

Preparation of tartramide acetal **106**

Preparation of the primary amide of propiophenone dimethyl tartrate acetal **106** was achieved by reaction of propiophenone dimethyl tartrate acetal **90** with concentrated aqueous ammonia (see Scheme 59).



90 **106**

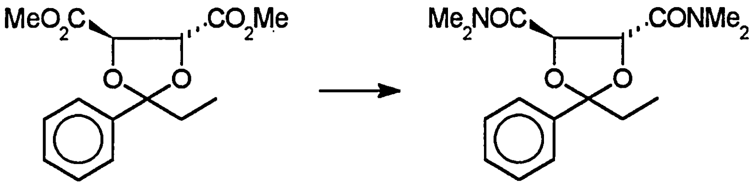
Reagent: conc. aqueous ammonia

Scheme 59

After 24 hours TLC analysis showed complete conversion of the starting acetal **90**. The crude product was isolated by removal of water, methanol and excess ammonia under reduced pressure to give the product (99%) as a paste which solidified. Prolonged standing of this amorphous solid afforded a small amount of a white crystalline solid, but crystallisation of the remaining material failed.

Preparation of tartramide acetal 107

Direct preparation of the tartramide acetal **107** from propiophenone dimethyl tartrate acetal **90** was achieved using neat dimethylamine (see Scheme 60).



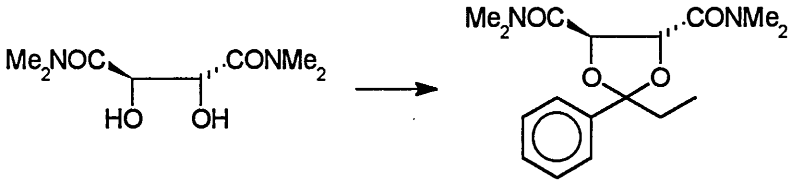
90 **107**

Reagent: $HNMe_2$

Scheme 60

Dimethylamine was distilled from a 40% w/v aqueous solution, dried over KOH and collected at -78 °C as previously outlined. Propiophenone dimethyl tartrate acetal **90** was dissolved in dry methanol and cooled to -78 °C prior to the addition of dimethylamine. The reaction was allowed to proceed at -5 °C over 3 days, when TLC analysis indicated complete conversion of the starting material. Removal of methanol and excess dimethylamine gave the product as a white paste (99%) which slowly crystallised.

Having prepared the crystalline tartramide **105** it was converted into the corresponding propiophenone acetal **107** by reaction with propiophenone **82** trimethyl orthoformate and methanesulphonic acid (see Scheme 61).



105 **107**

Reagents: propiophenone, trimethyl orthoformate, methanesulphonic acid

Scheme 61

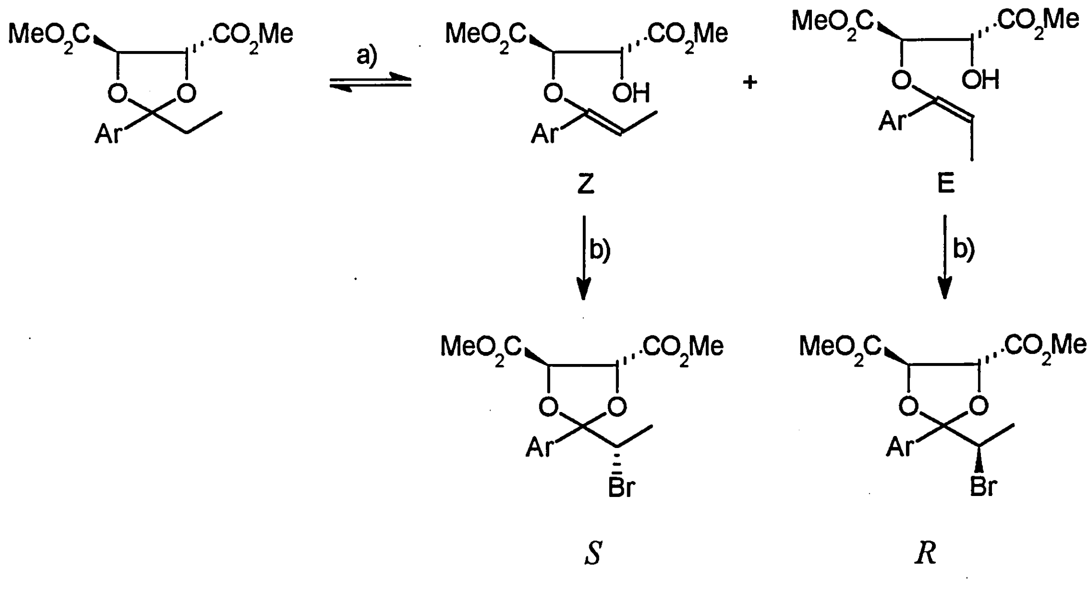
The crude product **107** was isolated as a pale yellow greasy solid, which was purified by flash chromatography to give a pale yellow solid in 74% yield. The ^1H NMR spectrum resolved each of the methyl groups at 2.80ppm, 2.95ppm, 3.15ppm and 3.25ppm again showing the restricted rotation in the amide.

Comparing both methods of preparing the tartramide acetal **107** it is clear that the first method is better in that it gave a better yield and did not require flash chromatography to purify the product.

We have thus shown that modifications to the chiral auxiliary can induce some crystallinity into the acetals, though less effectively than we had hoped. We have also shown that **107** can be prepared by modification of the chiral auxiliary either before acetal preparation or after the acetal has been prepared.

Preparation of bromoacetals

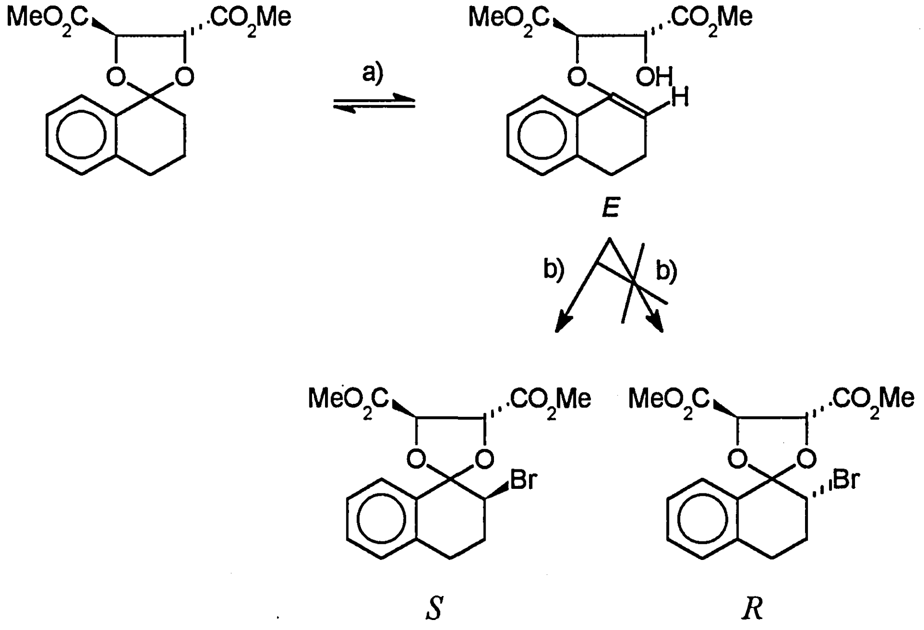
Bromination of dimethyl tartrate acetals is achieved in the presence of anhydrous acid to give a mixture of diastereoisomers. The mechanism involves the acid catalysed generation of an enol ether by the opening of the 1,3-dioxolane, followed by reaction with bromine to give the bromoacetal. A mechanism for the bromination reaction *via* a mixture of *E* and *Z* enol ethers has been proposed by the 'Zambon group' [29, 31] which suggests that the *E* enol ether would give the (*R*) diastereoisomer (see Scheme 62). The term (*R*) or (*S*) diastereoisomer refers to the stereochemistry at the CHBr stereocentre.



Reagents: a) H$^+$ b) Br$_2$

Scheme 62

The Zambon group attempted to prove this mechanism of bromination by using a conformationally fixed substrate where the geometry of the enol is known (see Scheme 63).[31]

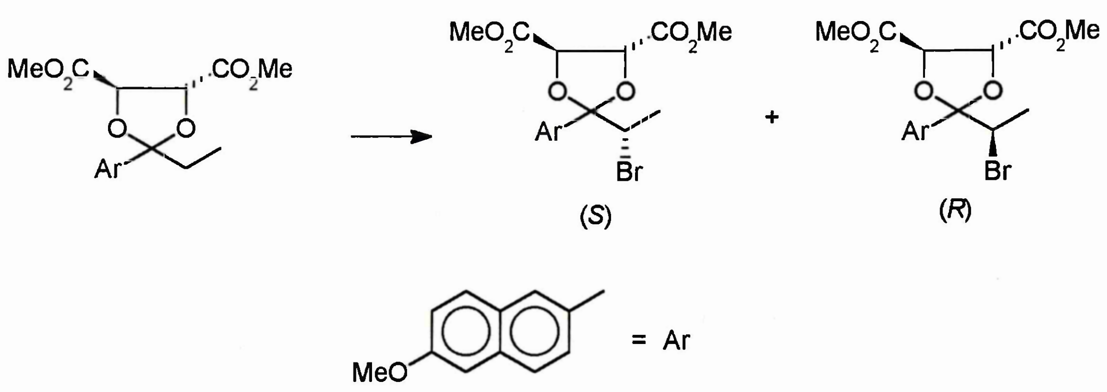


Reagents: a) H^+ b) Br_2

Scheme 63

The geometry of the enol ether is known to be *E*, which was expected to give the (*R*) diastereoisomer, but the reaction gave predominantly the (*S*) diastereoisomer. Therefore at present there is no satisfactory mechanistic explanation for the stereochemical outcome of the bromination of dimethyl tartrate derived acetals.

The Zambon group suggest that the conditions under which bromination takes place have a significant influence on the diastereoisomeric excess (d.e.) of the bromoacetal. They compare the bromination in a range of solvents [29] for 6-methoxynaphthyl acetals (see Scheme 64 and Table 5) and describe the bromination of α-tetralone acetals with various brominating agents (see Scheme 65 and Table 6),[32] but there is no mention of very low temperature bromination.



Reagents: H^+, Br_2

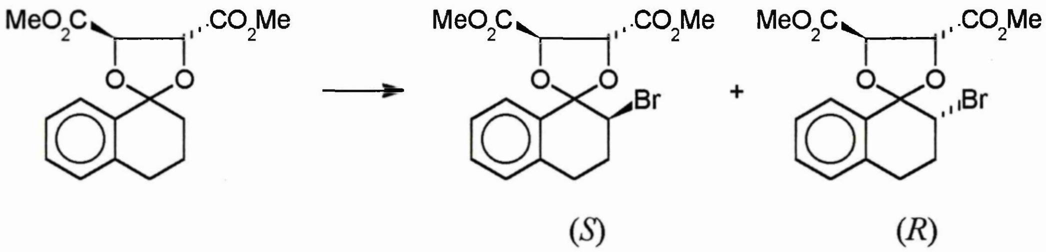
Scheme 64

Solvent	Temperature	Ratio S /R[#]
Carbon Tetrachloride	**-10**	**93:7**
Carbon Tetrachloride	**15**	**92:8**
Dichloromethane	**-10**	**90:10**
Chloroform	**-10**	**92:8**
1,2 Dichloroethane	**-10**	**90:10**
Toluene	**-10**	**93:7**
Chlorobenzene	**-10**	**91:9**
Ethyl acetate	**-10**	**94:6**
Acetic acid	**15**	**88:12**

Refers to the stereochemistry at CHBr.

Table 5

The data in Table 5 show that ethyl acetate is the best solvent for the reaction, closely followed by carbon tetrachloride and chloroform. Generally as the solvents become more polar we see a decrease in the d.e. of the product. The use of other sources of bromine has been investigated by Giordano *et al*, suggesting that for the bromination of acetals the choice of brominating agent determines which diastereoisomer is produced (see Scheme 65 and Table 6).[32]



Reagents: H^+, Br_2

Scheme 65

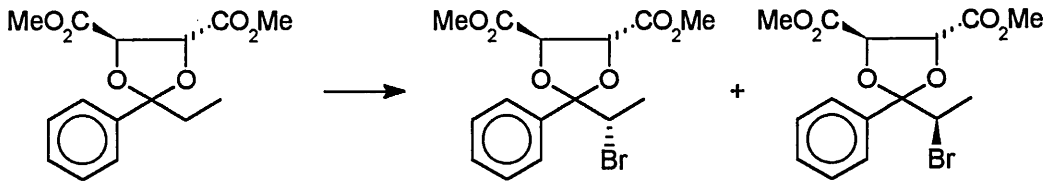
Some of the references in Table 6 indicate that the use of tetraalkylammonium / tetraalkylphosphonium tribromide salts or pyridinium tribromide salts with solvents such as THF or acetonitrile produce the opposite diastereoisomer at the CH-halogen stereocentre. The references associated with Figures 62-65 and Tables 5 and 6 indicate that the mechanism of the bromination is sensitive to the type of solvent and brominating agent.

Halogenating Agent	Solvent	Temperature °C	Ratio *S* /*R*
Tetrabutylammonium tribromide	**DCM** [32]	**0**	**44:56**
Tetraethylammonium tribromide	**DCM** [32]	**0**	**38:62**
Pyridinium tribromide	**DCM** [32]	**0**	**42:58**
2,6-Dimethylpyridinium tribromide	**DCM** [32]	**0**	**53:47**
Tetrabutylphosphonium tribromide	**DCM** [32]	**0**	**45:55**
Tetrabutylammonium tribromide	**CH_3CN** [32]	**0**	**15:85**
Tetraethylammonium tribromide	**CH_3CN** [32]	**0**	**14:86**
Tetrabutylphosphonium tribromide	**CH_3CN** [32]	**0**	**14:86**
Tetrabutylammonium tribromide	**THF** [32]	**0**	**6:94**
Tetraethylammonium tribromide	**THF** [32]	**0**	**5:95**
Pyridinium tribromide	**THF** [32]	**0**	**5:95**
2,6-Dimethylpyridinium tribromide	**THF** [32]	**0**	**5:95**
Tetrabutylphosphonium tribromide	**THF** [32]	**0**	**6:94**
Bromine	**DCM** [32]	**-10**	**88:12**
Bromine	**CH_3CN** [32]	**-10**	**78:22**
Bromine	**CH_3CN** [32]	**15**	**71:29**
Bromine	**THF** [31]	**-10**	**58:42**
Bromine	**DCM** [31]	**-10**	**86:14**
Iodine chloride	**DCM** [31]	**-10**	**80:20**
Sulfuryl chloride	**DCM** [31]	**-10**	**88:12**

Table 6

Bromination of acetal **90**

To gain familiarity with the chemistry involved we looked at the bromination of propiophenone dimethyl tartrate acetal **90** using the method described in the literature by Castaldi *et al* (see Scheme 66).[29]



90 **108(*S*)** **108(*R*)**

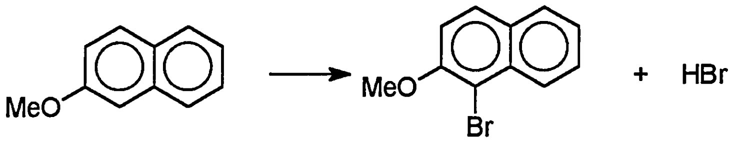
(Major diastereoisomer) (Minor diastereoisomer)

Reagents: Br_2, 2-methoxynaphthalene

Scheme 66

A solution of the starting material and 2-methoxynaphthalene (0.1 equivalents) dissolved in carbon tetrachloride was prepared to which a solution of bromine (2.1 equivalents) dissolved in carbon tetrachloride was slowly added. Upon complete conversion, as indicated by TLC analysis, the reaction was slowly poured into vigorously stirred saturated sodium carbonate solution from which it was then extracted.

The purpose of the 2-methoxynaphthalene was to generate anhydrous hydrogen bromide *in situ* (see Scheme 67).



Reagent: Br_2

Scheme 67

The 1-bromo-2-methoxynaphthalene produced in the reaction could only be removed by flash chromatography after which the bromoacetal **108** was obtained in only 74% (unoptimised) yield, with a ratio of **108(*S*)**: **108(*R*)** of 12:1 as determined by ^1H NMR analysis which compares favourably to that reported in the literature.[29] The ratio of diastereoisomers was determined from the methyl ester peaks which were resolved for each of the diastereoisomers (see in Figure 16).

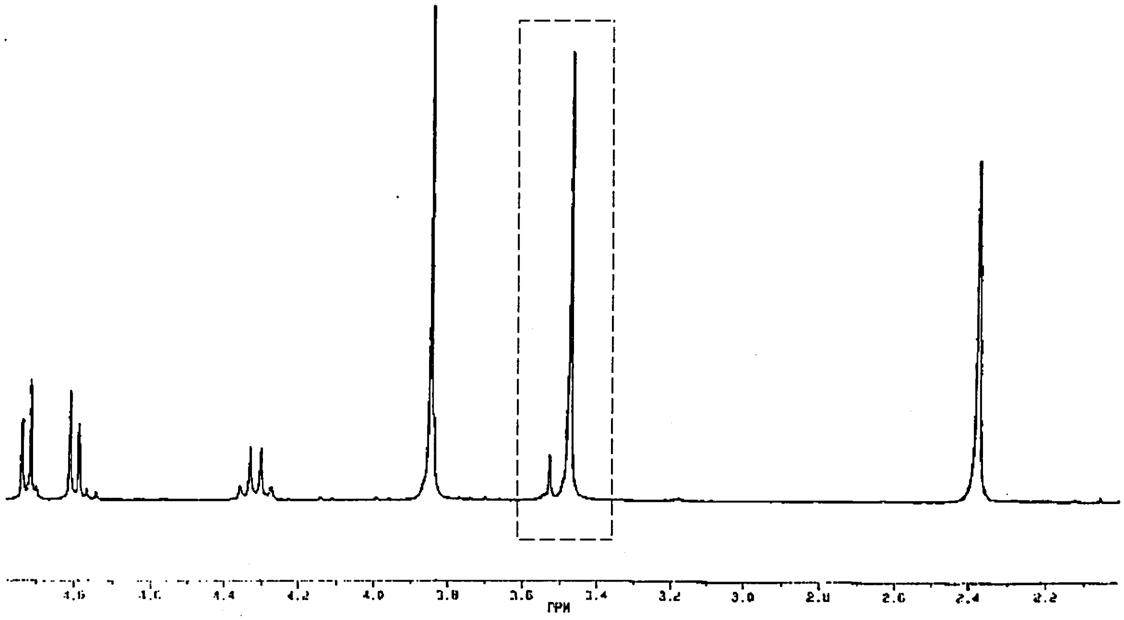


Figure 16

Our research into optimising the diastereoselectivity of the bromination reaction had identified several important parameters; i) the solvent, ii) the source of anhydrous acid, iii) the work-up procedure, iv) the source of bromine and v) the temperature.

i) The effect of changing the solvent

We wanted to keep the use of carbon tetrachloride to a minimum due to its effect on health and the environment, hence an investigation into using other solvents. Other anhydrous solvents such as DCM, THF, ethyl acetate and petroleum spirit were evaluated (see Table 7).

Solvent	Yield %	**108(*S*): 108(*R*)**
CCl_4	**74***	**12:1**
DCM	**95**	**8:1**
THF (dry)	**N /A ****	**3:1**
EtOAc (dry)	**N /A ****	**13:1**
Petrol (40-60)	**N /A ****	**N /A*****

* Unoptimised yield.

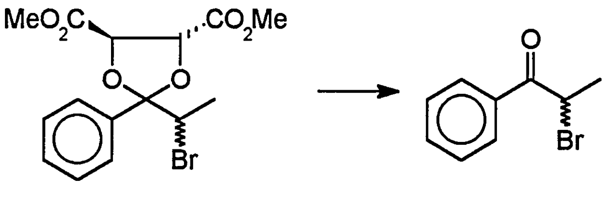
** Significant amounts of hydrolysis during the work-up.

*** The starting material did not dissolve in the petrol, petrol reacted with bromine.

Table 7

When DCM was substituted for carbon tetrachloride the diastereoisomeric ratio (*S*):(*R*) dropped from 12:1 to 8:1. Giordano *et al* suggested that bromination of dimethyl tartrate acetals in THF would give a poor diastereoisomeric ratio (*S*):(*R*) compared with that obtained in solvents such as DCM.[32] The ^1H NMR spectrum of the crude product from a reaction in THF showed that bromination had taken place and that the diastereoselectivity of the reaction was indeed poor (3:1), but not as bad as reported in the literature (3:2).

The use of ethyl acetate as a solvent looked very promising as the literature suggested that similar results as those for carbon tetrachloride could be obtained.[29] We found this to be the case, but problems in isolating the product were encountered due to significant hydrolysis to the bromoketone **89** (see Scheme 68).



108 **89**

Reagent: H_3O^+

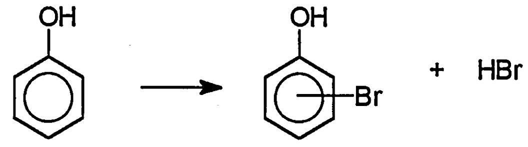
Scheme 68

Each of the solvents mentioned above (see Table 7) dissolved the starting material **90**, but when dry distilled petrol was used as the solvent the starting material had a very low solubility. Another difference between petrol and the other solvents was once the bromine addition had started, hydrogen bromide evolution occurred instantly as the bromine reacted with the petrol. The ^{1}H NMR spectrum of the material obtained from the reaction performed in petrol showed that the bromination of the propiophenone dimethyl tartrate acetal **90** had not taken place. A control reaction where bromine and petrol were mixed also produced copious amounts of hydrogen bromide. This reaction of bromine with petrol could have been anticipated since there were no precautions taken to exclude ultraviolet light.

We concluded that, where possible, compounds would be brominated in carbon tetrachloride, whilst those that were insufficiently soluble in carbon tetrachloride would be brominated in DCM. The exception was in our investigations to find the optimum brominating conditions where DCM was used instead of carbon tetrachloride.

ii) The effect of changing the source of anhydrous acid

As mentioned above, the use of 2-methoxynaphthalene as a source of anhydrous acid required the 1-bromo-2-methoxynaphthalene produced to be removed by chromatography. It was therefore decided that an alternative method for the generation of anhydrous HBr, which could remove the need for flash chromatography, would be investigated. An ideal alternative was to use phenol to generate the HBr as the by-product, bromophenol, would be extracted into the aqueous phase during the work-up procedure and therefore remove the need for flash chromatography. A search of the literature suggested that under these conditions only mono bromination of the phenol would take place (see Scheme 69).[43]



phenol bromophenol

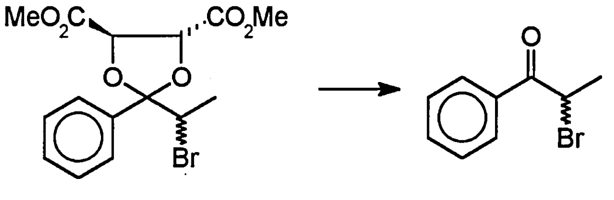
Reagent: Br_2

Scheme 69

The bromoacetal **108** obtained by this method had an identical (*S*):(*R*) ratio compared to the material obtained from the 2-methoxynaphthalene method, but was not contaminated by bromophenol. When methanesulphonic acid was used as the source of anhydrous acid and the amount of bromine used in the reaction was reduced to 1.05 equivalents, the ratio (*S*):(*R*) dropped from 8:1 to 4:1. A possible explanation for this can not be found at the present time. Since anhydrous hydrogen chloride gas was available this was also evaluated as a source of anhydrous acid. A small portion of solvent was saturated with anhydrous hydrogen chloride and added to the reaction prior to the addition of 1.05 equivalents bromine. The product was obtained in good yield with a (*S*):(*R*) ratio of 8:1 and this proved to be the most convenient source of anhydrous acid. Reducing the amount of bromine used in the reaction had no measurable effect on the diastereoselectivity of the reaction *c.f.* 8:1 with 2.1 equivalents and 8:1 with 1.05 equivalents of bromine.

iii) Work-up procedure

The literature method for the isolation of the bromoacetal was to slowly pour into saturated sodium carbonate solution,[29] but we found that this caused partial hydrolysis of the bromoacetal to the corresponding bromoketone (see Scheme 70). This would seem strange given that there is base present, but the rate at which the acid and base react could be slower than the rate of hydrolysis of the bromoacetal.



108 **89**

Reagent: H_3O^+

Scheme 70

In order to counteract this, various methods of isolating the product were evaluated. Slowly pouring the reaction mixture into concentrated ammonia solution allowed the product to be isolated with some hydrolysis. (In theory it is possible for ammonia to react with the tartrate ester groups, but this was not observed.) Slowly pouring the reaction mixture into cold 2N sodium hydroxide solution also showed some acetal hydrolysis and in theory there is a potential problem of ester hydrolysis, but this was not observed. Also investigated was pouring the reaction mixture into triethylamine to remove the acid in anhydrous conditions, followed by addition of sodium carbonate solution and extraction of the product with DCM. This proved to be too laborious and the product contained traces of triethylamine. Another alternative was to pour the reaction into di-potassium mono hydrogen phosphate solution buffered to pH 11. This method produced a small amount of hydrolysis. The best method was to remove the acid before any water came in contact with the product. This was achieved by slowly pouring the reaction mixture onto anhydrous potassium carbonate slurried in DCM, then adding water slowly to form a two phase system prior to isolation of the product by extraction. This method showed almost no acetal hydrolysis and the bromoacetal obtained **90** was relatively pure.

iv) Other sources of bromine

Accurately measuring liquid bromine on a small scale can cause problems due to its vapour pressure and hazardous nature, so other sources of bromine were investigated. Each reaction was performed under identical conditions of scale, solvent, temperature and acid catalysis. A solution of the propiophenone dimethyl tartrate acetal **90** in DCM was prepared, to which a small portion of hydrogen chloride saturated DCM was added. After stirring for 5 minutes the brominating agent was slowly added. Upon complete conversion, as indicated by TLC analysis, the reaction mixture was slowly poured onto anhydrous potassium carbonate slurried in DCM prior to the addition of water and isolation by extraction (see Table 8).

Brominating Agent	Yield %	d.e.
Bromine	**95**	**8:1**
Tetrabutylammonium tribromide	**57***	**3:1**
Solid supported bromine	**80**	**8:1**
pyridinium bromide perbromide	**N /A**	**4:1**

*Purification by flash chromatography

Table 8

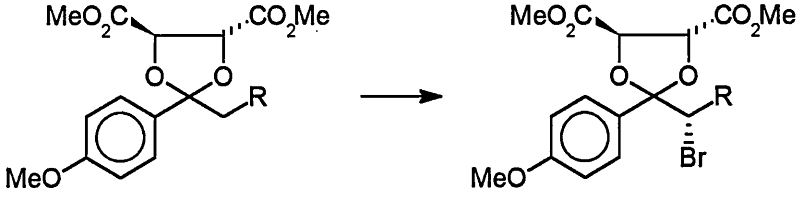
The use of tetrabutylammonium tribromide gave poor results, only 57% yield and a (*S*):(*R*) ratio of 3:1 (see Table 8) when compared to bromination using bromine. Isolation of the pure product **108** was complicated by the use of column chromatography to remove the residual tetrabutylammonium salts. It has been reported by Giordano *et al* that the use of tetrabutylammonium tribromide gives the opposite diastereoselection in the bromination of dimethyl tartrate acetals.[32] The product we obtained was the same diastereoisomer (^{1}H NMR analysis) as obtained when bromine was used. Solid supported bromine had the advantage that it was very easy to handle, but the amount of bromine contained was variable. The results obtained with solid supported bromine were similar to those with bromine (see Table 8). The polymer support could in principle be recovered and, according to the literature, reused.[44] The use of pyridinium bromide perbromide gave the bromoacetal with an (*S*):(*R*) ratio of 4:1 (see Table 8), but the crude product contained large amounts of pyridinium salts and was deemed not worth purifying. It was therefore obvious that liquid bromine was the best brominating agent despite the problems in its handling..

v) Effect of temperature

The temperature at which reaction takes place sometimes has a pronounced effect on the degree of stereospecificity of a reaction. In an attempt to increase the diastereoselectivity of the bromination, the reaction was carried out over a range of lower temperatures. When the reaction was carried out at -78°C no reaction was observed. Under these conditions there is insufficient energy to generate the enol and so bromination does not take place. At -40 °C bromination did take place at a very slow rate with DCM as the solvent, but the difference in the diastereoselectivity was minimal compared to bromination at room temperature. When we attempted to repeat the reaction at -40 °C using carbon tetrachloride (m.p. 23 °C) as the solvent unsurprisingly the starting material and solvent became frozen solid at about -25 °C. When bromination was carried out at -20 °C reaction took take place at an appreciable rate, but there was little or no change in the diastereoselectivity in either solvent. A temperature of -6 °C was relatively easy to achieve and maintain (ice / acetone) but once again there was little or no increase in diastereoselectivity. From our attempts to optimise the conditions for the bromination of acetal **90**, we have concluded that the diastereoselectivity of the bromination reaction depends mainly upon the solvent used, rather than the temperature at which the reaction takes place.

4-Methoxyphenyl substituted bromoacetals **109-111**

Once a method had been developed for the bromination of propiophenone dimethyl tartrate acetal **90** it was applied to the bromination of 4-methoxy substituted aryl alkyl acetals **91**, **92** and **96** (see Scheme 71).



91	**109**	R = CH_3, 97%, (*S*):(*R*) 19:1
92	**110**	R = CH_2CH_3, 91%, 19:1
96	**111**	R = Ph, 91%, 12:1

Conditions: HCl, Br_2, CCl_4, -6 °C

Scheme 71

The 4-methoxyphenyl substituted dimethyl tartrate acetal was dissolved in carbon tetrachloride to which was added a small portion of hydrogen chloride saturated CCl_4. The reaction was cooled to -6 °C in a ice /acetone bath prior to addition of bromine in CCl_4 over 2 hours whilst being vigorously stirred. When TLC analysis showed complete conversion of starting material the reaction was worked up by slow addition to CCl_4 slurried anhydrous potassium carbonate. 2,4-DNP Was found to be a convenient reagent for developing TLC plates. The starting acetals hydrolyse to the corresponding ketone because the spray reagent is prepared in acid. These ketones can then react with the 2,4 DNP to show an orange spot. The bromoacetals hydrolyse to the corresponding bromoketones in which the carbonyl is less reactive and therefore does not react with 2,4 DNP. The products were obtained in good yield as colourless / straw coloured viscous liquids, except for the bromoacetal **111** which was a low melting crystalline solid. Surprisingly, recrystallisation of **111** from various solvents failed to improve the (*S*):(*R*) ratio.

In order to prevent ring bromination the reaction mixture had to be maintained at -6 °C whilst the bromine was slowly added and the reaction mixture had to be stirred vigorously. Under these conditions good yields and the optimum (*S*):(*R*) ratios were obtained with very little ring bromination observed. Inspection of the ^{1}H NMR spectrum of the bromoacetal **110** revealed that the signals for the methylene protons adjacent to the CHBr stereocentre are non equivalent (diastereotopic) (see Figure 17) and are separated from each other by 0.3ppm at 1.65ppm and 1.95ppm. This non equivalence is due to each proton experiencing a slightly different chemical environment.

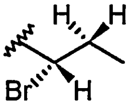
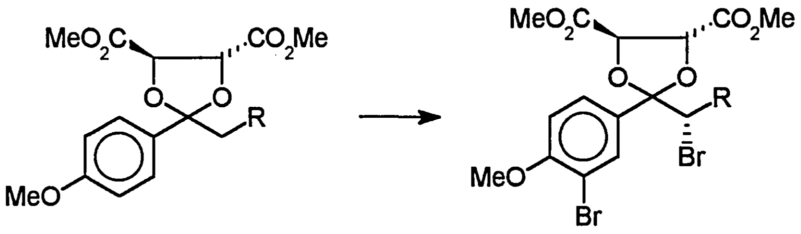


Figure 17

3-Bromo-4-methoxyphenyl substituted bromoacetals **112-116**

In the initial small scale bromination of 4-methoxyphenyl acetals some ring bromination was observed which was difficult to prevent. As it was difficult to stop this ring bromination it was therefore logical to see what synthetic use could be made of these ring brominated compounds **112-116**. The bromoacetals **112-116** were prepared using similar conditions to those used for the preparation of bromoacetals **109-111** except that 2.05 equivalents of bromine were used and the reaction was allowed to warm from -6 °C to room temperature during the reaction (see Scheme 72).



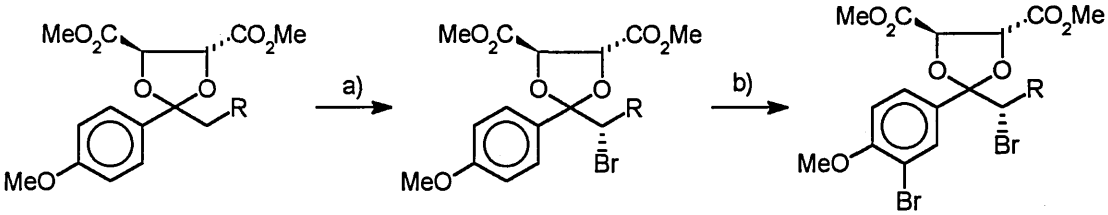
91	**112**	R = CH_3, 90%, (*S*):(*R*) 19: 1
92	**113**	R = CH_2CH_3, 91%, 19:1
93	**114**	R = $CH(CH_3)_2$, 95%, 12:1
94	**115**	R = $(CH_2)_3CH_3$, 91%, 12:1
95	**116**	R = $(CH_2)_7CH_3$, 98%, 10:1

Conditions: HCl, Br_2, CCl_4, -6 °C to r.t.

Scheme 72

The products **111-116** were isolated as colourless / straw coloured viscous liquids. The bromoacetal **111** crystallised as a low melting point solid, but attempts to significantly improve the (*S*):(*R*) ratio by recrystallisation were unsuccessful. Inspection of the ^{1}H NMR spectrum of the bromoacetal **113** showed similar diastereotopic protons as observed in the bromoacetal **110** at 1.65ppm and 1.95ppm. The phenomenon is also present in the bromoacetals **115** and **116** but to a lesser extent.

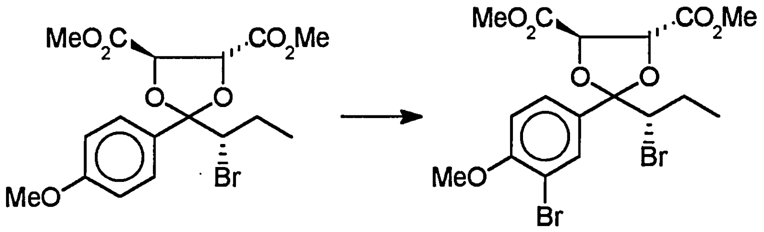
Following the reaction by GC it was confirmed that the first bromination was next to the acetal and upon warming the aromatic ring was brominated (see Scheme 73).



Conditions: a) HCl, Br_2, -6 °C b) HCl or HBr, Br_2, r.t.

Scheme 73

This is consistent with the earlier observations where we had shown that in the bromination of 4-methoxyphenyl substituted acetals it was possible to brominate next to the acetal without brominating the aromatic ring. We now attempted to prove that it was possible to brominate the aromatic ring without any racemisation of the chiral centre of the bromoacetal **110** (see Scheme 74) which we knew had a diastereoisomeric ratio of 19:1 as determined by ^{1}H NMR spectroscopy. A possible mechanism for racemisation to take place would be for the 1,3-dioxolane to open under the acidic conditions and close in a different configuration.



110 (*S*):(*R*) 19:1 **113** R = CH_2CH_3, 91%, 19:1

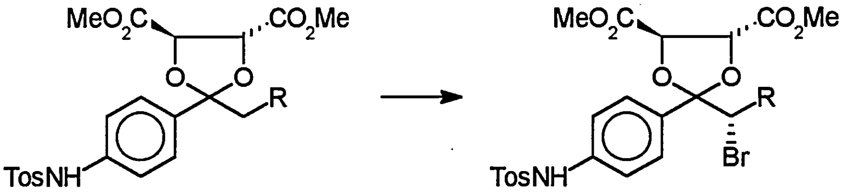
Conditions: HCl, Br_2, CCl_4, r.t.

Scheme 74

The bromoacetal **113** was isolated as a pale brown coloured viscous liquid (91% yield) and the diastereoisomeric ratio was 19:1 as determined by ^{1}H NMR spectroscopy indicating that racemisation of the CHBr chiral centre had not taken place.

<u>*p*-Toluenesulphonamide substituted bromoacetals **117-119**</u>

The bromination of sulphonamido substituted acetals in carbon tetrachloride was not possible due to their low solubility, hence DCM was used as solvent (see Scheme 75).



100 **117** R = CH_3, 80%, (*S*):(*R*) 10: 1

101 **118** R = CH_2CH_3, 66% *, 10:1

102 **119** R = $CH(CH_3)_2$, 23% **, 8:1

Conditions: DCM, HCl, Br_2, -6 °C

* Unoptimised yield.

** Pure fractions from flash chromatography, unoptimised yield.

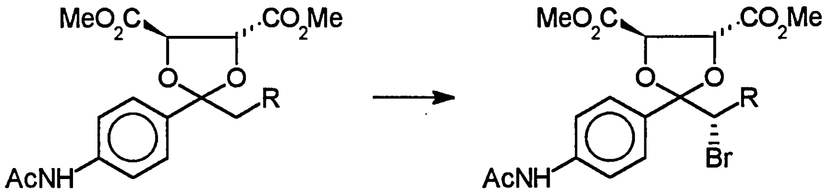
Scheme 75

Using reactions conditions similar to those used for the preparation of bromoacetals **109-111** 4-(*p*-toluenesulphonamido) substituted acetals **100-102** were brominated. The crude products were obtained as straw coloured viscous liquids that partially crystallised. Purification of the crude bromoacetals **117-119** was by flash chromatography, where needed, followed by (re)crystallisation from dry methanol gave the pure products **117-119**. The diastereoisomeric ratio of the bromoacetals was determined by ^{1}H NMR spectroscopy.

Since the bromoacetals **117-119** obtained were solids it was hoped that recrystallisation would confer a better (*S*):(*R*) ratio. The best solvent for recrystallisation was dry methanol, but the material recovered had essentially the same (*S*):(*R*) ratio as the starting material. Many solvents were tried but no significant improvement in (*S*):(*R*) ratios was obtained.

4-Acetamido substituted bromoacetal **120-121**

The method used for the bromination of 4-acetamido substituted acetals **98-99** was similar to that used for the bromination of 4-(*p*-toluenesulphonamido) substituted acetals **100-102** (see Scheme 76).



98
99

120 R = CH_3, 80%*
121 R = $(CH_2)_3CH_3$, 0%**

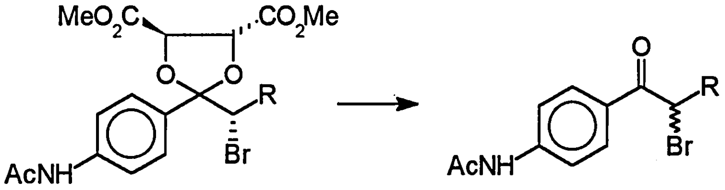
Conditions: DCM, HCl, Br_2, -6 °C

* Crude product which decomposed during flash chromatography.

** Decomposed during work up.

Scheme 76

The 4-acetamide substituted dimethyl tartrate acetals **98-99** were dissolved in DCM because they were insufficiently soluble in carbon tetrachloride. Isolation of the crude products was difficult due to a significant amount of hydrolysis of the bromoacetal upon work-up (see Scheme 77). Purification of the crude bromoacetal **120** by flash chromatography using petrol, ethyl acetate with a trace of triethylamine resulted in its decomposition to the corresponding bromoketone, while the bromoacetal **121** decomposed during the work up procedure.



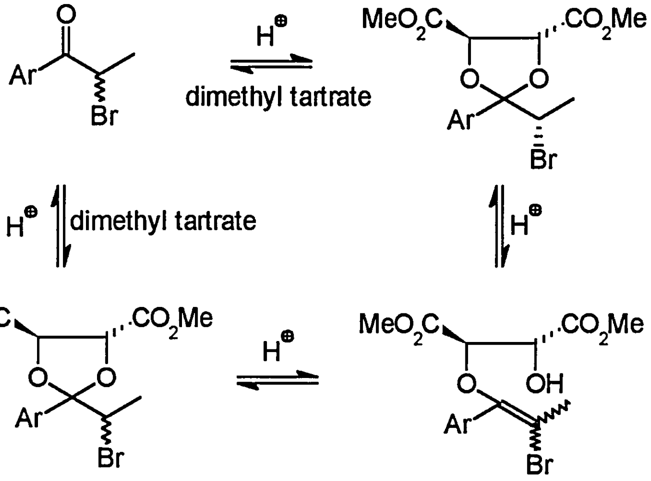
Reagent: H_3O^+

Scheme 77

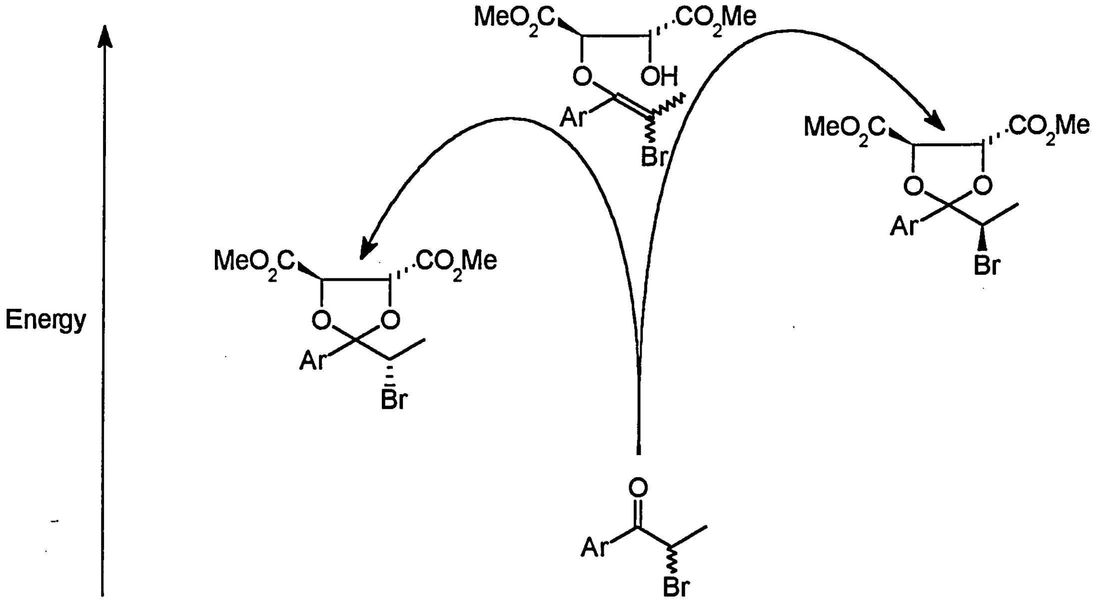
From these results it was clear that these acetamido substituted bromoacetals **120-121** were much less stable than the other bromoacetals investigated. Since other bromoacetals looked more promising, no further work was done on acetals containing the 4-acetamido substituent.

Conversion of bromoketones to bromoacetals

Having prepared a wide variety of bromoacetals of various diastereoisomeric excess, we asked the question 'Could diastereomerically enriched bromoacetals be prepared from racemic bromoketones according to the chemistry shown in Scheme 78'? Any possible stereochemical induction would arise as a result of thermodynamic control of the reaction (see Scheme 79).

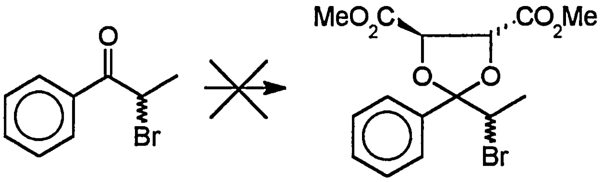


Scheme 78



Scheme 79

The preparation of bromoacetal **108** from racemic 2-bromopropiophenone **89** was attempted using identical conditions to those used for the preparation of propiophenone dimethyl tartrate acetal **90** but showed no sign of the required product (see Scheme 80).

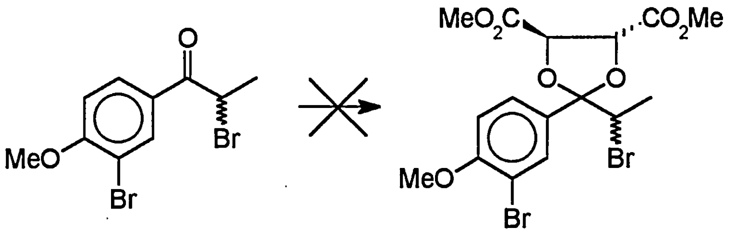


89 **108**

Reagents: dimethyl tartrate, trimethyl orthoformate, methanesulphonic acid

Scheme 80

A prolonged reaction time showed no evidence of the required product as only the starting materials were observed by TLC and ^1H NMR spectroscopy. This lack of reaction could be attributed to steric hindrance by the bromine, or the fact that the bromine deactivates the carbonyl. It has been reported by Giordano *et al* that racemic bromoketones cannot be converted to their corresponding dimethyl tartrate bromoacetals using the normal conditions, but when employing more vigorous conditions the transformation could be achieved, but the yields reported were less than 5% (see Scheme 81).[7]



80 **112**

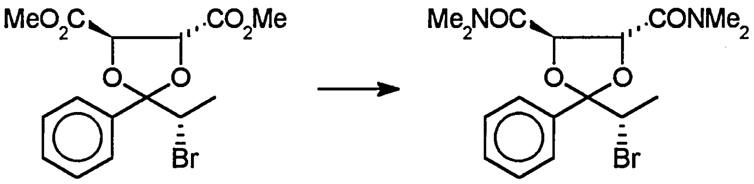
Reagents: dimethyl tartrate, dimethyl sulphite, trifluoromethanesulphonic acid, DCM

Scheme 81

When racemic 3'-bromo-4'-methoxy-2-bromopropiophenone **80**, dimethyl tartrate, dimethyl sulphite, in dry DCM and trifluoromethanesulphonic acid were stirred at room temperature for 5 hours no reaction was observed by TLC analysis. We found this somewhat disappointing but not entirely unexpected given that the literature had suggested problems.

Preparation of tartramide propiophenone bromoacetal 122

Earlier in this section we described how the dimethyl tartrate chiral auxiliary had been modified in order to prepare crystalline acetals with the aim of producing crystalline bromoacetals. We had shown that it was possible to take propiophenone dimethyl tartrate acetal and replace the ester groups by amides in order to get a crystalline solid. By analogy, it should be possible to substitute at the ester groups of propiophenone dimethyl tartrate bromoacetal **108** using dimethylamine (see Scheme 82).



108 **122**

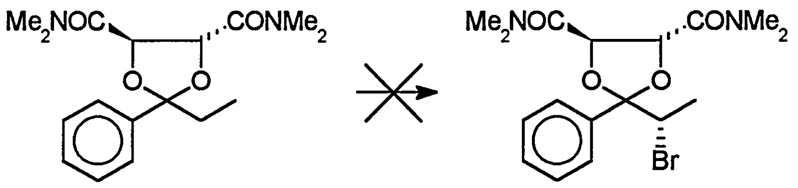
Conditions: $HNMe_2$, methanol

Scheme 82

The bromoacetal **108** was dissolved in dry methanol and cooled to -78 °C prior to the addition of dimethylamine. The reaction was allowed to proceed at -5 °C over 3 days after which TLC analysis indicated complete conversion of the starting material. The methanol and excess dimethylamine were removed under vacuum to give the product as a white paste (95% yield) which we were unable to crystallise.

Bromination of tartramide propiophenone acetal **107**

Having prepared the tartramide acetal **107** as a crystalline solid, it was hoped that when **107** was brominated that the bromoacetal **122** would also be a crystalline solid (see Scheme 83).



107 **122**

Conditions: DCM, HCl, Br_2 -6 °C

Scheme 83

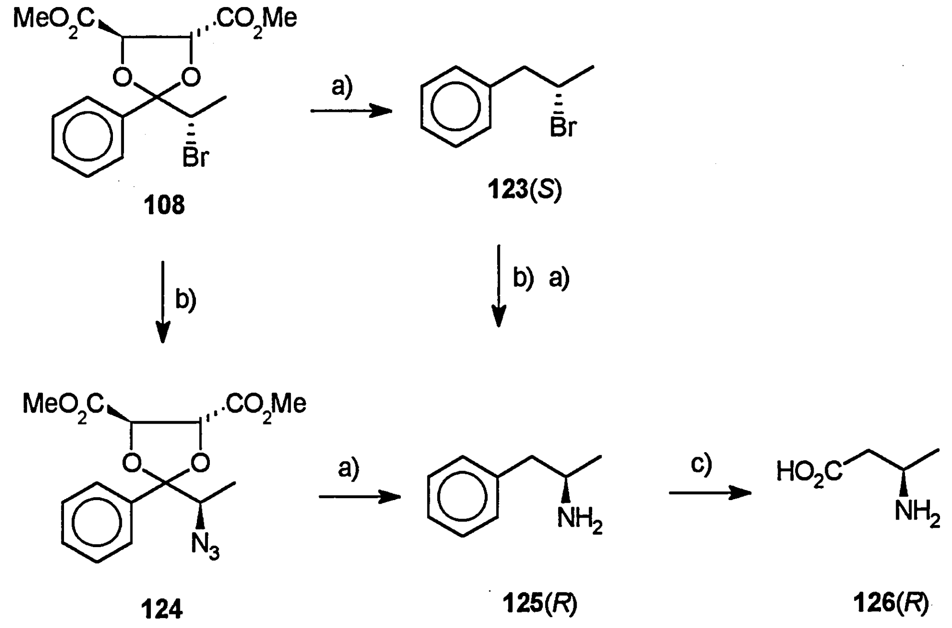
The propiophenone tartramide acetal **107** was dissolved in dry DCM and cooled to -6 °C prior to the addition of HCl and bromine. TLC analysis indicated that no reaction had taken place after 3 hours, hence more acid catalyst was added. The reaction was stirred overnight at room temperature during which time a reaction had taken place as indicated by the disappearance of bromine. The product was isolated and characterised by ^1H NMR spectroscopy and was found to be exclusively 2-bromopropiophenone **89**. This indicated that the product is unstable to the reaction conditions or to the work up procedure.

Due to time constraints further work into the new tartrate analogues was suspended, but further work into chiral auxiliaries derived from tartaric acid maybe be useful in providing products which are more highly crystalline and can be recrystallised to higher d.e.

Section 2

Strategy

Having prepared a range of aryl alkyl bromoacetals of reasonable diastereoisomeric excess, we wanted to prove that we could use them to prepare other chiral molecules. The literature relating to the synthesis of 2-arylpropanoic acids has described the conversion of bromoacetals to 2-bromoketones,[33] but we wanted to investigate the possibility of preparing enantiomerically pure β amino acids by using the aryl group as a 'masked' carboxylic acid.[45-47] However, before we could 'unmask' the carboxylic acid we had to find a way at some point of substituting the bromine for an amine and be able to remove the 1,3-dioxolane by 'hydrogenolysis', all without racemising the chiral centre. The overall strategy is outlined below (see Scheme 84).

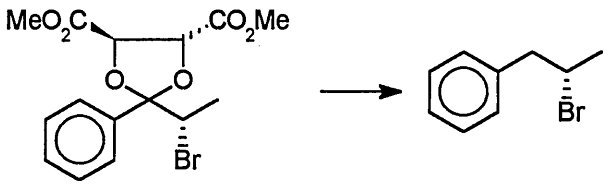


Reagents: a) H_2, Pd or Pt catalyst b) NaN_3, DMF c) Oxidation Ru catalyst

Scheme 84

Attempted hydrogenolysis of propiophenone dimethyl tartrate bromoacetal **108**

We investigated several methods of hydrogenolysis in order to facilitate the removal of the 1,3-dioxolane (see Scheme 85).



108 **123(*S*)**

Reagents: H_2, Pd or Pt catalyst

Scheme 85

Method 1 (Balloon / sonic bath)

Our initial method used the relatively simple set-up of a balloon filled with hydrogen attached to the top of a condenser above a flask containing the bromoacetal **108** and catalyst [5% Pd on carbon] in methanol. We stirred the reaction at room temperature for 24 hours but no reaction was observed by TLC analysis. The reaction was heated to reflux for 24 hours, but again no reaction was observed. A duplicate reaction was set up and was placed in a sonic bath and sonicated for 7.5 hours, after which it was allowed to stand over night prior to analysis by TLC which showed that only starting material was present. This initial lack of positive results forced us to look at reactions which used more vigorous conditions.

Method 2 (Hydrogenator)

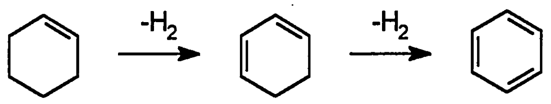
The bromoacetal **108** and catalyst [5% Pd on carbon] were stirred in methanol for 8.5 hours at atmospheric pressure of hydrogen, but TLC analysis showed only the presence of starting material which was recovered.

Method 3 (Balloon / HCl)

A variation to method 1 involved bromoacetal **108** being stirred with a catalyst [5% Pd on carbon] in super dry methanol saturated with dry hydrogen chloride gas. A balloon filled with hydrogen gas was attached and the reaction heated at reflux overnight. Again as in the previous attempts analysis of the reaction by TLC and ^{1}H NMR spectroscopy showed once again only the presence of starting material.

Method 4 (Transfer hydrogenolysis using cyclohexene)

The literature describes a method for the catalytic transfer hydrogenolysis of ethers in which cyclohexene is used as a source of hydrogen, with a catalyst containing palladium hydroxide supported on carbon [10% $Pd(OH)_2$ / C].[48] The cyclohexene 'transfers hydrogen' to the product in a stepwise manner to give first 1,3-cyclohexadiene and eventually benzene (see Scheme 86).



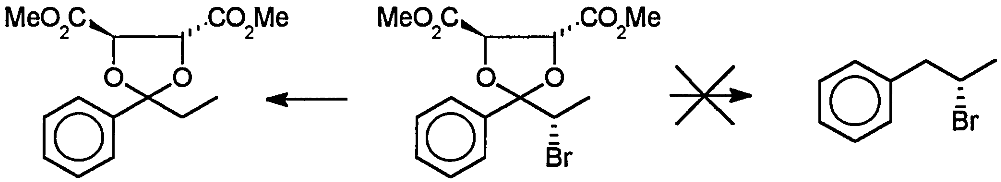
cyclohexene 1,3-cyclohexadiene benzene

Scheme 86

However when the bromoacetal **108**, catalyst and cyclohexene were heated at reflux in ethanol for 24 hours, after which TLC analysis indicated that only starting material was present.

Method 5 (Transfer hydrogenolysis using ammonium formate)

Our fifth method for attempted hydrogenolysis of the bromoacetal **108** used a catalyst [5% Pd on carbon] and ammonium formate as the source of hydrogen. The starting materials were heated at reflux in methanol overnight. Analysis next day by TLC showed several spots after which the crude product was isolated and purified by flash chromatography. Analysis of the pure fractions by ^1H NMR spectroscopy revealed that one of the products was the acetal **90**, while the other was the starting bromoacetal **108**. The results from this method suggest that the C-Br bond is weaker than the corresponding benzylic C-O bond (see Scheme 87).



90 **108** **123(*S*)**

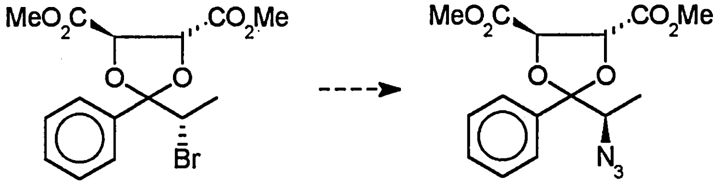
Reagents: ammonium formate, 5% Pd / C

Scheme 87

We concluded that hydrogenolysis of the bromoacetal **108** was not as straightforward as we had initially anticipated.

Attempted azide displacement of bromine from bromoacetal

Our alternative strategy was to replace the bromine from the bromoacetal **108** with an azide group (see Scheme 88), which we would then convert by reduction to an amine in the hydrogenolysis reaction. We anticipated that the C-N bond would be stronger than the C-Br bond and therefore would be less likely to break during the hydrogenolysis reaction.



108 **124**(*R*)

Conditions: NaN_3, DMF or NMP

Scheme 88

Method 1

Our first attempt at displacing the bromine of the bromoacetal **108** involved stirring the bromoacetal with sodium azide using dry DMF as a solvent.[49, 50] The reaction was stirred for 24 hours at room temperature, after which analysis by TLC indicated that no reaction had taken place. The mixture was then heated at 55 °C for 48 hours but again TLC analysis indicated that no reaction had taken place. A trace of water was added in order to make sure that some of the azide was in solution, but after 48 hours heating at 65 °C TLC analysis showed no reaction. Finally the temperature of the reaction was increased to 90 °C which resulted in the formation of a black intractable solid.

Method 2

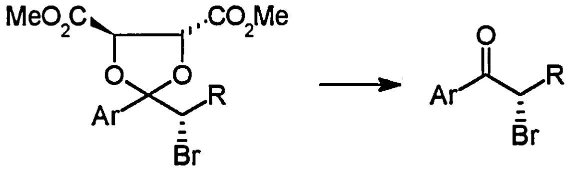
We repeated the reaction using NMP [*N*-methyl-2-pyrrolidinone] instead of DMF and heated the reaction at reflux. Analysis by TLC after 6 hours showed numerous spots, but isolation of a product from which we were able to deduce a structure proved very difficult.

This reluctance of the bromine to be displaced by an incoming nucleophile was somewhat surprising given that bromide is usually a very good leaving group. A possible explanation could be that the direction of attack required by an incoming nucleophile for displacement of the bromine is blocked by another part of the molecule.

We regrettably came to the conclusion that modification of the bromoacetal **108** was not as straight forward as we had hoped and therefore our strategy for the preparation of β amino acids was not possible.

Preparation of enantiomerically pure bromoketones

The literature relating to the synthesis of arylpropanoic acids describes the preparation of enantiomerically pure bromoketones from dimethyl tartrate bromoacetals (see Scheme 89).[33]

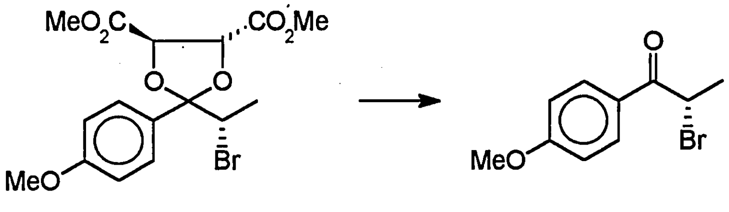


Reagents: Methanesulphonic acid, H_2O

Scheme 89

The method described involves the acid hydrolysis of the bromoacetal using methanesulphonic acid with 2.5 equivalents of water to give the crude bromoketone. The bromoacetal is soluble in the methanesulphonic acid while the product is not. Where the bromoketone was a solid it could be purified by recrystallisation from methanol to give the enantiomerically pure (*S*)-bromoketone.

We repeated the literature method for preparing enantiomerically pure bromoketones using the bromoacetal **114** which was dissolved in methanesulphonic acid prior to the dropwise addition of water (see Scheme 90).



114 **78**(*S*) 58% yield, ~80% e.e.

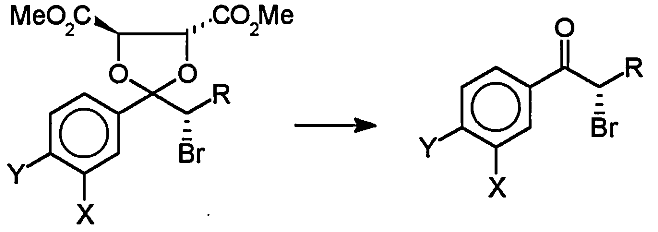
Reagents: methanesulphonic acid, H_2O

Scheme 90

The reaction was followed by GC until complete conversion had taken place during which time the product was observed to precipitate out of the methanesulphonic acid. The reaction mixture was slowly poured onto stirred crushed ice /ether from which the crude product was isolated as a viscous liquid. Attempted purification by crystallisation of the crude bromoketone **78**(*S*) from methanol gave a low melting crystalline solid (m.p. 63-64°C), which had a similar melting point to the one quoted in the literature for the racemic bromoketone **78** (lit m.p. racemic 66-67°C).[33] The enantiomeric excess (e.e.) was first determined by optical rotation which indicated an e.e. of about 80%, but after five days storage ^{1}H NMR analysis in the presence of Eu(hfc)$_3$ showed it to be almost racemic. This suggested that the bromoketone **78**(*S*) was not very stable to racemisation although no mention was made of this in the literature report. However these workers do not quote a value for the melting point of enantiomerically pure bromoketone **78**(*S*).

We first resolved the enantiomers of racemic **78** by ^{1}H NMR spectroscopy using a chiral shift reagent and then applied this knowledge to determine the enantiomeric excess of the 'chiral' material. The method for determining the optimum separation of peaks was by trial and error, *i.e.* a spectrum was obtained without any chiral shift reagent, then a small amount was added and the spectrum recorded again. This was continued until the best resolution of one or more peaks was obtained and continued until all resolution was lost. The first peaks to be resolved were those for the methyl next to the chiral centre, but these peaks coincided with those of the chiral shift reagent and were therefore of no use for the accurate determination of enantiomeric excess. After addition of more shift reagent the signals corresponding to the different *ortho*-protons on the aromatic ring were resolved. They were resolved down to the baseline thus enabling an accurate determination to be made. Further additions enabled the *meta*-protons and *para*-methoxy signals to be resolved by which time all the other peaks were very broad. It was noted that the more chiral shift reagent in the solution the wider the peaks became and it was therefore a compromise between concentration, separation and resolution. At all times great care had to be used in order to prevent water being absorbed by the chiral shift reagent, since the chiral shift reagent would preferentially bind water rather than the sample. The most convenient method for preventing contamination and monitoring the quantity of shift reagent required, was to prepare a concentrated solution of shift reagent in $CDCl_3$.

The method for preparing the bromoketone **78**(*S*) from the bromoacetal **109** was applied to the bromoacetals **91-98** some of which contained an aromatic bromine and the 4-(*p*-toluenesulphonamido) substituted bromoacetal **117** (see Scheme 91).



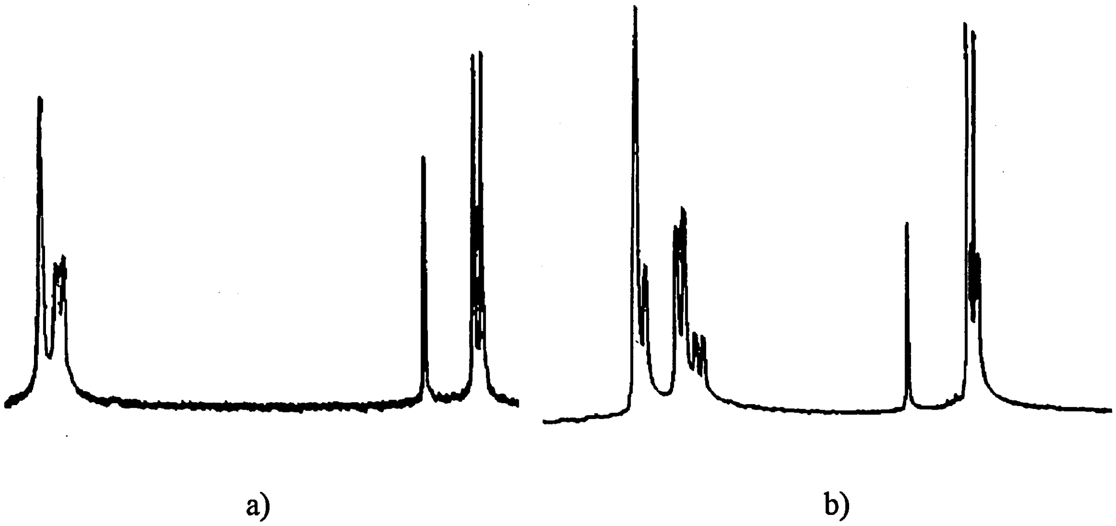
109 X = H, Y = MeO	**78**(*S*)	R = CH_3, 58%, ~80%*
110 X = H, Y = MeO	**79**(*S*)	R = CH_2CH_3, 65%, 92%
111 X = H, Y = MeO	**87**	R = Ph, 45%, N/A
112 X = Br, Y = MeO	**80**(*S*)	R = CH_3, 52% yield, >98% e.e.*
113 X = Br, Y = MeO	**81**(*S*)	R = CH_2CH_3, 50%, >98%*
114 X = Br, Y = MeO	**83**(*S*)	R = $CH(CH_3)_2$, 70%, 71%
115 X = Br, Y = MeO	**84**(*S*)	R = $(CH_2)_3CH_3$, 67%, 66%
116 X = Br, Y = MeO	**85**(*S*)	R = $(CH_2)_7CH_3$, 43%, >98%*
117 X = H, Y = TosNH	**88**	R = CH_3, 0%, N/A

* After recrystallisation.

Reagents: methanesulphonic acid, H_2O

Scheme 91

Each reaction was followed by GC until almost complete conversion had taken place and again the product was observed to precipitate out of the methanesulphonic acid. The reason for isolating the product just before GC indicated complete conversion was that it took 20 minutes for analysis of the reaction mixture, during which time the reaction would have gone to completion. We were concerned that prolonged contact with the highly acid medium would racemise some of the product and therefore lower the final e.e. The crude product was isolated as either a viscous liquid or low melting solid. The enantiomerically pure product was obtained by (re)crystallisation from methanol and the enantiomeric excess (e.e.) was measured by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ (see Figure 18).



a) Bromoketone with chiral shift reagent.

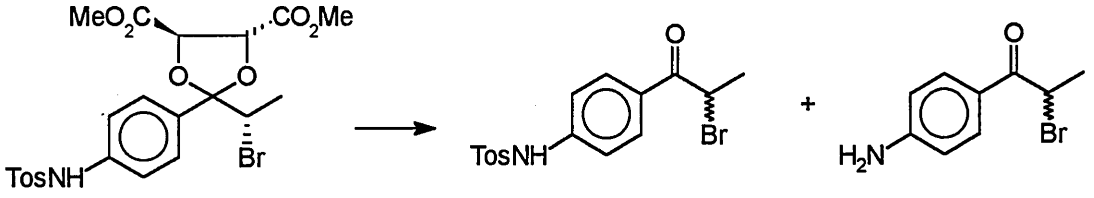
b) Bromoketone with chiral shift reagent and spiked.

Figure 18

Confirmation of the products was obtained from high resolution mass spectroscopy and from ^{1}H NMR spectroscopy which showed the loss of the signals corresponding to the methyl esters.

The bromoketones **79-81, 83-85, 87** and **89** were stored for up to several weeks prior to being used in further reactions without a measurable change in e.e, but the bromoketone **78**(*S*) racemised upon standing. The crude bromoketone **79**(*S*) had an e.e. of 92%, but recrystallisation to enantiomeric purity was not attempted. It was stored for several months at -4 °C, during which time no significant loss in e.e. was observed by ^{1}H NMR analysis. We were unable to recrystallise the bromoketones **83** and **84** to enantiomeric purity despite repeated efforts using various solvents and we were unable to determine the enantiomeric excess of the bromoketone **87** because we were unable to resolve the enantiomers by ^{1}H NMR spectroscopy.

The method for converting the methoxy substituted bromoacetals **109-116** to the corresponding (*S*)-bromoketones **78-81, 83-85** and **87** was also applied to the bromoacetal **117** containing the 4-(*p*-toluenesulphonamido) substituent. Under these conditions the acetal group of **117** was partially hydrolysed, but unfortunately so was the sulphonamide group as indicated by ^{1}H NMR spectroscopy. The addition of more water caused complete hydrolysis of the acetal and led to the isolation of a mixture of amine **127** and sulphonamide **88** (see Scheme 92).



117(*S*) **88** **127**

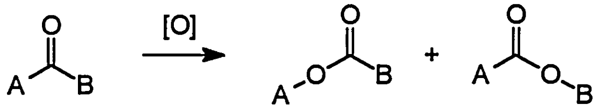
Reagents: methanesulphonic acid, H_2O

Scheme 92

A single attempt to convert this mixture into the sulphonamide **88** by reaction with tosyl chloride gave a complex mixture of products, but this reaction is worth further investigation.

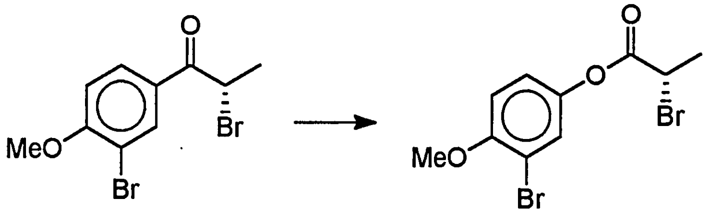
<u>Baeyer-Villiger reaction of bromoketones</u>

Once we had developed a method for the preparation of these enantiomerically enriched (*S*)-bromoketones **80(*S*)-81(*S*)** and **83(*S*)-85(*S*)** we investigated their conversion into the corresponding aryl bromoesters by the Baeyer-Villiger oxidation reaction. This overall reaction 'inserts' an oxygen between the carbonyl carbon and one of the substituents in a ketone. In theory two products can be formed but usually one predominates depending on the migratory aptitude of the substituents attached to the ketone (see Scheme 93).



Scheme 93

An investigation into the migratory aptitude of various substituents has shown that for aryl alkyl ketones the aryl group will migrate in preference to the alkyl group.[51-54] The literature also suggests that the effect of the bromine attached to the alkyl substituent reduces the migratory aptitude of the alkyl substituent.[51, 55, 56] Therefore we expected for our bromoketone that only aryl migration should be observed. We applied several literature methods for the Baeyer-Villiger oxidation of ketones in order to determine which was the optimum (see Scheme 94).



80(*S*) **128**(*S*)

Conditions: MCPBA, Na_2HPO_4, $CHCl_3$, r.t.

or MCPBA, Na_2HPO_4, CH_2ClCH_2Cl, reflux

or $(CF3CO)_2O$, urea.H_2O_2, r.t.

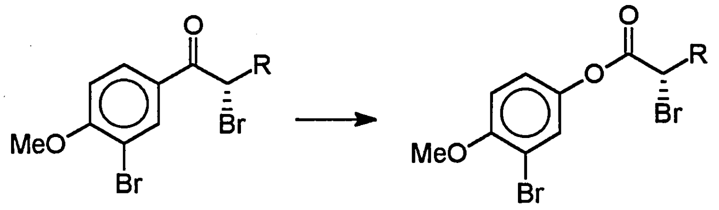
Scheme 94

In the first method the starting aryl bromoketone **80**(*S*) was dissolved in chloroform to which di-sodium hydrogen phosphate and 3-chloroperoxybenzoic acid (MCPBA) were added.[57] The reaction was followed by ^{1}H NMR spectroscopy because analysis by TLC showed that the starting material and product had the same R_f in a wide variety of solvents. When complete conversion had taken place, the product was isolated and purified by flash chromatography to afford an excellent yield (98%) of the pure product as an almost colourless liquid.

The second method was similar to the first except that the solvent was 1,2 dichloroethane and the reaction was heated at reflux.[51] As in the first method the reaction was monitored by ^{1}H NMR spectroscopy until complete conversion of the starting material had taken place at which point the product was isolated in good yield (79%).

In the third and final method the oxidising agent was trifluoroperacetic acid prepared *in situ* by reaction of urea / hydrogen peroxide addition product and trifluoroacetic anhydride.[55] The reaction was monitored by ^{1}H NMR spectroscopy for 4 days with no sign of reaction, and further additions of urea / hydrogen peroxide addition product and trifluoroacetic anhydride failed to initiate a reaction.

It was very clear that the best method for the Baeyer-Villiger oxidation of our (*S*)-α-bromoketone **80(*S*)** was to stir with MCPBA and di-sodium hydrogen phosphate in chloroform at room temperature. We applied these reaction condition to the (*S*)-α-bromoketones **81(*S*)**, **83(*S*)-85(*S*)** (see Scheme 95)



81(*S*)	**129(*S*)** R = CH_2CH_3, 87%
83(*S*)	**130(*S*)** R = $CH(CH_3)_2$, 70%
84(*S*)	**131(*S*)** R = $(CH_2)_3CH_3$, 85%
85(*S*)	**132(*S*)** R = $(CH_2)_7CH_3$, 82%

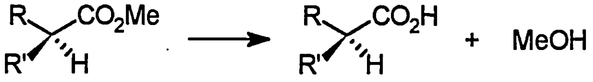
Conditions: MCPBA, Na_2HPO_4, $CHCl_3$, r.t.

Scheme 95

The products were characterised by high resolution mass spectrometry, IR spectroscopy and ^{1}H NMR spectroscopy. The IR spectrum of the bromoketones showed an absorption around 1670 cm^{-1} which became 1760 cm^{-1} in the bromoester. The ^{1}H NMR spectrum of the starting bromoketones **80(*S*)**, **81(*S*)** and **83(*S*)-85(*S*)** had a signal around 4.8-5.2ppm (C<u>H</u>Br) which became 4.25 - 4.40ppm in the ester. This was accompanied by a change in the ^{13}C NMR spectrum in which the signal for the carbonyl carbon changed from about 191ppm to around 168ppm. We attempted to determine the enantiomeric excess of these aryl bromoesters by ^{1}H NMR in the presence of Eu(hfc)$_3$ using the method developed for the aryl bromoketones. As before, our initial work concentrated on resolving the enantiomers of the corresponding racemic aryl bromoesters. When the chiral shift reagent was added several peaks moved, but none were resolved sufficiently to be of any quantitative use. This was a surprise based on our earlier results with the bromoketones; we suspect that the chiral shift reagent binds in a different way to these aryl (*S*)-bromoesters **127(*S*)-132(*S*)** compared to the aryl (*S*)-bromoketones **80(*S*),81(*S*)** and **83(*S*)-85(*S*)**. An alternative method for determining whether the Baeyer-Villiger reaction had racemised the chiral centre was to use either chiral GC or chiral HPLC. The method of choice would be chiral HPLC because there is no restriction regarding molecular mass and volatility as there is in chiral GC. Chiral GC stationary phases in general have a maximum temperature for use of about 200°C after which they degrade. Unfortunately we did not have access to chiral HPLC but we did have chiral GC. The aryl (*S*)-bromoesters **127(*S*)-131(*S*)** were not sufficiently volatile for their enantiomeric excess to be measured directly, so we investigated their conversion (*via* the (*S*)-bromoacids **133(*S*)-137(*S*)**) into the corresponding methyl (*S*)-bromoesters **138(*S*)-142(*S*)** for GC analysis. As an alternative we also investigated the conversion of (*S*)-bromoesters **128(*S*)**, **129(*S*)** and **131(*S*)** into the amides **144(*R*)** and **145(*S*)-148(*S*)** from which we would attempt to determine their enantiomeric excess using ^{1}H NMR spectroscopy. These two approaches are discussed below.

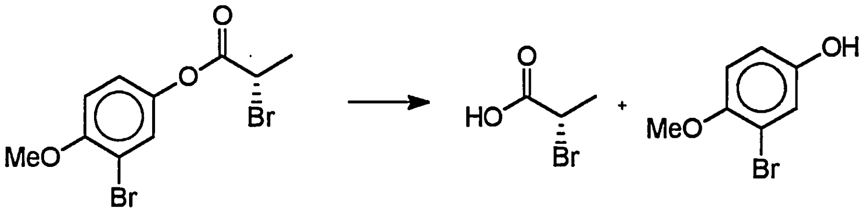
Enantiomerically pure (*S*) 2-bromoacids

An investigation into the hydrolysis of esters with a chiral α-carbon (see Scheme 96) has been reported by Evans *et al* in which various methods are compared; in each of the methods reported a small amount of racemisation is observed.[58-62]



Scheme 96

Evans *et al* suggested that using lithium hydroxide (LiOH) and hydrogen peroxide (H_2O_2) would hydrolyse the ester with the minimum of racemisation (see Scheme 97).

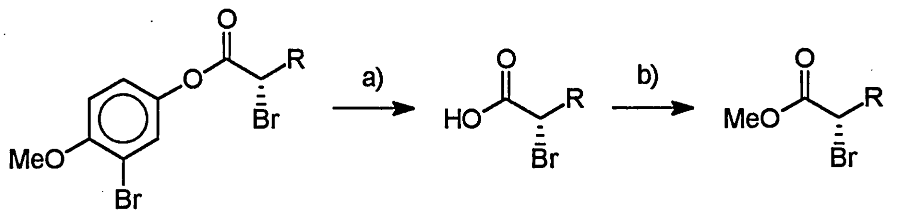


128(*S*) **133(*S*)**

Reagents: lithium hydroxide, H_2O_2

Scheme 97

The method required a solution of the aryl bromoester **128(*S*)** in THF and water to which a mixture of lithium hydroxide and hydrogen peroxide was added. A sample was removed after 5 minutes, acidified and analysed by TLC which showed complete conversion of the starting material. It was observed that as soon as the lithium hydroxide was added a flash of colour was observed in the solution. The crude product was isolated and characterised by ^1H NMR spectroscopy. We discovered that we had prepared the bromoacid **133(*S*)** along with a number of other products but it was clear that the 3-bromo-4-methoxyphenol produced had been oxidised in the reaction. For comparison we repeated the reaction but did not add the hydrogen peroxide. Again we observed that as soon as the lithium hydroxide was added a momentary flash of green colour appeared in the solution. A sample was removed and acidified for TLC analysis within 10 seconds of the addition of the lithium hydroxide and showed no starting material. The ^1H NMR spectrum of the crude material showed only 3-bromo-4-methoxyphenol and the required bromoacid **133(*S*)**. The pure product was isolated by extraction with sodium hydrogen carbonate prior to being converted into the methyl ester **138(*S*)** by reaction with diazomethane and analysed by chiral GC. This procedure was repeated with the aryl bromoesters **129(*S*)-132(*S*)** to give the bromoacids **134(*S*)-137(*S*)** which were converted to the methyl bromoesters **139(*S*)-142(*S*)** (see Scheme 98).



128(*S*) R = CH_3	**133(*S*)** 72% yield	**138**	96% e.e.
129(*S*) R = CH_2CH_3	**134(*S*)** 60%	**139**	94%
130(*S*) R = $CH(CH_3)_2$	**135(*S*)** 63%	**140**	N/A
131(*S*) R = $(CH_2)_3CH_3$	**136(*S*)** 68%	**141**	N/A
132(*S*) R = $(CH_2)_7CH_3$	**137(*S*)** 55%	**142**	88%*

Reagents: a) LiOH b) CH_2N_2

* Analysis by ^{1}H NMR with Eu(hfc)$_3$

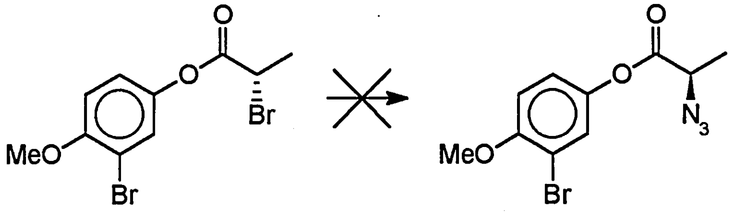
Scheme 98

When the methyl ester **142(*S*)** was analysed by chiral GC we were unable to resolve the enantiomers as we had for the methyl esters **138(*S*)** and **139(*S*)**. This was somewhat of a disappointment given the previous results which were obtained by this method, but we developed a method of analysis using ^{1}H NMR spectroscopy and the chiral shift reagent Eu(hfc)$_3$. The method for resolving each enantiomer of the methyl bromoester **142(*S*)** was similar to that used for the determination of enantiomeric excess of the (*S*)-bromoketones **80(*S*)**, **81(*S*)** and **83(*S*)-85(*S*)**. We first resolved the enantiomers of racemic **142(*S*)** and then applied this knowledge to determine the enantiomeric excess of the 'chiral' material. We had hoped that we could compare the enantiomeric excess results obtained by ^{1}H NMR and chiral GC for **138(*S*)** and **139(*S*)**, but we had insufficient material. The methyl bromoesters **140(*S*)** and **141(*S*)** were expected to be of moderate enantiomeric excess because they originally came from bromoketones which we could not crystallise to enantiomeric purity. Our one and only small scale attempt at preparing the methyl bromoesters **140(*S*)** and **141(*S*)** gave material which was not sufficiently pure for analysis by chiral GC or chiral ^{1}H NMR spectroscopy. As we had insufficient time and materials the series of reactions to prepare **140(*S*)** and **141(*S*)** was not repeated.

From the results it is clear that during the Baeyer-Villiger reaction and subsequent hydrolysis the chiral centre was not significantly racemised.

Attempted preparation of chiral azido esters

We wanted to prepare chiral azido esters by displacing the bromine with azide and inverting the chiral centre (see Scheme 99). We would then go on to convert this azido ester into an amino acid by reduction and hydrolysis.



128(*S*) **143(*S*)**

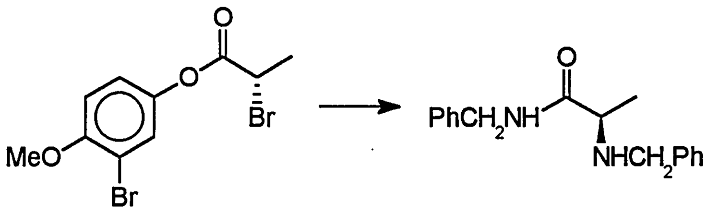
Conditions: NaN_3, DMF, 50 °C

Scheme 99

Our only attempt at preparing the azido ester **143(*S*)** from the bromoester **128(*S*)** used sodium azide stirred / dissolved in dry DMF and heated to 50 °C for 40 hours. Analysis by TLC showed the complete conversion of starting material, but ^{1}H NMR spectroscopy of the crude product indicated that we had obtained a mixture of products in which we had lost the aryl functionality rather than the bromine. We were not that surprised at this result as we had noted the relative ease with which we had base hydrolysed these bromoesters, and this line of research was not pursued any further.

Enantiomerically pure 2(*S*)-bromoamides

Reaction of the aryl bromoesters **128(*S*)**, **129(*S*)** and **131(*S*)** with a primary amine would be expected to give an amide. The exact product depends on the amount of primary amine used e.g. with two equivalents the bromine and aryloxy groups might both be displaced to give an amino amide (see Scheme 100).



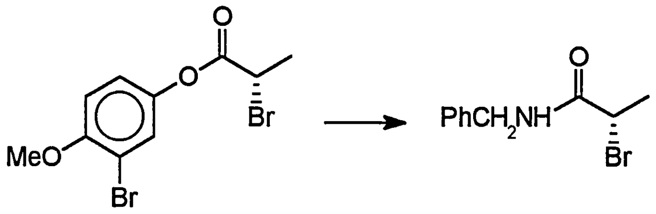
128(*S*) **144(*R*)**

Reagents: benzylamine, K_2CO_3, toluene

Scheme 100

The bromoester **128(*S*)** was dissolved in dry toluene to which anhydrous potassium carbonate and 2.2 equivalents of benzylamine were added. The mixture was heated at reflux for 26 hours before TLC indicated that no starting material remained. The crude product was isolated as a white crystalline solid whose ^{1}H NMR spectrum showed overlapping signals for the two sets of benzyl and aromatic protons, which we anticipated would impede any attempt to determine the enantiomeric excess on this compound.

To overcome the problem of the overlapping benzyl signals we prepared the *N*-benzyl bromoamide **145(*S*)** using only one equivalent of benzylamine. It might be possible with one equivalent, to get a mixture of products from displacement of the aryloxy or the bromine, but from the work in the preparation of the bromoacids we had shown that the aryloxy is a very good leaving group and hence we expected would be displaced in preference to the bromine (see Scheme 101).

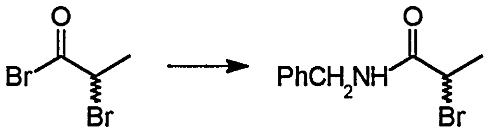


128(*S*) **145(*S*)**

Reagents: benzylamine, K_2CO_3, THF

Scheme 101

The product from this reaction was isolated as a crystalline solid in 73% yield. To help in developing a method for determining the enantiomeric excess of our 'chiral' material we prepared the corresponding racemic compound **145(*S*)** by reaction of benzylamine with racemic 2-bromopropionyl bromide (see Scheme 102).

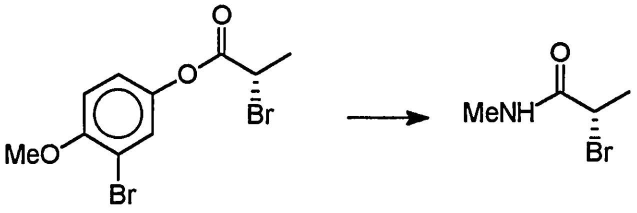


145

Reagents: benzylamine, K_2CO_3, THF

Scheme 102

When this racemic material was analysed by ^{1}H NMR spectroscopy in the presence of chiral shift reagent $Eu(hfc)_3$ we found that we could not resolve the signals for of the enantiomers. Clearly this meant that we could not determine the enantiomeric excess of the enantiomerically enriched material. We did discover that the most promising signals which were moved by the shift reagent belonged to the benzyl protons, suggesting that a simple *N*-methyl amide might be a better compound from which to determine the enantiomeric excess (see Scheme 103).

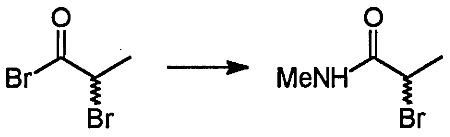


128(*S*) **146(*S*)**

Reagents: $MeNH_2$, K_2CO_3, THF

Scheme 103

The aryl bromoester **128(*S*)** was dissolved in THF prior to the addition of 1.1 equivalents of 40% w/w aqueous solution methylamine. When TLC analysis showed the complete conversion of starting material the crude product was isolated as a crystalline solid. To help in developing a method for determining the enantiomeric excess of our 'chiral' materials we prepared the corresponding racemic compound **146** from racemic 2-bromopropionyl bromide and 40% w/w aqueous methylamine (see Scheme 104).

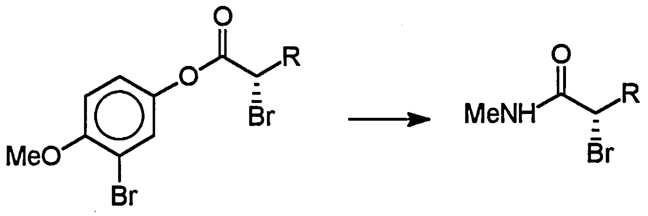


146

Reagents: $MeNH_2$, K_2CO_3, THF

Scheme 104

This enabled us to develop a method to determine the enantiomeric excess by ^{1}H NMR in the presence of Eu(hfc)$_3$. Once we had developed a method for the preparation and determination of enantiomeric excess of the *N*-methyl bromoamide **146(*S*)** from the aryl bromoester **128(*S*)** it was applied to the preparation of the bromoamides **147(*S*)** and **148(*S*)** from the aryl bromoesters **129(*S*)** and **131(*S*)** respectively (see Scheme 105).

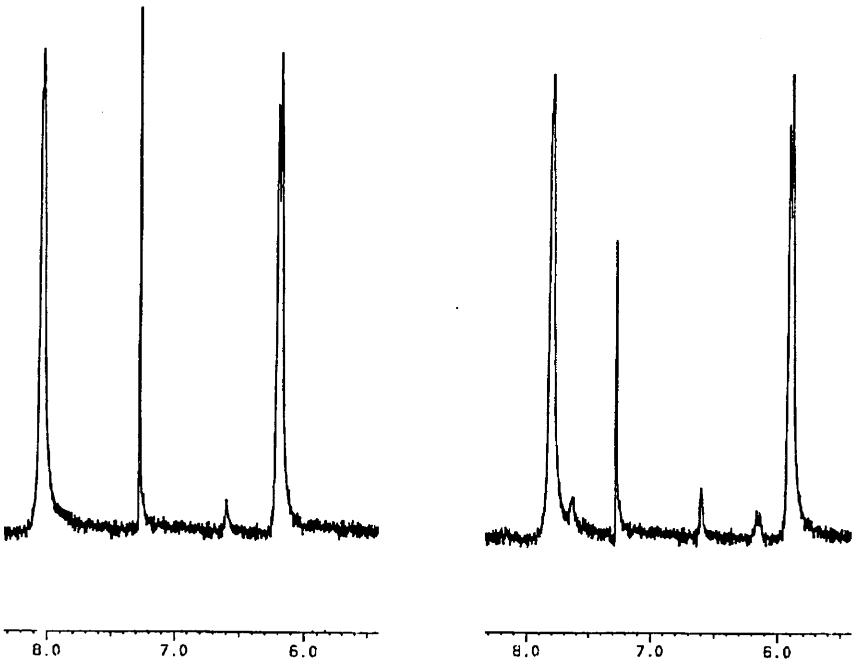


128(*S*) R = CH_3	**146(*S*)** 66% yield, >95% e.e.
129(*S*) R = CH_2CH_3	**147(*S*)** 58%, >95% e.e.
131(*S*) R = $(CH_2)_{36}CH_3$	**148(*S*)** 56%. 60% e.e.

Reagents: $MeNH_2$, K_2CO_3, THF

Scheme 105

As anticipated the amount of chiral shift reagent used for determination of the enantiomeric excess of these bromoamides was less than that used for the bromoketones because the shift reagent interacts more strongly with the nitrogen than with the carbonyl oxygen. The proton ($C\underline{H}Br$) was shifted the most but not resolved while the *N*-methyl protons could be moved to an empty region of the spectrum and resolved to the baseline. This looked very promising for the determination of enantiomeric excess, but these *N*-methyl signals were broad at the baseline. This made it difficult to determine the exact amount of the minor isomer accurately in the enantiomerically enriched material. Therefore the maximum enantiomeric excess that we can reliably quote is >95% (see Figure 19).



a) b)

a) Bromoamide with chiral shift reagent.

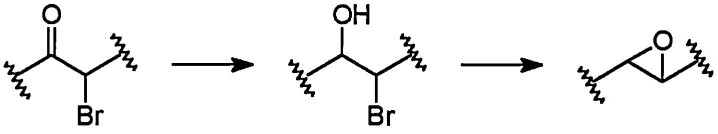
b) Bromoamide with chiral shift reagent and spiked.

Figure 19

The results from ^{1}H NMR spectroscopy and chiral GC analysis compare very favourably for the methyl esters **138**(*S*), **139**(*S*) and *N*-methyl amides **146**(*S*), **147**(*S*) derived from the aryl bromoesters **128**(*S*) and **129**(*S*).

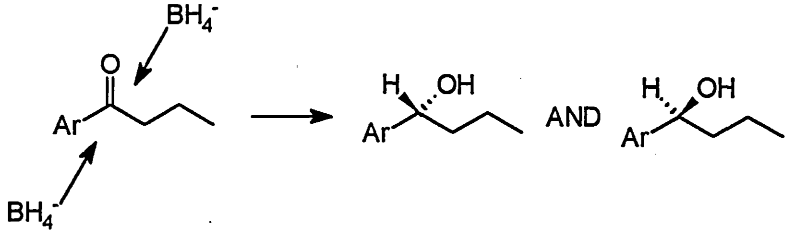
Enantiomerically pure bromohydrins

Over the last decade much work has gone in to the preparation of enantiomerically pure epoxides because they are useful precursors to a wide variety of compounds. With this in mind we looked at the preparation of bromohydrins from our enantiomerically pure bromoketones. Conversion of bromohydrins into epoxides has been well documented in the literature (see Scheme 106).[63-66]



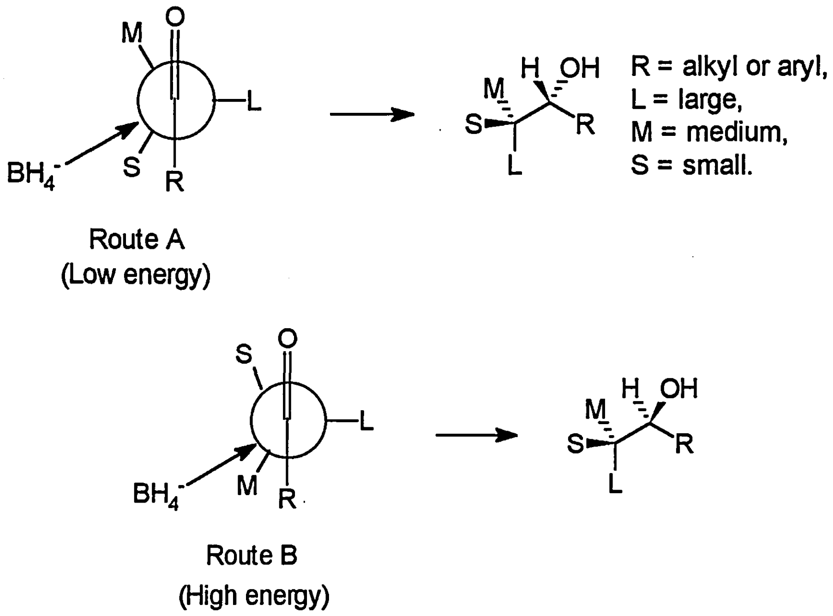
Scheme 106

Under 'normal' conditions reduction of ketones gives rise to racemic products because the reducing agent can attack from either face of the carbonyl (see Scheme 107).



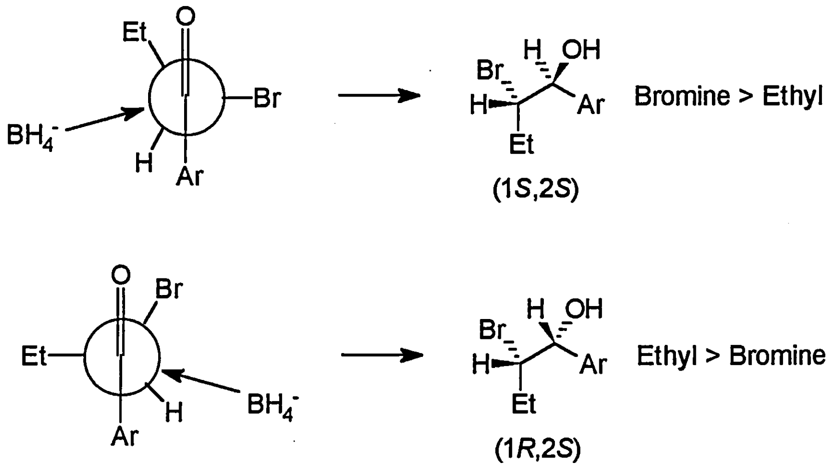
Scheme 107

A considerable amount of research has been done in order to predict the stereochemical outcome of the reduction of α-substituted ketones of known conformation. The most widely accepted theory is the Felkin-Anh model in which the relative size of the substituents governs the stereochemical outcome (see Scheme 108) of the reaction unless other factors such as chelation take place.[67] Route A (see Scheme 108) minimises the steric interaction of the incoming borohydride nucleophile, while route B is of higher energy due to the disfavoured interaction between the borohydride and the group M. Route B gives rise to the opposite diastereoisomer compared to route A and therefore the difference in the energy required for route A compared to route B will be reflected in the diastereoselectivity of the reduction.



Scheme 108

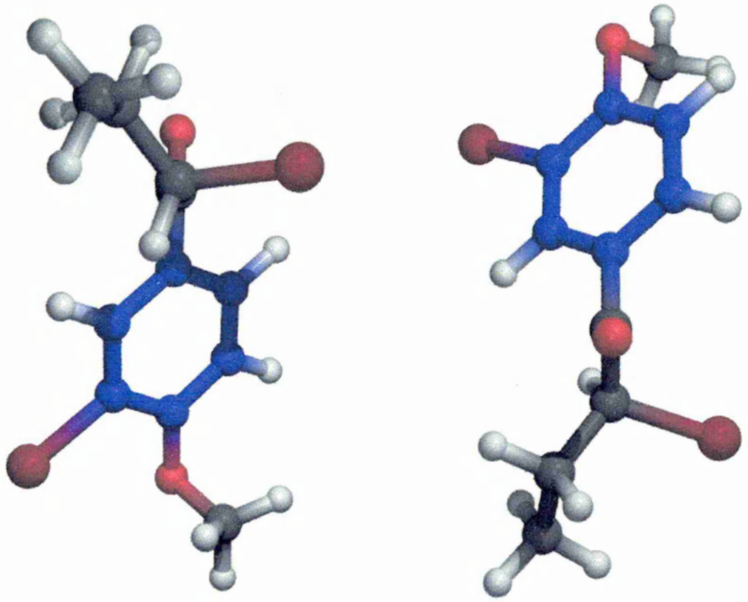
In order to use the model to predict the stereochemical outcome when applied to our bromoketone **81**(*S*) we need to know whether the bromine or the ethyl group is the larger. The Van der Waals radius of bromine is 195 pm, while the Van der Waals radius of a methyl group is 200 pm. We felt that it was reasonable to approximate the ethyl group to a methyl when it was viewed from one end. The difference in size between the bromine and the 'ethyl' group is relatively small and therefore we would predict poor stereoselectivity. Assuming that the reaction only took place by the low energy route (route A) the stereochemical outcome is governed by the relative sizes of the substituents (see Scheme 108). If bromine was larger than the ethyl group we would get product with the 1*S*,2*S* relative configuration; if the ethyl group was larger than bromine we would get the 1*R*,2*S* product (see Scheme 109).



Scheme 109

We had the opportunity to do some simple molecular modelling in order to predict whether the bromine or the ethyl group is the largest substituent and therefore be able to predict the stereochemical outcome of the reduction of the bromoketone **81**(*S*). We used the PCModel software package to model the bromoketone **81**(*S*) using the MM2 force field.[68]

Viewing the minimised structure along the C2-C1 bond (see Figure 20a) and from above (see Figure 19b) it is clear that the carbon-bromine bond is perpendicular to the carbonyl bond. Comparing Scheme 108 with Figure 20a it is clear that this conformation corresponds to the one described by the Felkin-Anh model which has the bromine as the largest substituent and the ethyl group and the hydrogen take up the medium and small substituent positions respectively. In this conformation the Felkin-Anh model predicts that the reduction using sodium borohydride would give a product with a (1*S*,2*S*) configuration.



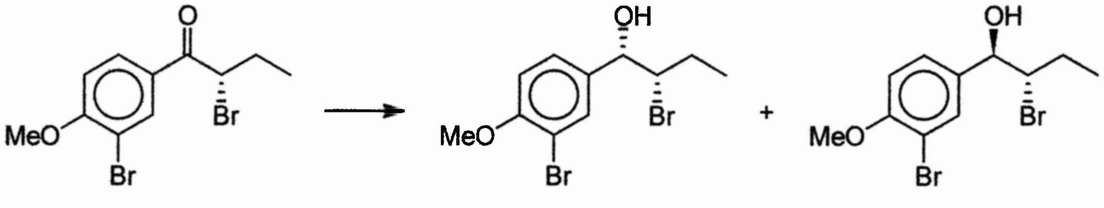
a) b)

a) Along C2-C1 bond.

b) From above.

Figure 20

Our initial method was to dissolve the bromoketone **81**(*S*) in bench methanol prior to the addition of sodium borohydride. Analysis by TLC of an acidified sample after 5 minutes showed complete disappearance of the starting material **81**(*S*) with only one product being observed. The crude product was isolated and purified by flash chromatography to give the pure product as a colourless liquid in 68% yield (see Scheme 110).

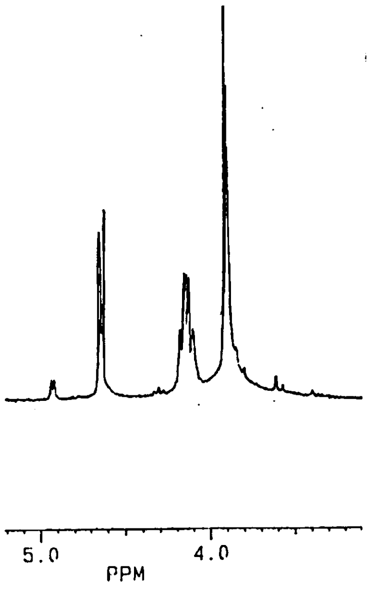


81(*S*) **149**(1*S*,2*S*) **14**(1*R*,2*S*)

Conditions: NaBH$_4$, MeOH, r.t.

Scheme 110

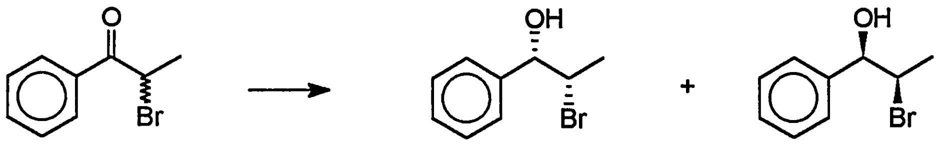
Analysis by ^{1}H NMR showed that there was a mixture of diastereoisomers as indicated by a large doublet at 4.65ppm (7.1 Hz) which was 13 times larger by integration than the doublet at 5.00ppm (4.1Hz). We knew from the literature that microbial reduction of 2-chloropropiophenone led to the preparation and characterisation of all the diastereoisomers of 2-chloro-1-phenyl-1-propanol by ^{1}H NMR spectroscopy.[63] Using this information we were able to ascribe which diastereoisomer we had prepared from our (*S*)-bromoketone **81(*S*)**. The literature states that in the (1*R*,2*S*) chlorohydrin the doublet belonging to C<u>H</u>(OH) is at 4.94ppm with a coupling constant of 3.6Hz, while the (1*R*,2*R*) chlorohydrin, which is equivalent to the (1*S*,2*S*) chlorohydrin, has a doublet belonging to C<u>H</u>(OH) at 4.60ppm with a coupling constant of 7Hz. Therefore from this information we can determine that the major product from the reduction of our (*S*)-bromoketone is the (1*S*,2*S*) bromohydrin (see Figure 21).



Reduction at room temperature

Figure 21

It has also been reported by Shibata *et al* that α-bromoketones can be reduced under 'ionic conditions' by di-*N*-butyl tin hydride in the presence of 4-dinitrobenzene.[69] In this method the di-*N*-butyl tin hydride acts as a hydride donor in a similar way to borohydride. They applied this method of reduction to the racemic bromoketone **89** and the product they obtained was exclusively the *threo* bromohydrin (see Scheme 111).



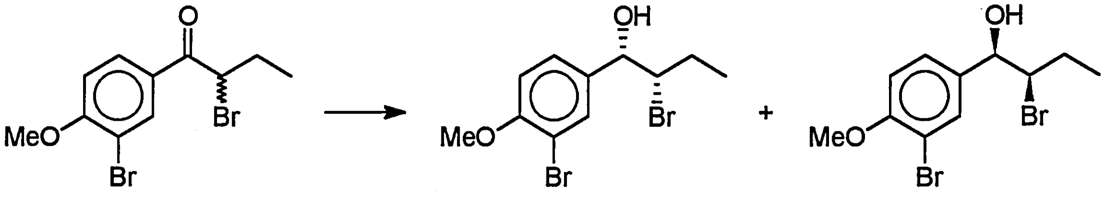
89

Reagents: $^{n}BuSnH_2$, 4-dinitrobenzene

Scheme 111

The published results enabled use to deduce the stereochemistry of our major product and also enabled us to determine that in the reduction reaction the bromine has a larger size relative to the ethyl group.[69] This conclusion supports the results obtained from our molecular modelling, but does seem to contradict the expected result based on the Van der Waals radii. Our simple use of Van der Waals radii was not a sufficiently accurate model to allow us to determine the stereochemical outcome of the reduction.

Better stereoselectivity can often be achieved by using a lower reaction temperature and indeed when the reaction was repeated at a temperature of -78 °C only one diastereoisomer was observed by ^1H NMR spectroscopy (the minor isomer with the signal at 5.00ppm was not observed). We hoped that in the reduction of the carbonyl group the CHBr stereocentre had been unchanged, but there was a possibility that the borohydride, due to its basic nature, had partially racemised the CHBr stereocentre prior to reduction of the carbonyl. In order to investigate this possibility the racemic bromoketone **81** was reduced at -78 °C to give a pair of enantiomeric bromohydrins **149**(1*S*,2*S*) and **149**(1*R*,2*R*) (see Scheme 112).

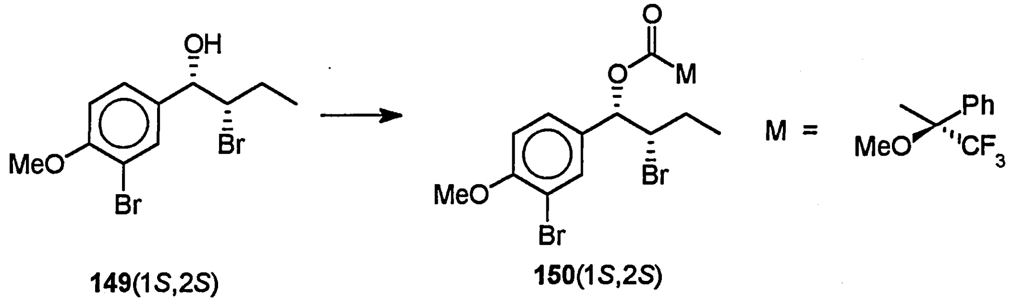


81 **149**(1*S*,2*S*) **149**(1*R*,2*R*)

Conditions: $NaBH_4$, MeOH, -78°C

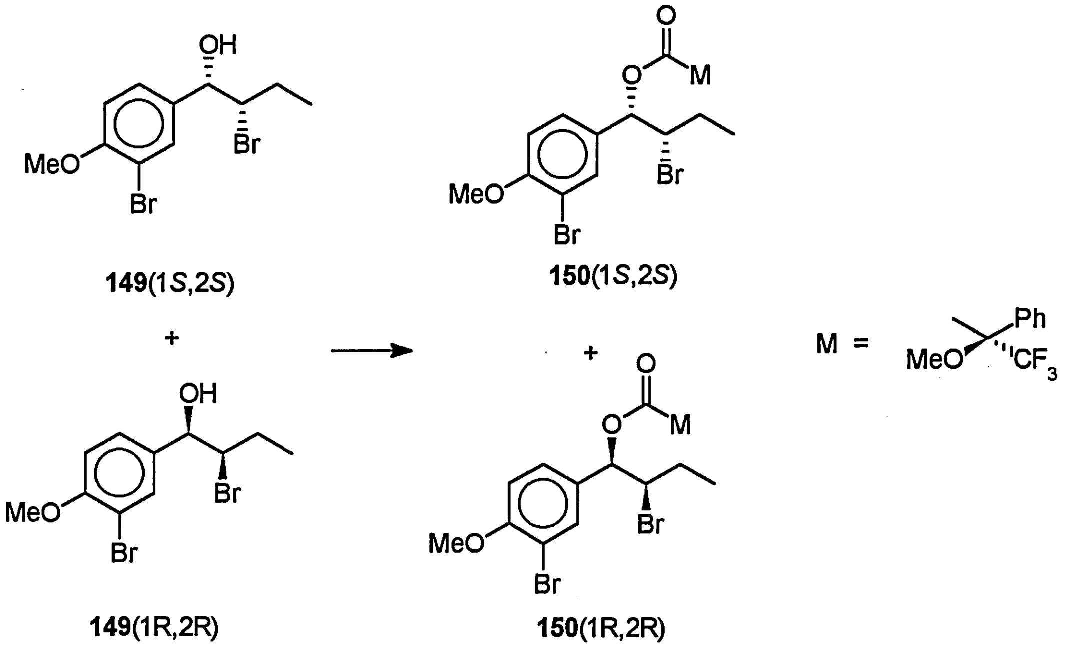
Scheme 112

When the pair of enantiomers **149**(1*S*,2*S*) and **149**(1*R*,2*R*) were analysed by ^1H NMR spectroscopy in the presence of chiral shift reagent $Eu(hfc)_3$ we were unable to sufficiently resolve any signals to allow integration. In order to solve this problem we prepared the Mosher's esters of the our 'chiral' bromohydrin **149**(1*S*,2*S*) (see Scheme 113) and the diastereomerically pure bromohydrins **149**(1*S*,2*S*) and **149**(1*R*,2*R*) (see Scheme 114).[70] This would convert enantiomers into diastereoisomers and so hopefully enable us to determine enantiomeric purity directly by ^{1}H NMR spectroscopy.



Reagents: [(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid] (*R*-Mosher's acid), dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP)

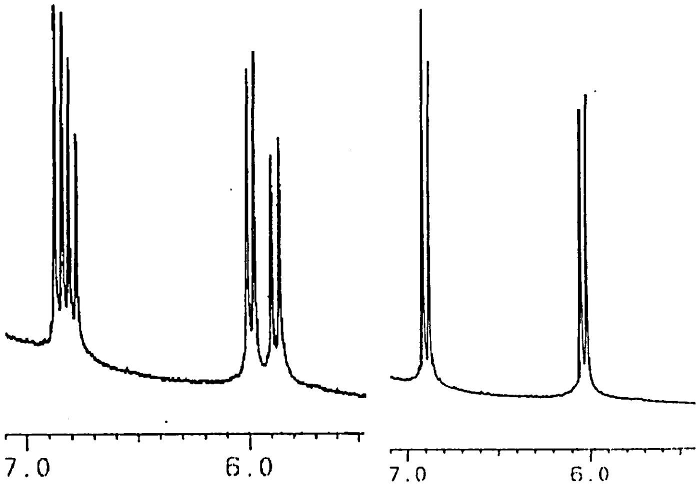
Scheme 113



Reagents: (*R*)-Mosher's acid, DCC and DMAP

Scheme 114

The reaction was monitored by TLC until no starting material was observed. It was important that complete conversion took place because it was possible that one enantiomer would react quicker than the other. The crude product was isolated as a colourless liquid and purified by flash chromatography. Comparison of the ^1H NMR spectra showed a pair of doublets at 5.90ppm and 6.00ppm in the material containing both **150**(1*S*,2*S*) and **150**(1*R*,2*R*), while in the material containing only **150**(1*S*,2*S*) there was only the signal at 6.00ppm. Another part of the spectrum where a good comparison could be made was for the hydrogen in the 5' position on the aromatic ring. In the material containing both **150**(1*S*,2*S*) and **150**(1*R*,2*R*) two doublets were observed at 6.80ppm and 6.85ppm, while in the material containing only **152**(1*S*,2*S*) only the signal at 6.85ppm was observed (see Figure 22).



a) b)

a) Mosher's esters **150**(1*S*, 2*S*) + **150**(1*R*, 2*R*).

b) Mosher's ester **150**(1*S*, 2*S*).

Figure 22

Vertical expansion of the baseline showed the minor diastereoisomer **150**(1*R*,2*R*) to be significantly less than 1% of the size of the major diastereoisomer **150**(1*S*,2*S*). Therefore we conclude that the reduction of the enantiomerically pure bromoketone **81**(*S*) at low temperature using sodium borohydride produces a single enantiomerically pure bromohydrin.

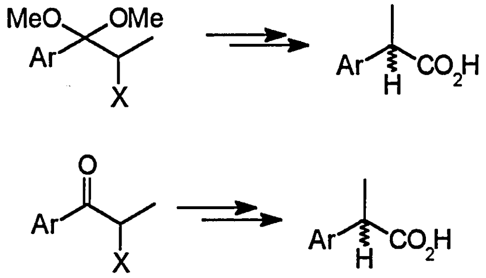
These results show that an enantiomerically pure bromoketone can be reduced to give a diastereomerically pure bromohydrin with the same stereochemistry as predicted by the Felkin-Anh model. We have shown that the borohydride does not racemise the CHBr stereocentre and that the product obtained is a single diastereoisomer. Clearly further work has to be done in order confirm that this high degree of diastereoselectivity can be achieved with other bromoketones rather than just the one described here.

Section 3

Strategy

Earlier sections describe how we prepared various bromoacetals, improved their diastereoisomeric excess and used them to prepared enantiomerically pure compounds *via* bromoketones. This section describes how we used the acetal functional group as a tool in the preparation of α-arylcarboxylic acids and their derivatives. Many of the compounds contain the *p*-toluenesulphonamide functional group because it was hoped that the products containing this substituent would be crystalline and hopefully enable recrystallisation to a higher enantiomeric excess.

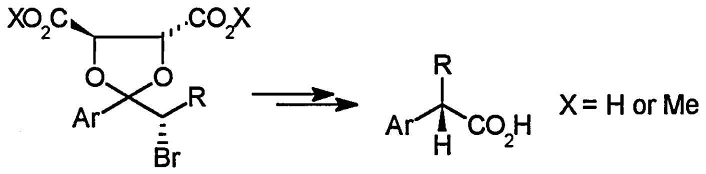
In the literature the rearrangement of aryl bromoacetals to arylcarboxylic acids has been well documented along with rearrangements of α-bromoketones, α-hydroxyketones and aryl alkyl ketones (see Scheme 114 and the introduction section).[7, 14, 16, 21-29]



X = Br, Cl, OMs, OTos, H

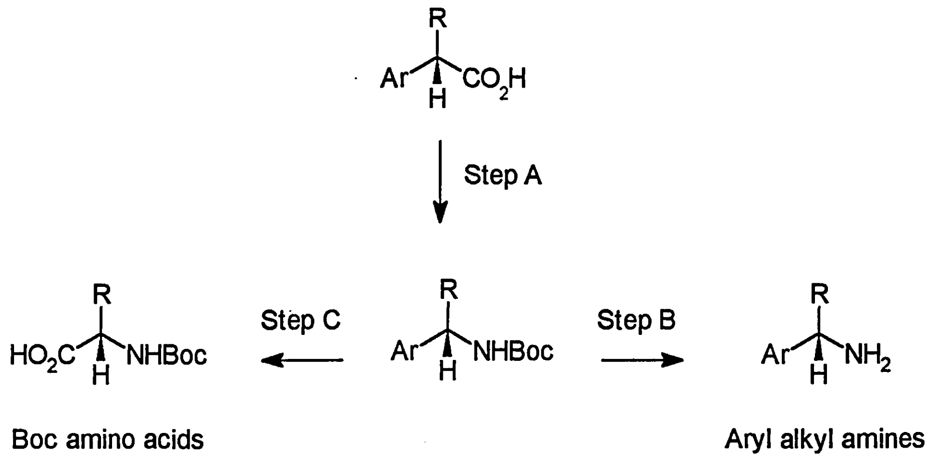
Scheme 115

A key feature of the rearrangement of tartaric acid derived bromoacetals is that it is possible to do the reaction under stereochemical control (see Scheme 116).[7, 29]



Scheme 116

This reaction has commercial application in the preparation of Naproxen **11**(*S*). We wanted to use the chemistry developed for the synthesis of Naproxen **11**(*S*) as a basis for the preparation of enantiomerically pure aryl alkyl amines and Boc protected amino acids (see Scheme 117).



Scheme 117

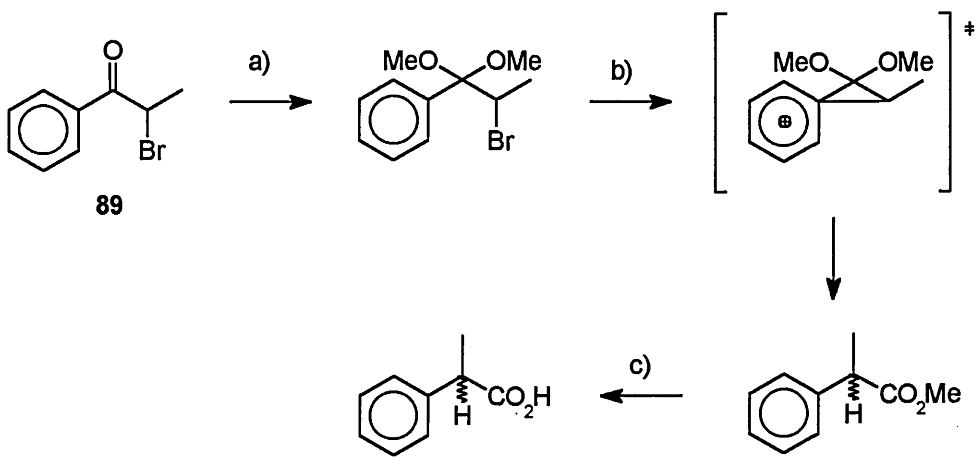
We planned to convert α-arylcarboxylic acids by the Curtius degradation into Boc protected amines (Step A),[49, 71, 75] which could then be deprotected (Step B) by treatment with trifluoroacetic acid.[60, 61, 62] Alternatively (after step A) we intended to oxidise the aryl component into a carboxylic acid (Step C) using a ruthenium catalyst.[45, 46, 47, 72, 73]

Rearrangement of bromoacetals

As briefly discussed in the introduction, the rearrangement of substituted acetals has been of synthetic use in the preparation of Ibuprofen and Naproxen **11**(*S*). The following pages will describe how we made use of this rearrangement reaction to prepare a range of racemic and enantiomerically enriched 2-arylcarboxylic acids. We knew from experience that in the characterisation of 'chiral' compounds it is often useful to have the corresponding racemic compound, hence various methods were investigated for preparing these compounds.

Racemic 2-arylcarboxylic acids

The rearrangement of 2-bromopropiophenone **89** with anhydrous zinc bromide (see Scheme 118) has been well documented in the literature.[22]



89

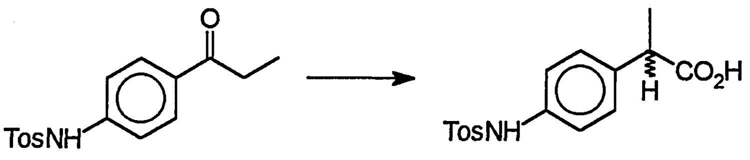
151

Reagents: a) MeOH, $ZnBr_2$, b) $ZnBr_2$, c) H_3O^+

Scheme 118

We repeated the reaction at reflux under a nitrogen atmosphere using 2-bromopropiophenone **89**, anhydrous zinc bromide and dry methanol in order to prepare the racemic acid **151**. The rearrangement reaction is believed to proceed via the dimethyl acetal intermediate which undergoes aryl migration.[22] A side product from this reaction is 2-methoxypropiophenone which occurs when the methoxyl migrates in preference to the phenyl group. The crude carboxylic acid was isolated by extraction prior to treatment with diazomethane which gave the methyl ester in 39% overall yield. Analysis by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ allowed us to determine the optimum amount of shift reagent required for the future determination of enantiomeric excess of enantiomerically enriched material.

An alternative to rearrangement of aryl bromoketones with zinc bromide is to rearrange aryl ketones with iodobenzene diacetate (see Scheme 119).[74]

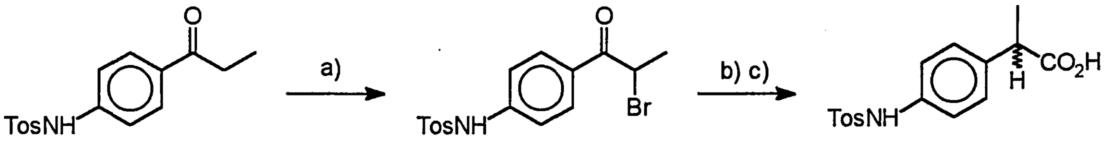


59 **152**

Reagents: $PhI(OAc)_2$, trimethyl orthoformate, conc. H_2SO_4

Scheme 119

We chose this method for the preparation of **152** because we had a large amount of the starting material **59**; only one step was required to prepare **152** rather than needing to prepare the bromoketone **88** from **59** using copper (II) bromide followed by rearrangement of **88** with $ZnBr_2$ (see Scheme 119). This one-step method gave the **152** in less time and in better yield than that which would have been obtained using the method in Scheme 120.



59 **88** **152**

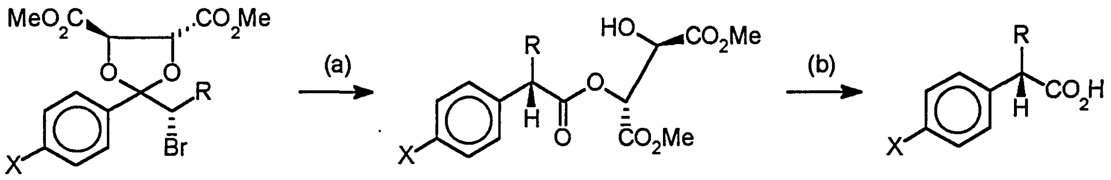
Reagents: a) $CuBr_2$, EtOAc, toluene b) MeOH, $ZnBr_2$ c) H_3O^+

Scheme 120

Enantiomerically enriched 2-arylcarboxylic acids /esters

Numerous methods for the rearrangements of racemic α-substituted ketones and acetals have been reported (see the introduction section),[14, 16, 21-24, 27, 28] but few have been reported as being successfully applied to the asymmetric synthesis of 2-arylcarboxylic acids. There are however a few notable exceptions to this which use silver salts to rearrange dimethyl tartrate bromoacetal diesters (see Scheme 121),[29] or which use refluxing phosphate buffer on tartaric acid bromoacetals (see Scheme 124).[7]

Method 1 (using $AgBF_4$)



108	X= H,	R = CH_3	**151(*S*)** 71%, 78% e.e.
117	X= TosNH,	R = CH_3	**152(*S*)** 46%, N/A*
118	X= TosNH,	R = CH_2CH_3	**153(*S*)** 34%, N/A*

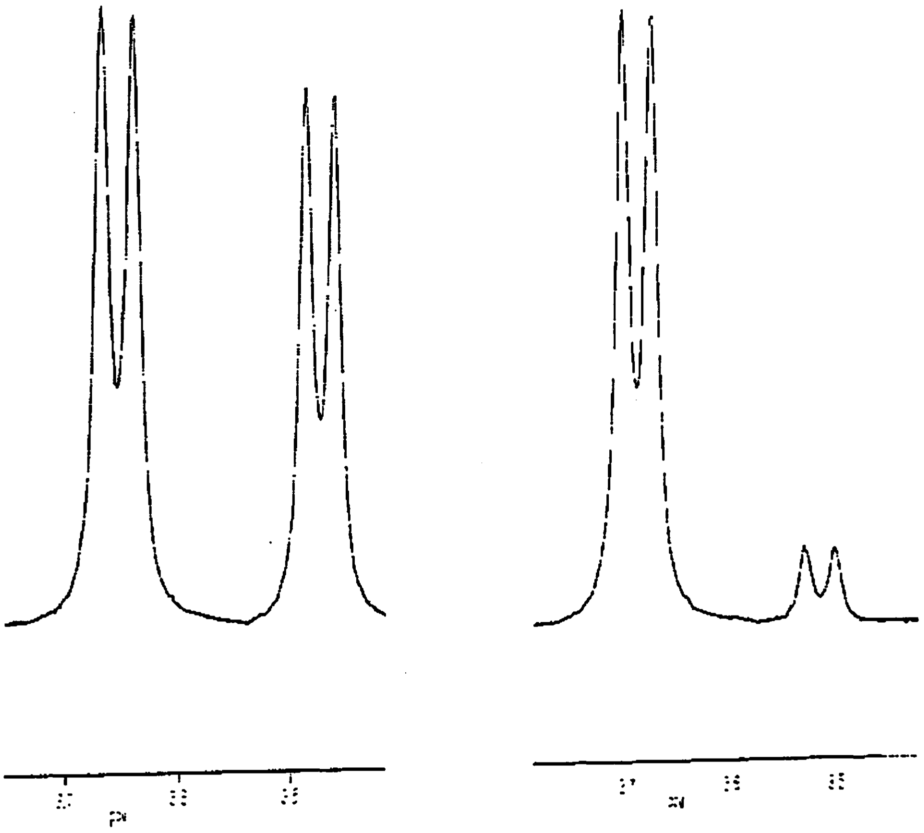
Reagents: (a) $AgBF_4$, 1,2-dichloroethane, H_2O (b) H_3O^+

* Product not reacted with diazomethane.

Scheme 121

The dimethyl tartrate bromoacetals **108**, **117** and **118** were treated with silver tetrafluoroborate, until TLC analysis showed the complete conversion of starting material, the crude carboxylic acid being isolated after removal of the dimethyl tartrate functional group under acid conditions (see Scheme 121). Treatment with diazomethane and purification by flash chromatography was performed prior to the determination of enantiomeric excess (e.e.) by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.

The ^{1}H NMR spectrum of the methyl ester of **151**(*S*) in the presence of chiral shift reagent resolved the aliphatic methyl group of each enantiomer as a doublet (see Figure 23).



a)

b)

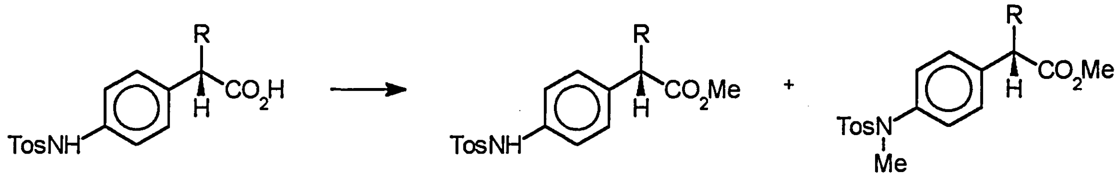
a) Racemic methyl 2-phenylpropanoate.

b) Enantiomerically enriched methyl 2-phenylpropanoate.

Figure 23

The enantiomeric excess of the methyl ester of **151**(*S*) was determined at 78% which was essentially identical with the diastereoisomeric excess of the starting bromoacetal obtained from a bromination using DCM as solvent. This confirms the literature observation in which the enantiomeric excess of the product is essentially the same as the diastereoisomeric excess of the bromoacetal.[29]

During the preparation of the methyl ester of **152**(*S*), so that its enantiomeric excess could be determined by ^{1}H NMR spectroscopy, we noticed that we had obtained two products from the reaction with excess diazomethane. After purification and analysis by ^1H NMR spectroscopy we were able to determine that one of the compounds was the required product **154(*S*)**, while the other was the analogous *N*-methyl ester **155(*S*)** (see Scheme 122).



152(*S*) **154(*S*)** **155(*S*)**

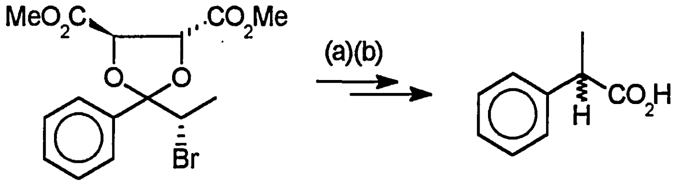
Reagent: CH_2N_2

Scheme 122

Preliminary chiral shift reagent studies on the enantiomerically enriched methyl ester **154(*S*)** indicated that the chiral shift reagent interacted with the sulphonamide functionality rather than with the methyl ester group. This could be clearly observed by the shifting of the aromatic protons associated with the *p*-toluenesulphonamide group whilst the aliphatic and aromatic protons next to the chiral centre remained in essentially the same place. Clearly the lone pairs on the nitrogen or oxygen of the sulphonamide are more accessible than those of the ester functionality.

<u>*Method 2*</u> (using $ZnBr_2$)

The use of $ZnBr_2$ has been reported in the literature to promote the rearrangement of substituted propiophenone bromoacetals to 2-arylpropanoic acids and so we hoped that anhydrous zinc bromide could be used as a cheaper alternative to silver tetrafluoroborate (see Scheme 123).[22]



108 **151**

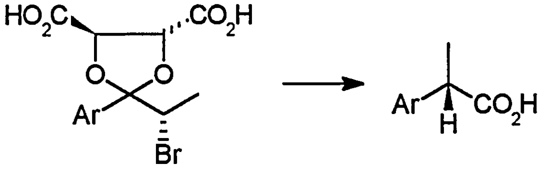
Conditions: (a) Δ, toluene, $ZnBr_2$, N_2 (b) H_3O^+

Scheme 123

The enantiomeric excess of the material obtained by this method as determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ was found to be zero. It is reasonable to assume that the mechanism for the rearrangement in the zinc method is different to the mechanism using silver tetrafluoroborate. This was a disappointment because this could have been an economical method for the preparation of chiral 2-arylcarboxylic acids.

Method 3 (rearrangement of bromoacetal diacids)

The literature relating to the asymmetric synthesis of Naproxen **11**(*S*) describes a rearrangement reaction where a tartaric acid bromoacetal was rearranged instead of the more usual methyl ester. The crucial aspect of this reaction was that the stereochemistry was controlled without the need for expensive silver catalysts (see Scheme 124).[7]

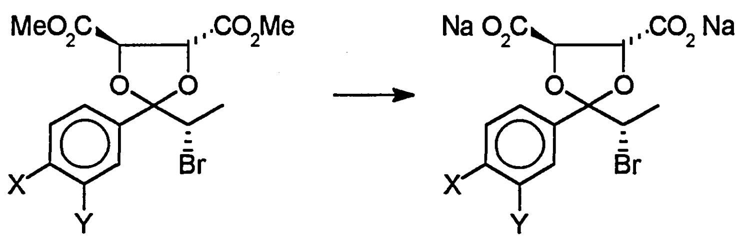


Conditions: Δ, pH 5.2 phosphate buffer

Scheme 124

The obvious extension for our work was to take the dimethyl tartrate bromoacetals **108**, **112** and **117** and convert them to the corresponding diacids **159-161**. We knew from experience that these bromoacetal diesters were sensitive to aqueous acidic conditions which would hydrolyse the acetal rather than the esters, so base hydrolysis was used instead. This gave rise to the possibility that the di-sodium salts **156-158** of these bromoacetals could be isolated as a crystalline solids and possibly recrystallised to a better diastereoisomeric excess prior to conversion to the diacids **159-161**.

The starting dimethyl tartrate bromoacetals **108**, **112** and **117** were dissolved in dry methanol prior to the addition of solid sodium hydroxide and two equivalents of water (see Scheme 125).



108	X= H, Y = H 78% d.e.	**156**	95% yield, 78% d.e.
112	X= MeO, Y = Br 71% d.e.	**157**	89%, 71% d.e.
117	X= TosNH, Y = H 82% d.e.	**158**	78%, N/A

Reagents: NaOH, H_2O

Scheme 125

The reaction was stirred for 4 days at room temperature prior to removal of the solvent under reduced pressure. Analysis of the ongoing reaction was problematic because the product and the mono sodium salt mono ester intermediate were difficult to differentiate by TLC, therefore a small sample was removed and analysed by ^{1}H NMR spectroscopy. The reaction was stirred until ^{1}H NMR showed the complete disappearance of the methyl ester signals around 4δ. The crude product isolated at the end of the reaction was an off-white hygroscopic crystalline solid. We attempted to recrystallise the di-sodium salts of **156** to a better diastereoisomeric excess, but preliminary results showed no improvement and so we did not pursue this further. The diastereoisomeric excess of the di-sodium salts **156** and **157** was determined by comparing the relative integrations of the 1,3-dioxolane protons (see Figure 24) but for **158** the ^{1}H NMR spectrum was inconclusive. The results for **156** and **157** indicate that the diastereoisomeric excess was unchanged in the reaction.

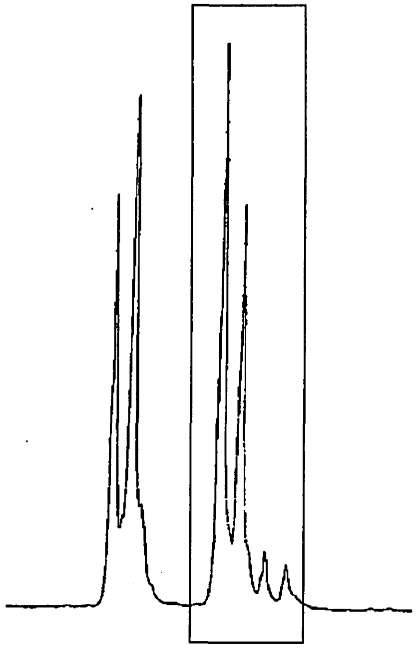
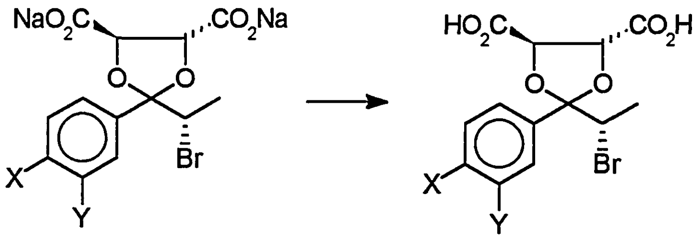


Figure 24

Conversion of these di-sodium salts into the corresponding bromoacetal diacids is in principle just a case of adding acid (see Scheme 126).



156	X= H, Y = H	**159**	74% yield
157	X= MeO, Y = Br	**160**	84%
158	X= TosNH, Y = H	**161**	83%

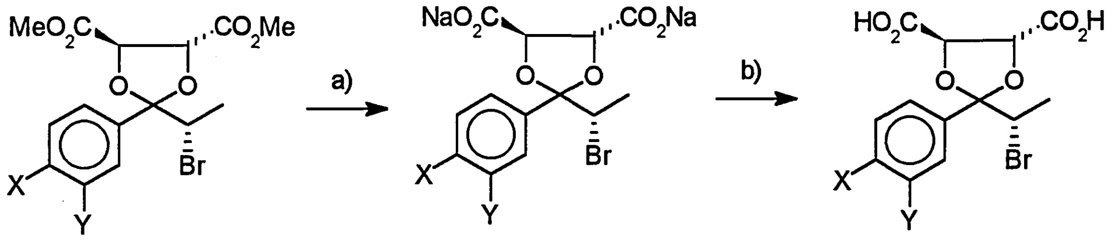
Reagent: H_3O^+

Scheme 126

Giordano *et al* suggested that the addition of dilute hydrochloric acid until pH 2 would not hydrolyse the acetal;[7] we thought this was very surprising because from experience we knew that the dimethyl tartrate bromoacetals were very susceptible to aqueous acid. We found, to our surprise, that the bromoacetal diacids **159-161** were indeed stable to aqueous acid at pH 2 for a short period of time. Thus the tartrate bromoacetal di-sodium salts **156-158** were dissolved in water and the pH was adjusted with 2N HCl until pH 2.

Immediate extraction gave the crude product in good yield.

Once we had shown that the conversion of these bromoacetal di-sodium salts **156-158** to the corresponding di-acids **159-161** was possible it was obvious to attempt the conversion of the bromoacetal di-esters **108**, **112** and **117** to the di-acids **159-161** without isolation of the di-sodium salts (see Scheme 127).



112 X= MeO, Y = Br **160** 78%

117 X= TosNH, Y = H **161** 44%

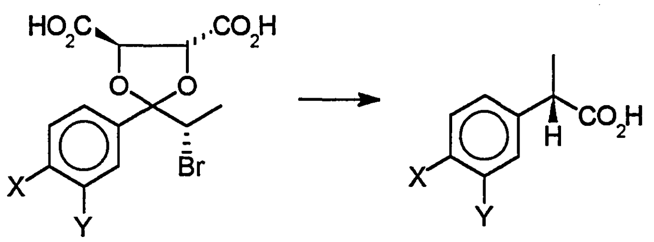
Reagents: a) NaOH, H_2O b) H_3O^+

Scheme 127

This direct method of preparation was essentially to hydrolyse the two ester groups using sodium hydroxide, acidify using 2N hydrochloric acid and extract the product.

The reactions in Scheme 126 have only been done once and the yields are unoptimised.

The bromoacetal diacids **159-161**, once prepared, were rearranged in refluxing aqueous phosphate buffer at pH 5.2 to give the arylcarboxylic acids **151**(*S*), **152**(*S*) and **162**(*S*) (see Scheme 128).[7]



159	X= H, Y = H	**151**(*S*) 44% yield, 78% e.e.
160	X= MeO, Y = Br	**152**(*S*) 32%, 71% e.e.
161	X= TosNH, Y = H	**162**(*S*) 36%, N/A*

Conditions: Δ, pH 5.2 phosphate buffer

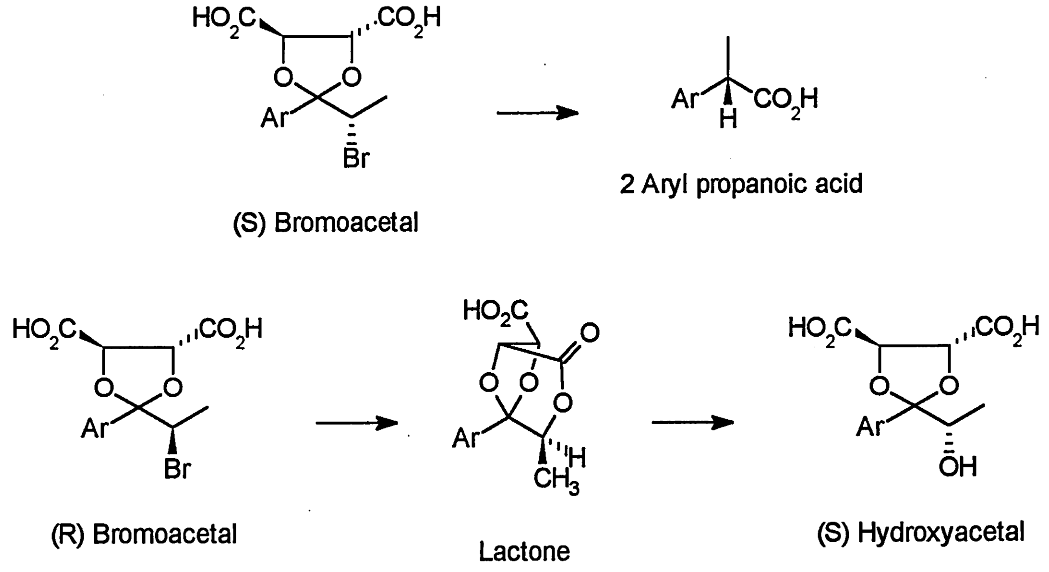
* Not treated with diazomethane.

Scheme 128

Once the crude material had been prepared it was treated with diazomethane and purified by flash chromatography prior to the determination of enantiomeric excess (e.e.) by ^1H NMR analysis in the presence of $Eu(hfc)_3$.

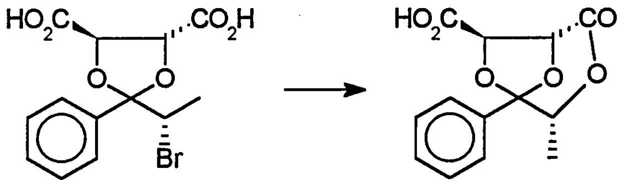
As mentioned previously, the enantiomeric excess of the compound **162**(*S*) where aryl contained the 4-*p*-toluenesulphonamido substituent could not be determined due to the chiral shift reagent interacting with the sulphonamide group rather than the ester. Therefore there was little point in treating this material with diazomethane. The product of this reaction was used as crude material in a subsequent reaction.

The results of the chiral shift studies on the compounds **151**(*S*) and **152**(*S*) showed that the rearrangement using phosphate buffer gave results very similar to those using silver tetrafluoroborate. This was in some ways a little disappointing given that in the literature it was mentioned that the (*S*)-diastereoisomer rearranged while the (*R*)-diastereoisomer lactonised and hydrolysed to give a (*S*)-hydroxyacetal, so it was possible to get a slight enantiomeric enrichment during the reaction (see Scheme 129).[7]



Scheme 129

We attempted to prepare these lactones by following the literature procedure (see Scheme 130).[7]



159 **163**

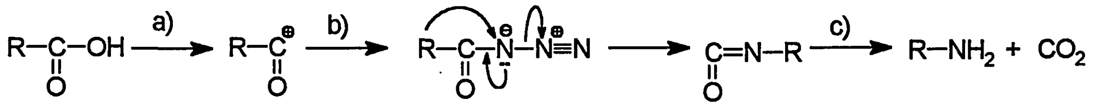
Conditions: NaH, DMF

Scheme 130

The bromoacetal **159** was dissolved in DMF to which sodium hydride was added and the reaction was heated to 105 °C for 36 hours. Analysis by TLC of a quenched sample showed numerous spots, but we were unable to remove sufficient DMF to allow characterisation of any of the products.

Conversion of carboxylic acid to amines and amides

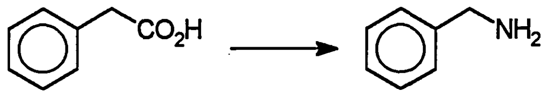
The conversion of a carboxylic acid to an amine using sodium azide and conc. sulphuric acid (Schmidt reaction) is known to give a product containing one less carbon with the stereochemistry at the migrating centre being retained even under the strongly acidic conditions. The reaction proceeds *via* an isocyanate which is hydrolysed to the amine (see Scheme 131).



Reagents: a) H^+ b) NaN_3 c) H_2O

Scheme 131

As a model reaction we first investigated the degradation of phenylacetic acid to benzylamine using sodium azide and conc. sulphuric acid (see Scheme 132).[75]

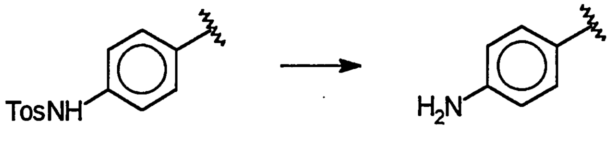


164 **165**

Reagents: NaN_3, $CHCl_3$, H_2SO_4

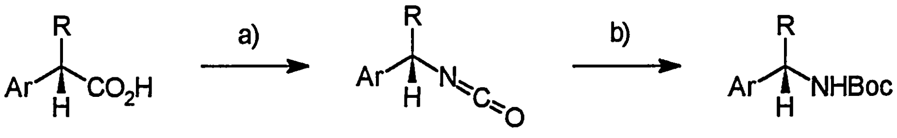
Scheme 132

Phenylacetic acid **164** was dissolved in conc. sulphuric acid / oleum and chloroform before sodium azide was added, after which the reaction effervesced. The crude product was isolated in 60% overall yield as a relatively pure liquid. The ^1H NMR spectrum clearly showed that the product was benzylamine **165**. Even though the yield was good it was clear that under these extremely acidic conditions the sulphonamide containing compounds (e.g. **162**) would be unstable (see Scheme 133).[35]



Scheme 133

Looking through the literature for less extreme reaction conditions we found a paper by Shioiri *et al* in which they describe the use of triethylamine, diphenylphosphoryl azide and anhydrous *t*-butanol (modified Curtius rearrangement) to give a Boc protected amine (see Scheme 134).[71, 76] This reaction too has been shown to retain the stereochemistry present in the starting material and would therefore lead to the possibility of preparing enantiomerically enriched amines.

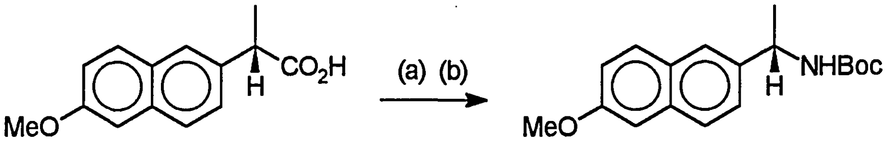


Reagents: a) Et_3N, Ph_2PON_3 b) ^tBuOH

Scheme 134

This modified Curtius degradation uses very mild conditions for the reaction in which *t*-butanol acts as the solvent for the reaction and a reagent in the conversion of an isocyanate to a Boc protected amine. This Boc protected amine may allow modifications to other parts of the molecule before being deprotected to give an amine.

We repeated the literature method for the conversion of a carboxylic acid to a Boc protected amine using commercially available chiral Naproxen **11**(*S*) as a model (see Scheme 135).



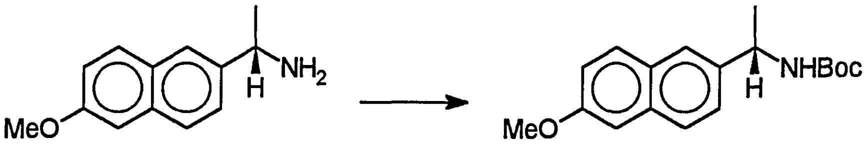
11(*S*) **166**(*S*)

Reagents: (a) Et_3N, Ph_2PON_3 (b) ^tBuOH

Scheme 135

The crude product obtained from this reaction was purified by flash chromatography to give the pure product **166**(*S*) as a white crystalline solid in good yield. Along with this, a mixed fraction was isolated containing the product **166**(*S*) and what ^1H NMR spectroscopy suggested was the corresponding amine **167**(*S*).

In order to confirm that this second product was the amine **167**(*S*) we took a small sample of the mixed fraction which also contained the Boc protected amine **166**(*S*) and converted any of the unprotected amine to the Boc protected amine by reaction with di-*t*-butyl pyrocarbonate (see Scheme 136).[77]

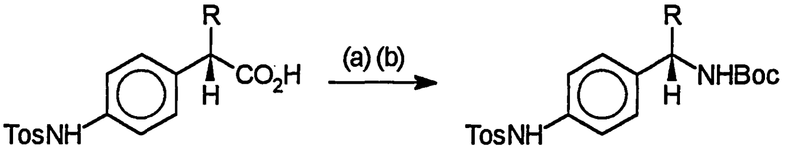


167(*S*) **166(*S*)**

Reagent: $(^tBuOCO)_2O$

Scheme 136

Once we had proved the method for the conversion of model carboxylic acids to Boc protected amines we applied it to the 2-arylcarboxylic acids **152**, **152(*S*)** and **153(*S*)** (see Scheme 137).



152 (*R/S*) R = CH_3	**168** (*R/S*)	36%
152(*S*) R = CH_3	**168(*S*)**	26%
153(*S*) R = CH_2CH_3	**169(*S*)**	0%

Reagents: (a) Et_3N, Ph_2PON_3 (b) ^tBuOH

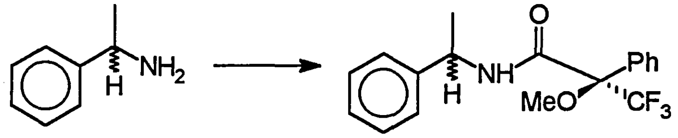
Scheme 137

When we applied the method to the racemic *p*-toluenesulphonamido substituted carboxylic acid **152** we obtained the Boc protected amine **168** and we had hoped we could resolve each of the enantiomers by ^1H NMR analysis in the presence of the chiral shift reagent $Eu(hfc)_3$. However, we were unable to resolve the enantiomers due to the chiral shift reagent interacting with the sulphonamide functional group in preference to the Boc protected amine. When we repeated the reaction using the enantiomerically enriched *p*-toluenesulphonamido substituted carboxylic acids **152(*S*)** and **153(*S*)** we were only able to isolate a crude Boc protected product **168(*S*)** from the reaction using the carboxylic acid **152(*S*)**, but were unable to isolate the corresponding product **169(*S*)** from the carboxylic acid **153(*S*)**.

It was evident that we needed an alternative strategy to resolve each enantiomer of **168** which we could then apply to determine the enantiomeric excess of the enantiomerically enriched Boc protected amine **168(*S*)**. One way would be to deprotect the Boc-protected amine **168** to give the free amine **170** and repeat the chiral shift experiment. We hoped that the Lewis acid would bind to the amine group rather than the sulphonamide substituent. Alternatively we could convert the amine **170** into the corresponding Mosher's amide and determine the enantiomeric excess from the resulting diastereoisomers by ^{1}H NMR analysis.

We had a very limited supply of material so we used α-methylbenzylamine as a model for the attempt at determining the enantiomeric excess using the chiral shift reagent. We knew that the enantiomers of α-methylbenzylamine could be resolved using chiral shift reagent, but we found that a large amount of shift reagent was required before they were resolved.[78] From our experience we suspected that complications might arise when we applied this method to the amine **170** containing the sulphonamide group.

The alternative method was to prepare the Mosher's amides of racemic α-methylbenzylamine **171** and hope that the resulting diastereoisomers could be resolved by ^{1}H NMR spectroscopy (see Scheme 138).



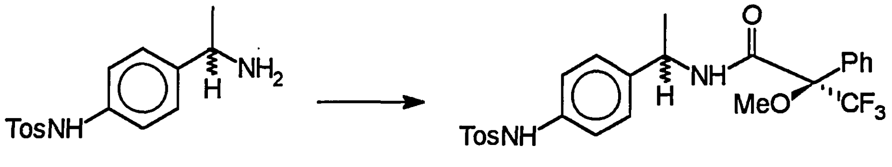
171 **172**

Reagents: (*R*)-Mosher's acid, DCC, DMAP

Scheme 138

Using the same method as that for the preparation of the Mosher's esters of bromohydrin **150**, we prepared the Mosher's amide of racemic α-methylbenzylamine **172**.[70] From the ^{1}H NMR spectrum we observed that the diastereoisomers were resolved but not as much as was hoped; the α-methyl groups in the two diastereoisomers slightly overlapped, while the methoxy groups were resolved but not to the baseline. In contrast the methine protons appeared as a poorly resolved multiplet.

With the knowledge that we could partially resolve the enantiomers of α-methylbenzylamine **171** when converted to the Mosher's amides **172**, we attempted to prepare the sulphonamide substituted Mosher's amide **173** from the amines **170** (see Scheme 139).

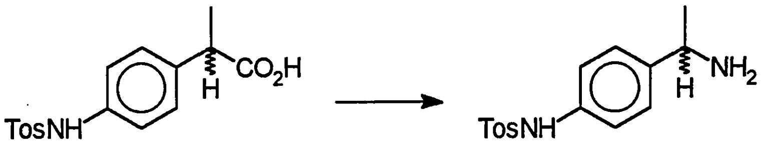


170 **173**

Reagents: (R)Mosher's acid, DCC and DMAP

Scheme 139

At this stage in our research we only had a very small amount of the Boc protected amine **168** and consequently we thought it would be better to prepare the amine **170** directly rather than deprotect what **168** we had. We prepared the racemic amine **168** from the racemic acid **152** (see Scheme 140);[71, 76] we would then convert **168** to the Mosher's amides **173** and hopefully prove that each enantiomer could be resolved.



152 **170**

Reagents: Et_3N, Ph_2PON_3, ^tBuOH

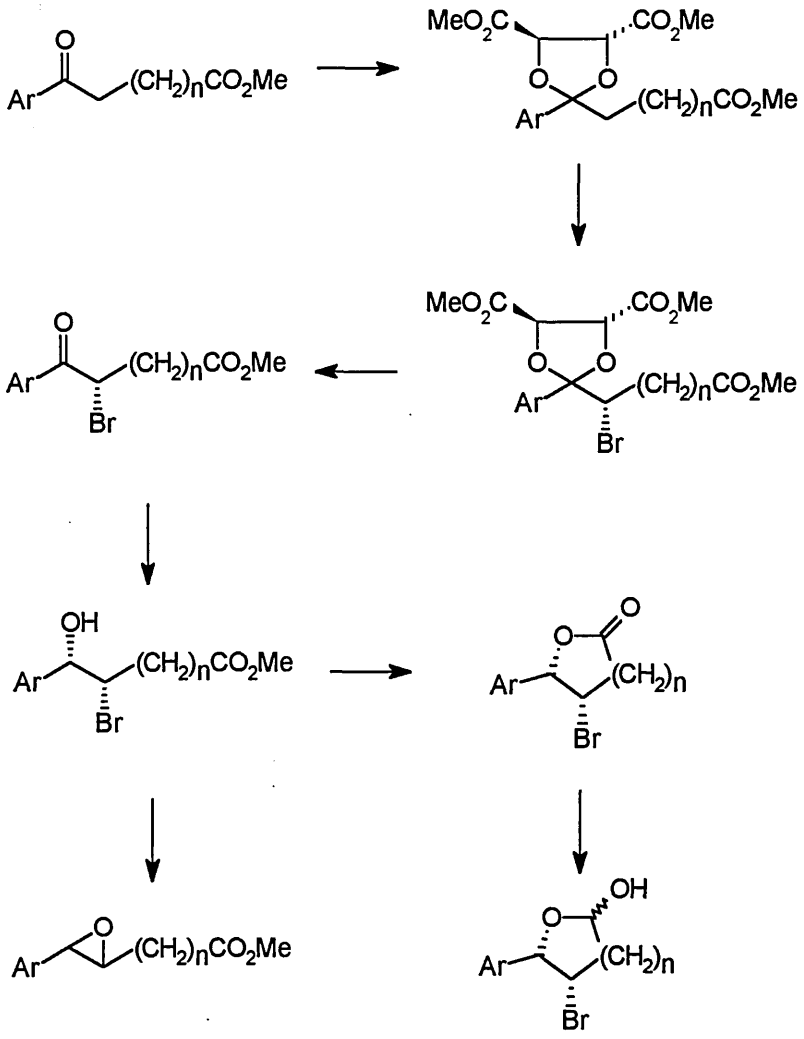
Scheme 140

The racemic amine **170** was prepared from the racemic acid **152** in poor yield, using diphenylphosphoryl azide, triethylamine and *t*-butanol which contained a trace of water. This trace of water was present so that the isocyanate intermediate would be converted directly to the amine **170** rather than the Boc protected amine **168**. We then attempted to convert this material to the Mosher's amide using the same conditions as for the α-methylbenzylamine reaction, no reaction was indicated after 3 days by TLC analysis or by ^1H NMR spectroscopy. Increasing the amount of reagents to approximately 10 equivalents still failed to produce any product.

We have shown that we can prepare 2-arylcarboxylic acids of moderate enantiomeric excess from tartrate bromoacetals and that a similar 2-arylcarboxylic acid then maybe rearranged to give Boc protected amine, but we have been unable to determine the enantiomeric excess of these Boc amines by ^{1}H NMR analysis. We have made some progress towards our ultimate aim of preparing chiral 2-aryl alkyl amines, but unfortunately we have been unable to attempt to convert them into amino acids due to a severe lack of time and materials. Further work needs to be done in order to optimise the synthesis of these Boc protected 2-aryl amines along with a method for determining their enantiomeric excess.

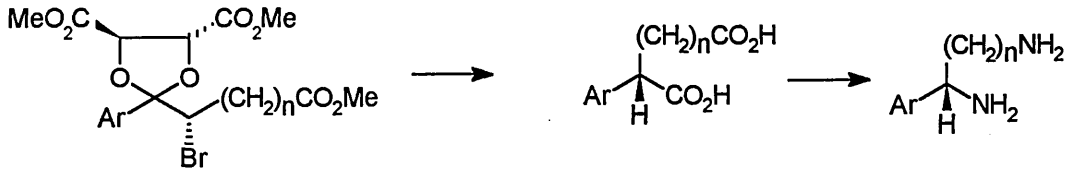
Future Work

The work done so far has been on relatively simple aryl alkyl ketones; we would therefore like to be able to extend this work to include various modifications to the alkyl and aryl groups. We could apply our work to include compounds in which the alkyl group contains an ester functionality, which would then give the possibility of preparing lactones of various ring sizes containing two chiral centres via a bromohydrin (see Scheme 141). Alternatively the bromohydrin maybe converted into an epoxide (see Scheme 141).



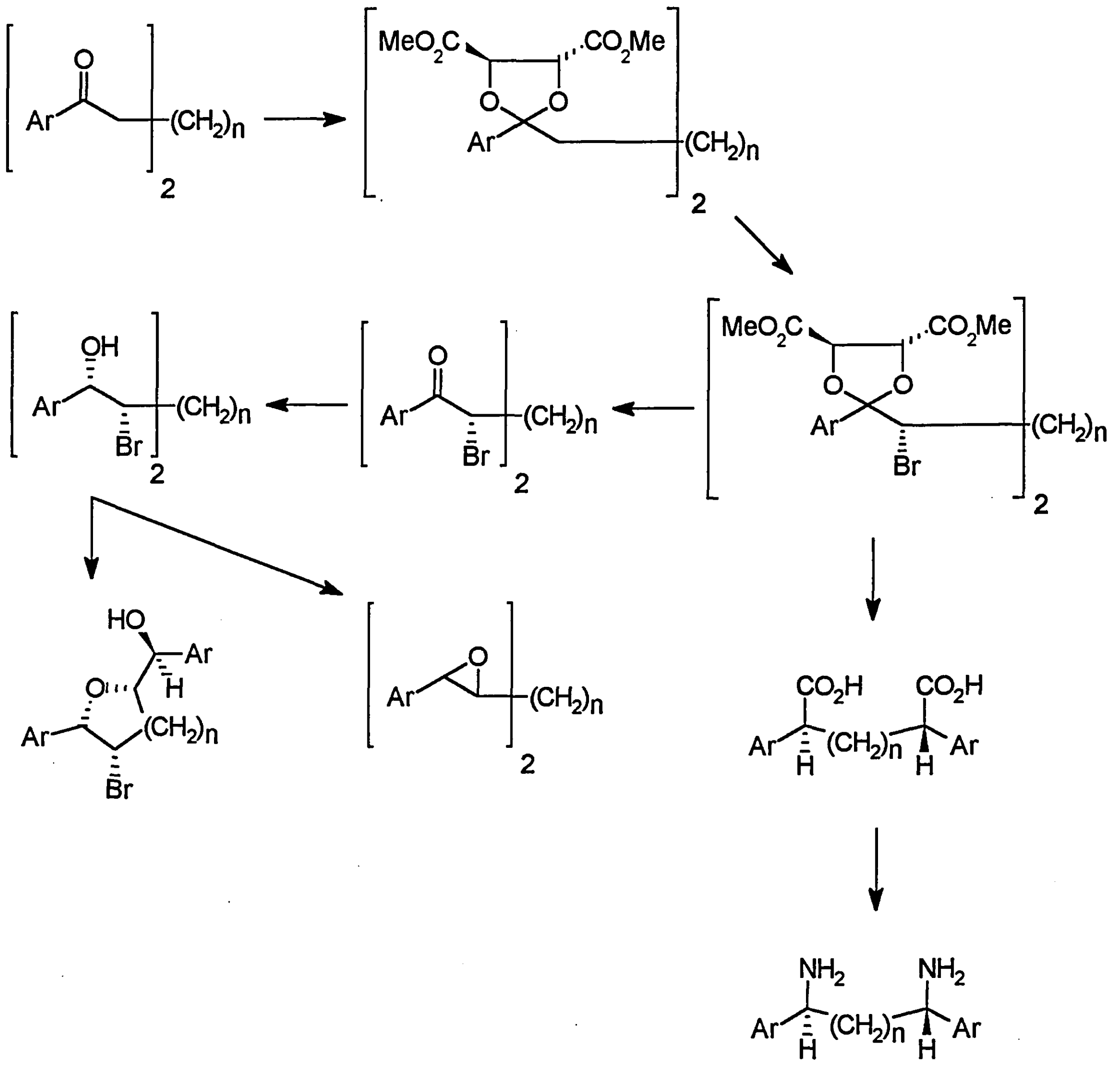
Scheme 141

On the other hand we could rearrange these bromoacetal esters to give a range of chiral diacids which could be converted into chiral diamines containing a single chiral centre (see Scheme 142).



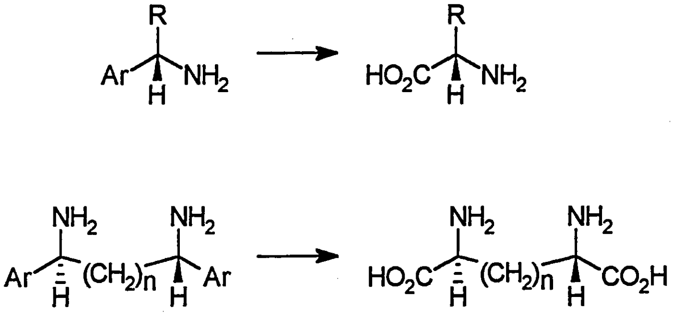
Scheme 142

The above examples have involved methods relating to the transformation of a single ketone, but it would be logical to investigate whether we could extend the chemistry described to more complex systems involving two or more ketones. This could lead to the preparation of chiral diacids, diamines, new chiral ligands, resolving agents *etc.* (see Scheme 143).



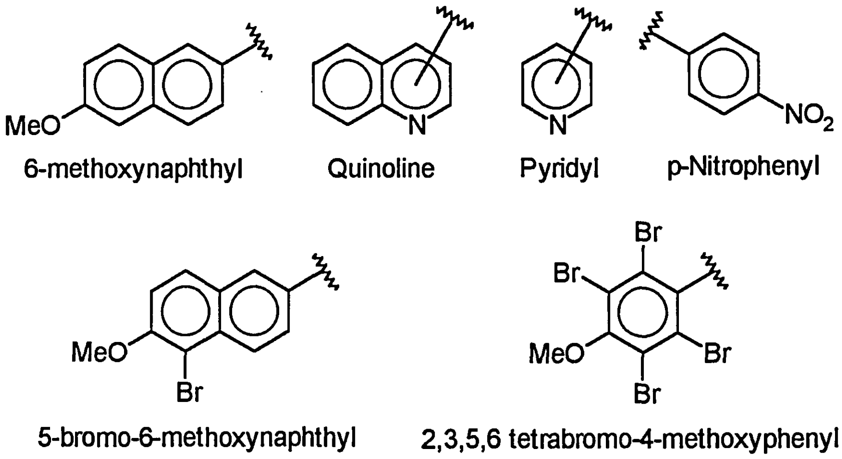
Scheme 143

As mentioned in the discussion our intention was to investigate the conversion of an aromatic ring into a carboxylic acid using a ruthenium catalyst and thereby prepare novel amino acids from our aryl amines (see Scheme 144).[71, 76] We were optimistic that this transformation could be successfully applied to our enantiomerically enriched amines and subsequently extended to more complex systems (see Scheme 144).



Scheme 144

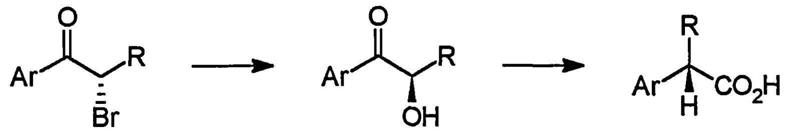
A recurring theme in our research involved the preparation of crystalline solids so that we would have the opportunity to crystallise them to enantiomeric purity. We made some preliminary investigations into modifications of the aryl group, but never discovered a suitable aryl functional group. The use of 6-methoxynaphthyl and 5-bromo-6-methoxynaphthyl groups has been documented in the literature regarding arylpropionic acids. Could our work be applied to include heterocycles such as pyridyl, quinoline, or poly-substituted anisole derivatives ? (see Scheme 145).


6-methoxynaphthyl Quinoline Pyridyl p-Nitrophenyl

5-bromo-6-methoxynaphthyl 2,3,5,6 tetrabromo-4-methoxyphenyl

Scheme 145

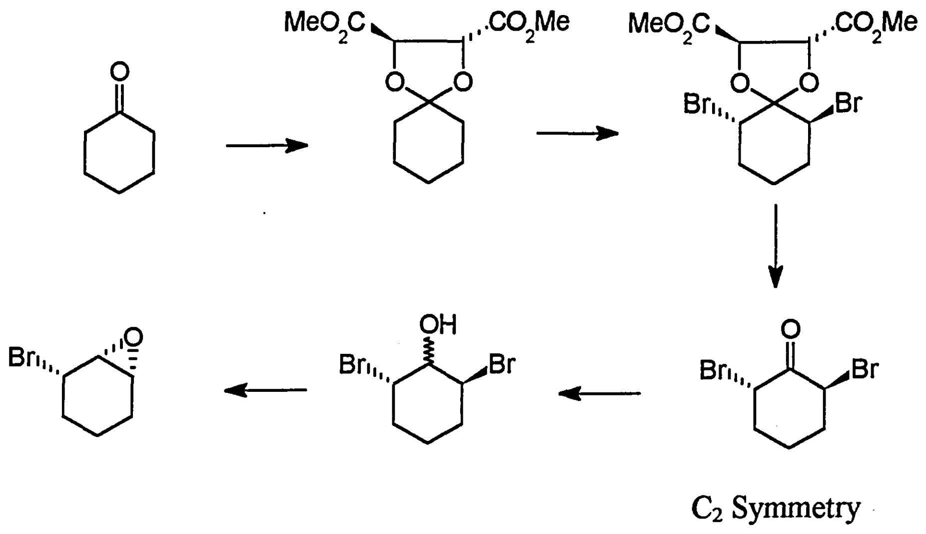
We have already discussed the preparation of enantiomerically pure bromoketones, but according to Sonawane *et al* these can be transformed into the corresponding hydroxyketone as a single enantiomer, which can be rearranged to give the corresponding 2-arylcarboxylic acid as a single enantiomer (see Scheme 146).[16, 26]



Scheme 146

At present the e.e. of our 2-arylcarboxylic acid depends upon the d.e. of our bromoacetals. If we could apply the chemistry developed by Sonawane *et al* we would be able to produce 2-arylcarboxylic acids as single enantiomers rather than as enantiomerically enriched mixtures.

We have so far looked at aryl alkyl ketones, it would be interesting to see what chemistry could be developed from relatively simple dialkyl ketones (see Scheme 147).



Scheme 147

The C_2 symmetric bromoketone would be prepared using the methods already discussed in the Experimental Section. When the C_2 symmetric bromoketone is reduced the stereochemistry of the new stereogenic centre is not important because when it is converted to the epoxide it will react with the bromine which is in the more favourable orientation to give a single epoxide.

These suggestions may result in new applications of dimethyl tartrate bromoacetals in asymmetric synthesis.

Experimental

General Information

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a ATI Mattson Genesis Series FTIR spectrophotometer. Samples were prepared as potassium bromide (KBr) discs or as liquid films. ^{1}H NMR / ^{13}C NMR spectra were obtained using a Bruker 250AC spectrometer at 250 MHz and 62.88 MHz respectively. ^{1}H NMR data are given on the δ scale using tetramethylsilane as the internal reference. Abbreviations for the form of signals are as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants (*J*) are given in Hz. Samples for ^{1}H NMR spectra were prepared in deuterated chloroform unless otherwise stated.

High resolution mass spectra were obtained on a VG Micromass 70 / 70F mass spectrometer fitted with a MSS data system.

Thin layer chromatography (TLC) was performed on Merck 555 Alufolien Kieselgel $60F_{254}$ plates. Flash chromatography was performed on Sorbsil C-60H (40-60μm) silica gel using distilled solvents.

Petroleum ether refers to the fraction boiling between 40°C and 60°C. Dry tetrahydrofuran (THF) was obtained by distillation from potassium metal. Dry pyridine was obtained by distillation from potassium hydroxide and stored over potassium hydroxide. Dry dichloromethane (DCM) was obtained by distillation from P_2O_5. Dry dimethylformamide (DMF) was obtained by heating over calcium hydride followed by distillation under reduced pressure onto type 4Å molecular sieves. Carbon tetrachloride (CCl_4) was dried over type 4Å molecular sieves. The chiral shift reagent europium heptafluorobutyrylcamphorate is denoted as $Eu(hfc)_3$. Dimethyl tartrate refers to dimethyl (2*R*,3*R*)-2,3-dihydroxybutanedioate, (*R*) Mosher's acid refers to (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, DCC and DMAP refer to 1,3-dicyclohexylcarbodiimide and 4-dimethylaminopyridine respectively.

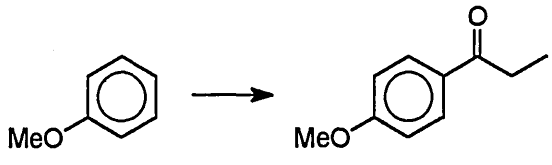
Pure *p*-toluenesulphonyl chloride (tosyl chloride) was obtained by dissolution in a minimum amount of chloroform followed by dilution with 5 volumes of petrol to precipitate impurities. The filtered solution was then decolourised using activated carbon, filtered and concentrated.

All reactions requiring inert atmospheres were performed under nitrogen.

Preparation of ketones

4-Methoxyphenyl substituted alkyl ketones

1-(4-Methoxyphenyl)-1-propanone **21**

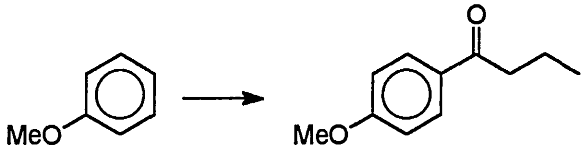


20 **21**

The propionyl chloride (76.8g, 0.83mol) was dissolved in bench DCM (750ml) prior to the addition of anhydrous aluminium chloride (119.5g, 0.895mol) whilst maintaining the temperature below 20°C. After stirring for 5 minutes, anisole **20** (68.9g, 0.638mol) was added over 30 minutes, whilst maintaining the temperature below 20°C. Stirring was maintained for a further 30 minutes prior to removal and work up of a sample and analysis by TLC (4:1 petrol / ethyl acetate). When analysis by TLC showed complete conversion of anisole, the reaction mixture was stirred into crushed ice (500g) / conc. HCl (50g) and extracted with DCM (2 x 200ml). The combined organic extracts were washed with 10% w/w aqueous $NaHCO_3$ (2 x 250ml) and water (250ml) prior to drying with $MgSO_4$. The solvent was removed under reduced pressure to yield the crude title compound as a colourless crystalline solid (96.3g, 92%), m.p. 26-28°C (lit., 27-29°C).[79] (Found M^+, 164.0815. $C_{10}H_{12}O_2$ requires M, 164.0837); ν_{max} (KBr disk)/cm^{-1} 3042, 2973 and 2936 $C\text{-}H_{(str)}$ and 1680 ketone $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J*=7, CH_3), 2.85 (2H, q, *J*=7, CH_2), 3.80 (3H, s, OCH_3), 6.85 (2H, d, *J*=9, aromatic) and 7.90

(2H, d, J=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.4 and 31.4 (aliphatic), 55.4 (MeO), 113.8, 130.0, 130.3 and 163.5 (aromatic) and 199.2 (C=O).

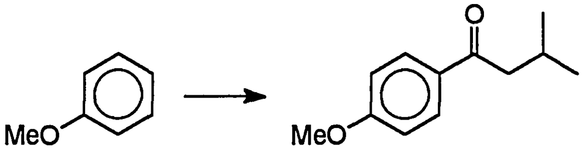
1-(4-Methoxyphenyl)-1-butanone 22



20 **22**

This compound was prepared from anisole **20** (68.9g, 0.638mol) using the method described above for the preparation of **21** but using butyryl chloride (88.4g, 0.83mol), DCM (750ml) and anhydrous aluminium chloride (119.5g, 0.895mol). The title compound was isolated as a colourless oil (106.8g, 94%). (Found M$^+$, 178.1006. $C_{11}H_{14}O_2$ requires M, 178.0994); ν_{max} (film)/cm^{-1} 3056, 2974 and 2936 C-H$_{(str)}$ and 1675 ketone C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, J=7, CH_3), 1.75 (2H, q, J=7, $CH_3C\underline{H_2}$), 2.85 (2H, t, J=7, $COCH_2$), 3.90 (3H, s, OCH_3), 6.95 (2H, d, J=9, aromatic) and 7.90 (2H, d, J=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.1, 18.2 and 40.3 (aliphatic), 55.6 (MeO), 113.9, 130.5 and 163.6 (aromatic) and 199.2 (C=O).

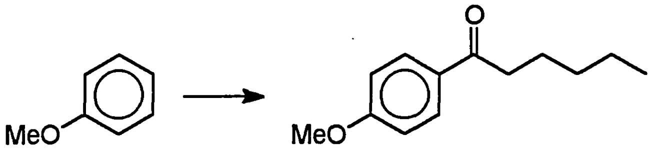
1-(4-Methoxyphenyl)-3-methyl-1-butanone 23



20 **23**

This compound was prepared from anisole **20** (68.9g, 0.638mol) using the method described above for the preparation of **21** but using isovaleryl chloride (100.1g, 0.83mol), DCM (750ml) and anhydrous aluminium chloride (119.5g, 0.895mol). The title compound was isolated as a colourless oil (116.4g, 95%). (Found M$^+$, 192.1153. $C_{12}H_{16}O_2$ requires M, 192.1150); ν_{max} (film)/cm^{-1} 3052, 2974 and 2936 C-H$_{(str)}$ and 1673 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (6H, d, J=7, 2 x CH_3), 2.20 (1H, m, CH), 2.70 (2H, d, J=7, $COCH_2$), 3.75 (3H, s, OCH_3), 6.85 (2H, d, J=9, aromatic) and 7.85 (2H, d, J=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.0, 25.6 and 47.4 (aliphatic), 55.7 (MeO), 113.9, 122.0, 130.7 and 163.6 (aromatic) and 199.2 (C=O).

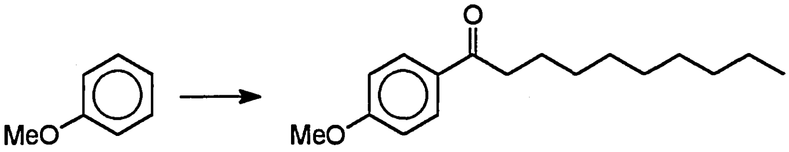
1-(4-Methoxyphenyl)-1-hexanone **24**



20 **24**

This compound was prepared from anisole **20** (68.9g, 0.638mol) using the method described above for the preparation of **21** but using hexanoyl chloride (111.7g, 0.83mol), DCM (750ml) and anhydrous aluminium chloride (119.5g, 0.895mol). The title compound was isolated as a colourless low melting solid (123.6g, 94%), m.p. 37-40°C. (Found M^+, 206.1332. $C_{13}H_{18}O_2$ requires M, 206.1307); ν_{max} (KBr disk)/cm^{-1} 3042, 2977 and 2938 C-$H_{(str)}$ and 1671 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, J=7, CH_3), 1.25-1.40 (4H, m, CH_3-($C\underline{H}_2$)$_2$-), 1.65 (2H, q, J=7, $COCH_2C\underline{H}_2$), 2.85 (2H, t, J=7, $COCH_2$), 3.80 (3H, s, OCH_3), 6.85 (2H, d, J=9, aromatic) and 7.90 (2H, d, J=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.2, 21.6, 22.9, 24.5, 31.9, 34.2 and 38.4 (aliphatic), 55.5 (MeO), 113.9, 130.5 and 163.6 (aromatic) and 199.2 (C=O).

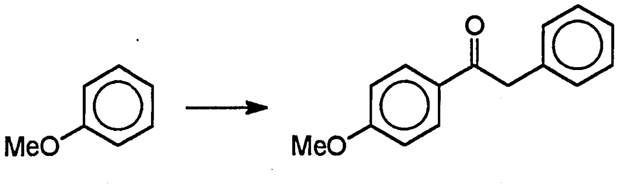
1-(4-Methoxyphenyl)-1-decanone **25**



20 **25**

This compound was prepared from anisole **20** (68.9g, 0.638mol) using the method described above for the preparation of **21** but using decanoyl chloride (158.3g, 0.83mol), DCM (750ml) and anhydrous aluminium chloride (119.5g, 0.895mol). The title compound was isolated as a colourless low melting solid (165.6g, 99%), m.p. 44-45°C. (Found M^+, 262.1934. $C_{17}H_{26}O_2$ requires M, 262.1933); ν_{max} (KBr disk)/cm^{-1} 3049, 2973 and 2931 C-$H_{(str)}$ and 1670 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, J=6, CH_3), 1.10-1.40 (12H, m, CH_3-($C\underline{H}_2$)$_6$-), 1.70 (2H, m, J=7, $CH_3C\underline{H}_2$), 2.90 (2H, t, J=7, $COCH_2$), 3.85 (3H, s, OCH_3), 6.90 (2H, d, *J*=9, aromatic) and 7.90 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.4, 22.9, 24.9, 29.6, 29.8, 32.2, 34.3 and 38.5 (aliphatic), 55.6 (MeO), 113.9, 130.6 and 163.6 (aromatic) and 199.4 (C=O).

1-(4-Methoxyphenyl)-2-phenyl-1-ethanone **26**

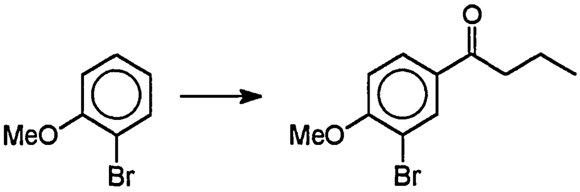


20 **21**

This compound was prepared from anisole **20** (68.9g, 0.638mol) using the method described above for the preparation of **21** but using phenylacetyl chloride (128.3g, 0.83mol), DCM (750ml) and anhydrous aluminium chloride (119.5g, 0.895mol). The title compound was isolated as a colourless crystalline solid (165.6g, 89%), m.p. 110-113°C. (Found M^+, 226.0984. $C_{15}H_{14}O_2$ requires M, 226.0994); ν_{max} (KBr disk)/cm^{-1} 3061, 3001, 2973 and 2931 C-H$_{(str)}$ and 1668 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 3.85 (3H, s, OCH_3), 4.25 (2H, s, CH_2), 6.95 (2H, d, *J*=7, aromatic), 7.35 (5H, m, aromatic) and 8.05 (2H, d, *J*=7, aromatic); δ_C (62.88 MHz; $CDCl_3$) 45.6 (aliphatic), 55.8 (MeO), 114.2, 127.2, 129.0, 129.8, 131.4, 132.7, 135.4 and 164.0 (aromatic) and 196.9 (C=O).

3-Bromo-4-methoxyphenyl substituted alkyl ketones

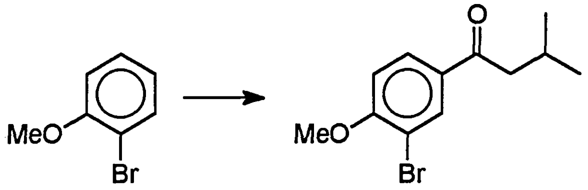
1-(3-Bromo-4-methoxyphenyl)-1-butanone **40**



39 **40**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using butyryl chloride (3.70g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mol). The title compound was isolated as a colourless crystalline solid (5.95g, 87%), m.p. 68-70°C. (Found M^+, 256.0096. $C_{11}H_{13}{}^{79}BrO_2$ requires M, 256.0098); ν_{max} (film)/cm^{-1} 3049, 3009, 2979 and 2930 C-$H_{(str)}$ and 1680 ketone C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, CH_3), 1.60 (2H, sextet, *J*=7, $CH_3C\underline{H}_2$), 2.70 (2H, t, *J*=7, $COCH_2$), 3.80 (3H, s, OCH_3), 6.75 (1H, d, *J*=8, aromatic), 7.20 (1H, dd, *J*=8 and 2, aromatic) and 8.00 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.1, 18.0 and 40.3 (aliphatic), 56.7 (MeO), 111.3, 112.0, 129.4, 131.3, 133.6 and 159.6 (aromatic) and 197.8 (C=O).

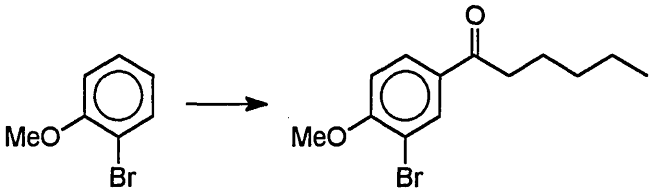
1-(3-Bromo-4-methoxyphenyl)-3-methyl-1-butanone **41**



39 **41**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using isovaleryl chloride (4.18g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mol). The title compound was isolated as a colourless oil (5.95g, 85%). (Found M^+, 270.0254. $C_{12}H_{15}{}^{79}BrO_2$ requires M, 270.0255); ν_{max} (film)/cm^{-1} 3048, 3010, 2961 and 2946 C-$H_{(str)}$ and 1682 ketone C=$O_{(str)}$;δ_H (250 MHz; $CDCl_3$) 0.90 (6H, d, *J*=7, 2 x $C\underline{H}_3$), 2.20 (1H, m, CH), 2.70 (2H, d, *J*=7, $COCH_2$), 3.90 (3H, s, OCH_3), 6.85 (1H, d, *J*=8, aromatic), 7.80 (1H, dd, *J*=8 and 2, aromatic) and 8.10 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.1, 25.5 and 47.3 (aliphatic), 56.8 (MeO), 111.4, 112.2, 129.6, 131.8, 133.9 and 159.7 (aromatic) and 197.9 (C=O).

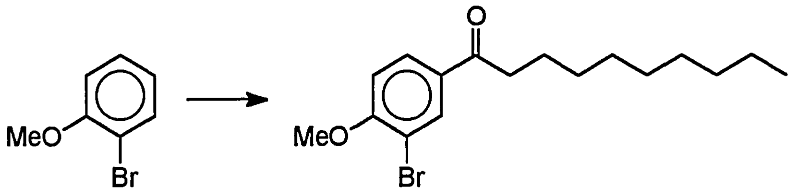
1-(3-Bromo-4-methoxyphenyl)-1-hexanone **42**



39 **42**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using hexanoyl chloride (4.67g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mol). The title compound was isolated as a colourless low melting solid (5.99g, 79%), m.p. 46-47°C. (Found M$^+$, 284.0412. $C_{13}H_{17}{}^{79}BrO_2$ requires M, 284.0428); ν_{max} (film)/cm^{-1} 3043, 3005, 2989 and 2931 C-H$_{(str)}$ and 1669 ketone C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.35 (4H, m, -($C\underline{H}_2$)$_2$-), 1.70 (2H, m, $COCH_2C\underline{H}_2$), 2.90 (2H, t, *J*=7, $COCH_2$), 3.95 (3H, s, OCH_3), 6.95 (1H, d, *J*=8, aromatic), 7.90 (1H, dd, *J*=8 and 2, aromatic) and 8.15 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.3, 22.8, 24.4, 31.8 and 38.5 (aliphatic), 56.7 (MeO), 111.4, 112.2, 129.5, 131.4, 133.8 and 159.7 (aromatic) and 198.2 (C=O).

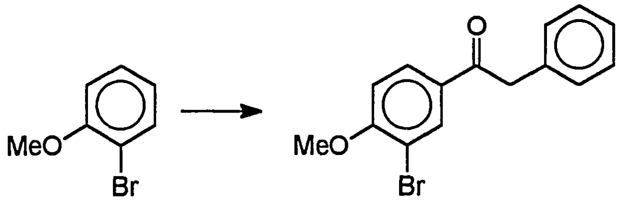
1-(3-Bromo-4-methoxyphenyl)-1-decanone **43**



39 **43**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using decanoyl chloride (6.61g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mol). The title compound was isolated as a colourless low melting solid (7.62g, 84%), m.p. 35-37°C. (Found M$^+$, 340.1026. $C_{17}H_{25}{}^{79}BrO_2$ requires M, 340.1038); ν_{max} (film)/cm^{-1} 3049, 3012, 2986 and 2925 C-H$_{(str)}$ and 1665 ketone C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.15- 1.50 (12H, m, -(CH_2)$_6$-), 1.70 (2H, m, $COCH_2C\underline{H}_2$), 2.90 (2H, t, *J*=7, $COCH_2$), 3.95 (3H, s, OCH_3), 6.90 (1H, d, *J*=8, aromatic), 7.90 (1H, dd, *J*=8 and 2, aromatic) and 8.15 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.4, 22.9, 24.7, 24.9, 29.7, 32.2, 34.4 and 38.5(aliphatic), 56.6 (MeO), 111.3, 112.2, 129.5, 131.4, 133.8 and 159.7 (aromatic) and 198.3 (C=O).

1-(3-Bromo-4-methoxyphenyl)-2-phenyl-1-ethanone **44**

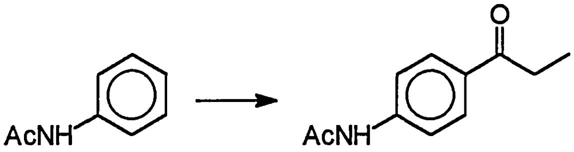


39 **44**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using phenylacetyl chloride (5.36g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mol). The title compound was isolated as a colourless crystalline solid (6.33g, 78%), m.p. 122-124°C. (Found M^+, 304.0098. $C_{15}H_{13}{}^{79}BrO_2$ requires M, 304.0099); ν_{max} (film)/cm^{-1} 3061, 3015, 3006 and 2979 C-H$_{(str)}$ and 1672 ketone C=O$_{(str)}$;δ_H (250 MHz; $CDCl_3$) 3.95 (3H, s, OCH_3), 4.25 (2H, s, CH_2), 6.90 (1H, d, *J*=8, aromatic), 7.20-7.40 (5H, m, aromatic), 7.95 (1H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 47.5 (aliphatic), 56.4 (MeO), 112.5, 114.6, 126.7, 128.9, 129.8, 130.8, 131.1, 131.8, 136.0 and 161.3 (aromatic) and 191.9 (C=O).

4-Acetamidophenyl substituted alkyl ketones

1-(4-Acetamidophenyl)-1-propanone **46**

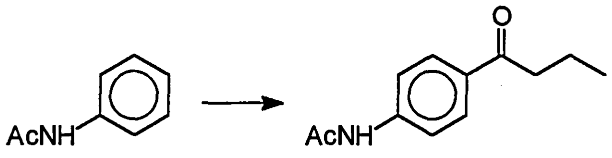


45 **46**

Propionyl chloride (20.8g, 0.225mol) was dissolved in carbon disulphide (CS_2) (350ml) prior to the addition of aluminium chloride (60.1g, 0.450mol) whilst maintaining the temperature below 10°C. After stirring for 10 minutes acetanilide **45** (20.0g, 0.148mol) was added in one portion to the reaction mixture, which was then heated at reflux until TLC analysis (4:1 petroleum ether / ethyl acetate, multiple elution) indicated complete conversion of starting material. The reaction was allowed to settle into two layers, from which the upper layer (CS_2) was decanted. The lower layer was then diluted with DCM (300ml) before being stirred into ice (300g) / conc. HCl (30g) and extracted with DCM

(2 x 150ml). The combined organic extracts were then washed with 2N HCl (100ml), water (100ml), 10% w/w aqueous $NaHCO_3$ (2 x 100ml) and water (100ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude title compound. Purification by recrystallisation from methanol gave the pure title compound as pale yellow needle shaped crystals (28.0g, 99%), m.p. 169-170°C. (Found M^+, 191.0964. $C_{11}H_{13}NO_2$ requires M, 191.0946); ν_{max} (KBr disk)/cm^{-1} 3109 and 3060 N-$H_{(str)}$, 2973 and 2936 C-$H_{(str)}$, 1680 ketone C=$O_{(str)}$ and 1666 amide C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7, CH_3), 2.20 (3H, s, $COCH_3$), 3.00 (2H, q, *J*=7, CH_2), 7.60 (2H, d, *J*=9, aromatic), 7.70 (1H, s, N-H) and 7.95 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 7.3, 24.3 and 30.4 (aliphatic), 119.0, 131.6, 133.7 and 142.2 (aromatic), 168.6 (N-C=O) and 198.3 (C=O).

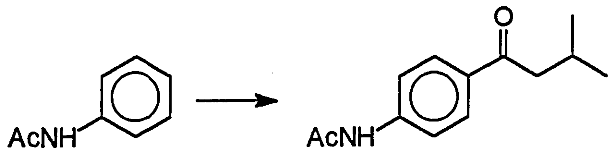
1-(4-Acetamidophenyl)-1-butanone **47**



45 **47**

This compound was prepared from acetanilide **45** (20.0g.148mol) using the method described above for the preparation of **46** but using butyryl chloride (24.0g, 0.225mol), CS_2 (350ml) and anhydrous aluminium chloride (60.1g, 0.450mol). The title compound was isolated as pale yellow needle shaped crystals (27.3g, 90%), m.p. 152-154°C. (Found M^+, 205.1117. $C_{12}H_{15}NO_2$ requires M, 205.1103); ν_{max} (KBr disk)/cm^{-1} 3109 and 3060 N-$H_{(str)}$, 2978 and 2930 C-$H_{(str)}$, 1685 ketone C=$O_{(str)}$ and 1666 amide C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, *J*=7, CH_3), 1.80 (2H, m, $CH_3C\underline{H}_2$), 2.25 (3H, s, $CO\underline{CH}_3$), 2.95 (2H, t, *J*=7, $CO\underline{CH}_2$), 7.50 (1H, s, N-H), 7.60 (2H, d, *J*=8, aromatic) and 7.95 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl3) 13.8, 24.3, 17.7 and 40.4 (aliphatic), 118.8, 131.3, 134.7 and 141.4 (aromatic), 168.6 (N-C=O) and 199.8 (C=O).

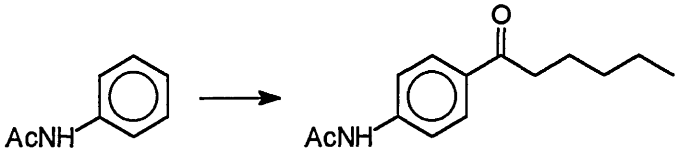
1-(4-Acetamidophenyl)-3-methyl-1-butanone **48**



45 **48**

This compound was prepared from acetanilide **45** (20.0g.148mol) using the method described above for the preparation of **46** but using isovaleryl chloride (27.1g, 0.225mol), CS_2 (350ml) and anhydrous aluminium chloride (60.1g, 0.450mol). The title compound was isolated as pale yellow needle shaped crystals (30.8g, 95%), m.p. 87-88°C. (Found M^+, 219.1248. $C_{13}H_{17}NO_2$ requires M, 219.1259); ν_{max} (KBr disk)/cm^{-1} 3115 and 3063 N-$H_{(str)}$, 2965 and 2926 C-$H_{(str)}$, 1681 ketone C=$O_{(str)}$ and 1667 amide C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (6H, d, *J*=7, 2 x CH_3), 2.20 (3H, s, $COCH_3$), 2.30 (1H, m, CH), 2.80 (2H, d, *J*=7, CH_2), 7.60 (2H, d, *J*=8, aromatic), 7.65 (1H, s, N-H) and 7.95 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.1, 24.9, 25.7 and 47.7 (aliphatic), 119.4, 129.8, 133.2 and 142.9 (aromatic), 169.7 (N-C=O) and 200.1 (C=O).

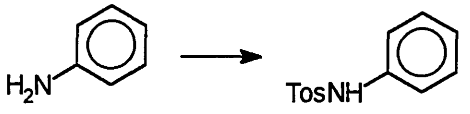
1-(4-Acetamidophenyl)-1-hexanone **49**



45 **49**

This compound was prepared from acetanilide **45** (20.0g.148mol) using the method described above for the preparation of **46** but using hexanoyl chloride (30.3g, 0.225mol), CS_2 (350ml) and anhydrous aluminium chloride (60.1g, 0.450mol). The title compound was isolated as pale yellow needle shaped crystals (32.8g, 95%), m.p. 162-164°C. (Found M^+, 233.1409. $C_{14}H_{19}NO_2$ requires M, 233.1416); ν_{max} (KBr disk)/cm^{-1} 3108 and 3061 N-$H_{(str)}$, 2973 and 2936 C-$H_{(str)}$, 1678 ketone C=$O_{(str)}$ and 1666 amide C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.35 (4H, m, -$(CH_2)_2$-), 1.75 (2H, m, $COCH_2C\underline{H}_2$), 2.25 (3H, s, $COCH_3$), 2.95 (2H, t, *J*=7, $COCH_2$), 7.45 (1H, s, N-H), 7.60 (2H, d, *J*=9, aromatic) and 7.95 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.6, 25.1 and 31.9 (aliphatic), 119.2, 129.7, 132.9 and 142.4 (aromatic), 168.9 (N-C=O) and 200.1 (C=O).

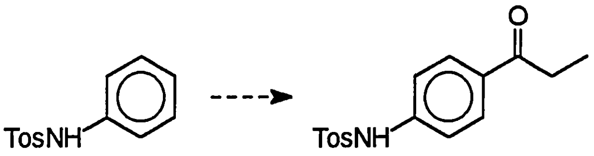
<u>*N*-Phenyl-*p*-toluenesulphonamide **50**</u>



Aniline **50**

Aniline (10.00g, 108mmol) was dissolved in dry pyridine (200ml) prior to the addition of *p*-toluenesulphonyl chloride (22.5g, 118mmol). The reaction was stirred for 48 hours at room temperature prior to being poured into conc. HCl (100g) / ice (400g). The product was filtered off under reduced pressure and washed with 2N HCl (100ml) and water (200ml). The crude product was slurried in petrol and filtered under reduced pressure to give the title compound as a pale grey coloured crystalline solid (25.5g, 96%) m.p. 101-103°C. (Found M$^+$, 247.0682. $C_{13}H_{13}NO_2S$ requires M, 247.0667); ν_{max} (KBr disk)/cm^{-1} 3254-3246 N-H$_{(str)}$, 2970-2917 C-H$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 2.35 (3H, s, ArCH$_3$), 7.10 (2H, m, aromatic), 7.20 (5H, m, aromatic), 7.75 (2H, m, aromatic), 7.95 (1H, s, N-H); δ_C (62.88 MHz; CDCl$_3$) 21.8 (aliphatic), 121.6, 125.4, 127.7, 129.6, 130.0, 136.3, 137.2 and 144.2 (aromatic).

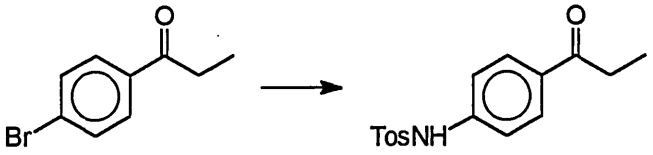
<u>Attempted preparation of 1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **59**</u>



50 **59**

N-Phenyl-*p*-toluenesulphonamide **50** (15.00g, 60.0mmol), aluminium chloride (48.5g, 360mmol) and propionyl chloride (33.3g, 360mmol) were dissolved in CS$_2$ (200ml) and heated at reflux. Analysis by TLC (2:1 petrol / ethyl acetate) after 20 hours showed numerous spots, none of which were identified as the desired product.

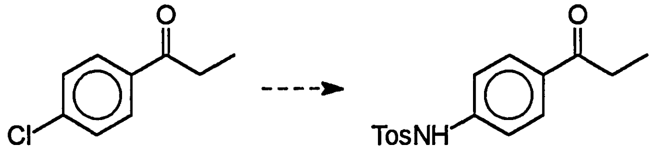
1-(4-*p*-Toluenesulphonamidophenyl)-1-propanone **59**



53 **59**

4-Bromopropiophenone **53** (2.00g, 9.4mmol), *p*-toluenesulphonamide (3.22g, 18.8mmol), anhydrous potassium carbonate (2.00g, 14.5mmol) and copper(II) acetate (0.2g, 1.09mmol) were dissolved in dry DMF (25ml) and heated at reflux overnight. Analysis by TLC (2:1 petrol / ethyl acetate) showed complete reaction. The mixture was allowed to cool to room temperature prior to being poured into 2N HCl (100ml) and extracted with DCM (2 x 50ml). The combined organic extracts were washed with 2N HCl (50ml), water (50ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to give a brown liquid. Purification by flash chromatography (2:1 petrol / ethyl acetate) to yield the title compound as a pale yellow solid (2.76g, 97%) m.p. 192-194°C. (Found M^+, 303.0917. $C_{16}H_{17}NO_3S$ requires M, 303.0929); ν_{max} (KBr disk)/cm^{-1} 3232, 3204 N-$H_{(str)}$, 2974, 2939, 2876 C-$H_{(str)}$ and 1667 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7, CH_3), 2.40 (3H, s, $ArCH_3$), 2.95 (2H, q, *J*=7, CH_2), 7.15 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (1H, s, N-H), 7.75 (2H, d, *J*=8, aromatic) and 7.85 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.1, 20.9 and 30.8, (aliphatic), 117.9, 126.7, 129.4, 129.8, 131.6, 136.5, 142.2 and 143.6 (aromatic) and 198.9 (C=O).

Attempted preparation of 1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **59**

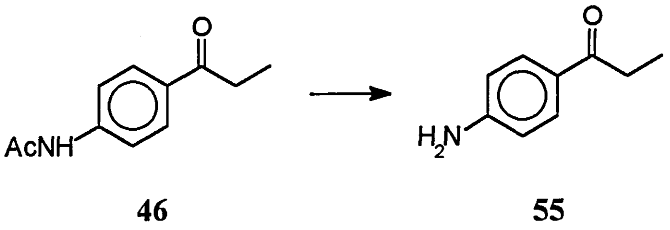


54 **59**

The attempted preparation of this compound was from 4-chloropropiophenone **54** (1.58g, 9.4mmol) using the method described above for the preparation of **59** from **53**. Heating at reflux for 10 days failed to yield the required product.

4-Aminophenyl substituted alkyl ketones

1-(4-Aminophenyl)-1-propanone 55



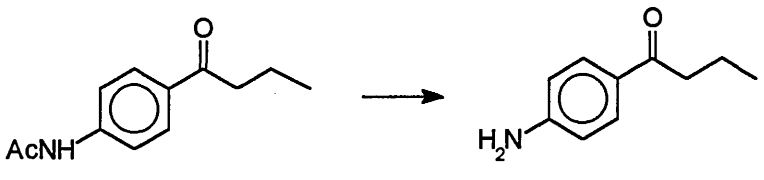
Method 1

1-(4-Acetamidophenyl)-1-propanone **46** (17.4g, 91.3mmol) was heated at reflux in 2N HCl (100ml) / bench ethanol (100ml) until analysis by TLC (4:1 petroleum ether / ethyl acetate) indicated complete conversion of the starting material. The reaction was then cooled and the ethanol removed under reduced pressure before the addition of 5N NaOH until greater than pH 11 to precipitate the crude product. The crude product was isolated by vacuum filtration and washed with water (100ml) to give a brown solid which was then purified by recrystallisation from methanol to yield the title compound as a pale brown crystalline solid.

Method 2

1-(4-Acetamidophenyl)-1-propanone **46** (17.4g, 91.3mmol) was refluxed in 2N HCl (200ml) until analysis by TLC (4:1 petroleum ether / ethyl acetate) indicated complete conversion of the starting material. The reaction was then cooled to room temperature before the addition of 5N NaOH until greater than pH 11 to precipitate the crude product. The crude solid was isolated by vacuum filtration and washed with water to give a pale brown solid which was purified by recrystallisation from methanol to yield the title compound as A straw coloured solid (12.1g, 89%), m.p. 135-137°C (lit., 140°C).[79] (Found M^+, 149.0838; $C_9H_{11}NO$ requires M, 149.0841). ν_{max} (KBr disk)/cm^{-1} 3449 and 3358 N-H$_{(str)}$, 3042, 2980, 2942 and 2901 C-H$_{(str)}$ and 1651 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7, CH_3), 2.90 (2H, q, *J*=7, CH_2), 4.15 (2H, s, NH_2), 6.65 (2H, d, *J*=9, aromatic) and 7.80 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 9.0 and 31.4 (aliphatic), 114.1, 127.8, 130.8 and 151.3 (aromatic) and 199.7 (C=O).

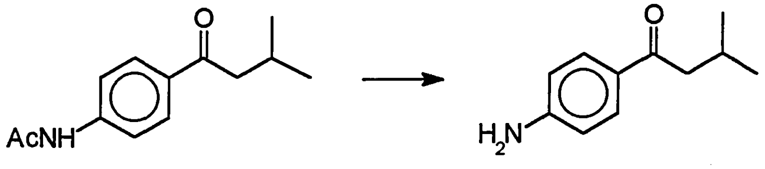
1-(4-Aminophenyl)-1-butanone 56



47 **56**

This compound was prepared from 1-(4-acetamidophenyl)-1-butanone **47** (18.7g, 91.3mmol) using 'method 2' described above for the preparation of **55**. The title compound was isolated as pale yellow needle shaped crystals (13.1g, 88%), m.p. 128-130°C. (Found M$^+$, 163.0109. $C_{10}H_{13}NO$ requires M, 163.0997); ν_{max} (KBr disk)/cm^{-1} 3446 and 3363 N-H$_{(str)}$, 3041, 2990, 2948 and 2900 C-H$_{(str)}$ and 1655 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, *J*=7, CH_3), 1.75 (2H, m, $CH_3\underline{CH_2}$), 2.85 (2H, t, *J*=7, $COCH_2$), 4.15 (2H, bs, NH_2), 6.65 (2H, d, *J*=9, aromatic) and 7.80 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.3, 18.6 and 40.3 (aliphatic), 114.1, 128.1, 130.9 and 151.3 (aromatic) and 199.2 (C=O).

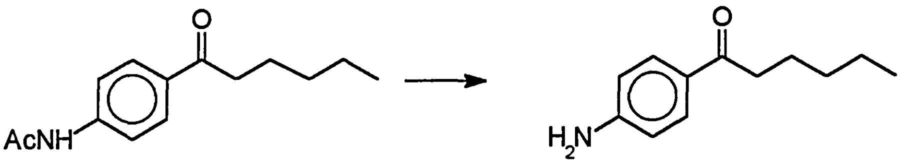
1-(4-Aminophenyl)-3-methyl-1-butanone 57



48 **57**

This compound was prepared from 1-(4-acetamidophenyl)-3-methyl-1-butanone **48** (20.0g, 91.3mmol) using 'method 2' described above for the preparation of **55**. The title compound was isolated as pale yellow needle shaped crystals (11.3g, 70%), m.p. 138-140°C. (Found M$^+$, 177.1141. $C_{11}H_{15}NO$ requires M, 177.1154); ν_{max} (KBr disk)/cm^{-1} 3456 and 3368 N-H$_{(str)}$, 3049, 2965, 2932 and 2897 C-H$_{(str)}$ and 1650 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (6H, t, *J*=7, 2 x CH_3), 2.25 (1H, m, CH), 2.75 (2H, d, *J*=7, CH_2), 4.15 (2H, bs, NH_2), 6.65 (2H, d, *J*=9, aromatic) and 7.80 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.2, 25.9 and 47.3 (aliphatic), 114.1, 128.4, 130.9 and 151.3 (aromatic) and 199.0 (C=O).

1-(4-Aminophenyl)-1-hexanone 58

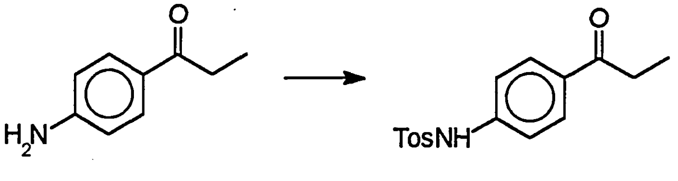


49 **58**

This compound was prepared from 1-(4-acetamidophenyl)-1-hexanone **49** (21.3g, 91.3mmol) using 'method 2' described above for the preparation of **55**. The title compound was isolated as pale yellow needle shaped crystals (16.4g, 94%), m.p. 132-134°C. (Found M$^+$, 191.1310. $C_{12}H_{17}NO$ requires M, 191.1311); ν_{max} (KBr disk)/cm^{-1} 3440 and 3332 N-H$_{(str)}$, 3051, 2980, 2929 and 2898 C-H$_{(str)}$ and 1659 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.35 (4H, m, -$(CH_2)_2$-), 1.70 (2H, m, $COCH_2C\underline{H_2}$), 2.85 (2H, t, *J*=8, $COCH_2$), 4.15 (2H, bs, NH_2), 6.65 (2H, d, *J*=9, aromatic) and 7.85 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.3, 22.9, 24.9, 32.0 and 38.3 (aliphatic), 114.1, 127.8, 130.8 and 151.3 (aromatic) and 199.3 (C=O).

p-Toluenesulphonamidophenyl substituted alkyl ketones

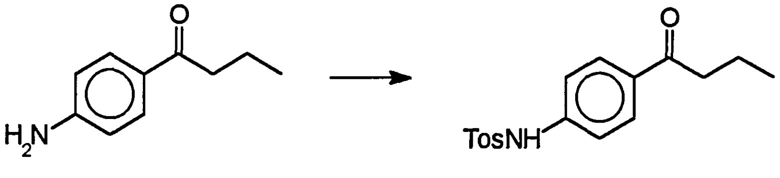
1-(4-*p*-Toluenesulphonamidophenyl)-1-propanone 59



55 **59**

The 1-(4-aminophenyl)-1-propanone **55** (9.54g, 64.0mmol) was dissolved in dry pyridine (150ml) prior to the addition of *p*-toluenesulphonyl chloride (12.8g, 67.2mmol). When TLC analysis (4:1 petroleum ether / ethyl acetate) showed the complete disappearance of starting material, the reaction was poured into 4N HCl (300ml) from which the crude product precipitated out. The crude product was isolated by vacuum filtration, washed with 4N HCl, water and purified by recrystallisation from methanol to yield the title compound as a pale brown crystalline solid (19.0g, 98%) m.p. 192-194°C. (Found M$^+$, 303.0928. $C_{16}H_{17}NO_3S$ requires M, 303.0929); ν_{max} (KBr disk)/cm^{-1} 3232 and 3204 N-H$_{(str)}$, 2974, 2939 and 2876 C-H$_{(str)}$ and 1667 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7, CH$_3$), 2.40 (3H, s, ArCH$_3$), 2.95 (2H, q, *J*=7, CH$_2$), 7.15 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (1H, s, N-H), 7.75 (2H, d, *J*=8, aromatic) and 7.85 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; CDCl$_3$) 8.1, 20.9 and 30.8, (aliphatic), 117.9, 126.7, 129.4, 129.8, 131.6, 136.5, 142.2 and 143.6 (aromatic) and 198.9 (C=O).

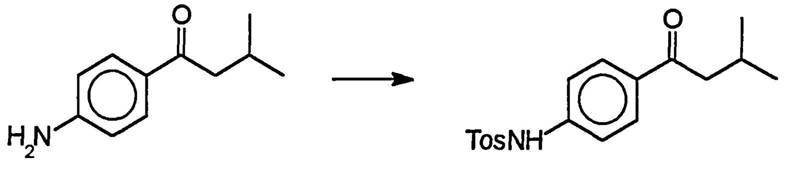
1-(4-*p*-Toluenesulphonamidophenyl)-1-butanone **60**



56 **59**

This compound was prepared from 1-(4-aminophenyl)-1-butanone **56** (10.4g, 64.0mmol) using the method described above for the preparation of **59**. Recrystallisation from methanol gave the title compound as a pale brown crystalline solid (18.5g, 91%) m.p. 191-193°C. (Found M$^+$, 317.1058. C$_{17}$H$_{19}$NO$_3$S requires M, 317.1086); ν_{max} (KBr disk)/cm^{-1} 3233 and 3200 N-H$_{(str)}$, 2979, 2949 and 2886 C-H$_{(str)}$ and 1670 C=O$_{(str)}$; δ_H (250 MHz; DMSO-d^6) 1.05 (3H, t, *J*=7, CH$_2$CH$_3$), 1.75 (2H, sextet, *J*=7, CH$_3$CH$_2$CH$_2$), 2.40 (3H, s, ArCH$_3$), 2.90 (2H, t, *J*=7.3, COCH$_2$), 7.05 (1H, s, N-H), 7.15 (2H, d, *J*=9, aromatic), 7.30 (2H, d, *J*=8, aromatic), 7.75 (2H, d, *J*=8, aromatic) and 7.85 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; DMSO-d^6) 13.6, 17.2 and 20.9 (aliphatic), 117.9, 126.7, 129.5, 129.9, 131.8, 136.5, 142.2 and 143.7 (aromatic) and 198.5 (C=O).

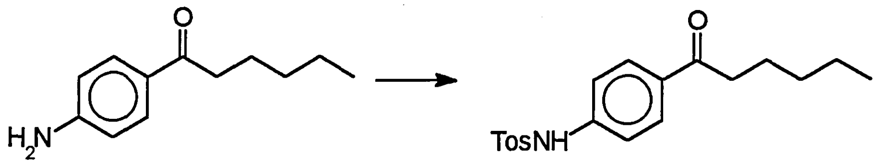
1-(4-*p*-Toluenesulphonamidophenyl)-3-methyl-1-butanone **61**



57 **61**

This compound was prepared from 1-(4-aminophenyl)-3-methyl-1-butanone **57** (11.3g, 64.0mmol) using the method described above for the preparation of **59**. Recrystallisation from methanol gave the title compound as a pale brown crystalline solid (19.9g, 94%) m.p. 164-166°C. (Found M$^+$, 331.1227. C$_{18}$H$_{21}$NO$_3$S requires M, 331.1242); ν_{max} (KBr disk)/cm^{-1} 3234 and 3200 N-H$_{(str)}$, 2979, 2930 and 2874 C-H$_{(str)}$ and 1659 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.95 (6H, d, *J*=7, 2 x (C<u>H</u>$_3$)$_2$CH), 2.25 (1H, m, CH), 2.40 (3H, s, ArCH$_3$), 2.75 (2H, d, *J*=7, CH$_2$), 7.05 (1H, s, N-H), 7.15 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.75 (2H, d, *J*=8, aromatic) and 7.85 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; CDCl$_3$) 21.9, 23.1, 25.5 and 47.6 (aliphatic), 119.2, 127.6, 130.1, 130.2, 133.8, 136.2, 141.4 and 144.8 (aromatic) and 199.4 (C=O).

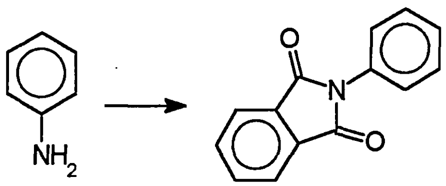
1-(4-*p*-Toluenesulphonamidophenyl)-1-hexanone **62**



58 **62**

This compound was prepared from 1-(4-aminophenyl)-1-hexanone **58** (12.2g, 64.0mmol) using the method described above for the preparation of **59**. Recrystallisation from methanol gave the title compound as a pale brown crystalline solid (19.9g, 90%) m.p. 154-156°C. (Found M$^+$, 345.1399. $C_{19}H_{23}NO_3S$ requires M, 345.1399); ν_{max} (KBr disk)/cm^{-1} 3238 and 3214 N-H$_{(str)}$, 2964, 2939 and 2876 C-H$_{(str)}$ and 1667 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.90 (3H, m, CH$_2$C<u>H</u>$_3$), 1.35 (4H, m, -(CH$_2$)$_2$-), 1.70 (2H, q, *J*=7, COCH$_2$C<u>H</u>$_2$), 2.40 (3H, s, ArCH$_3$), 2.90 (2H, t, *J*=7, COCH$_2$), 7.15 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8), 7.45 (1H, s, N-H), 7.75 (2H, d, *J*=8, aromatic) and 7.85 (2H, d, *J*=7, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.2, 21.9, 22.8, 24.4, 31.8 and 38.7 (aliphatic), 119.3, 127.6, 130.0, 130.2, 133.4, 136.2, 141.4 and 144.7 (aromatic) and 199.8 (C=O).

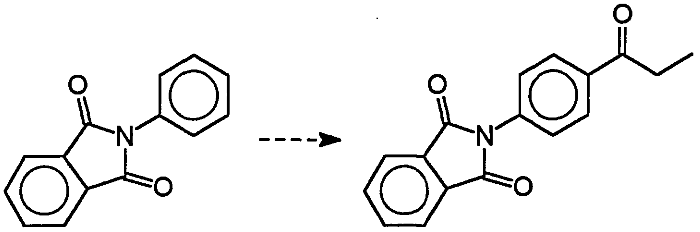
Preparation of *N*-phenyl phthalimide **63**



Aniline **63**

Aniline (10.00g, 108mmol) and phthalic anhydride (16.02g, 108mmol) were dissolved in glacial acetic acid (100ml) and heated at reflux for 36 hours. The reaction was allowed to cool to room temperature before being stirred into saturated aqueous Na_2CO_3 solution (500ml). The precipitated solid was filtered under vacuum and washed with water. The precipitated solid was recrystallised from a mixture of DCM (50ml) and petrol (75ml) to give a grey solid and an orange solution. The solid was filtered off under vacuum to give an orange solution. The solvent from the orange solution was removed under reduced pressure to give an off-white solid. The off-white solid was recrystallised from a minimum of toluene to afford the title compound as a cream coloured solid (20.5g, 85%) m.p. 209-211°C. (Found M^+, 223.0619. $C_{14}H_9NO_2$ requires M, 223.0633); ν_{max} (KBr disk)/cm^{-1} 1734, 1707 imide C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 7.65 (5H, m, aromatic), 8.00 (2H, m, aromatic), 8.10 (2H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 124.1, 126.9, 128.5, 129.5, 132.1 and 134.8 (aromatic) and 167.6 (2 x C=O).

Attempted preparation of 1-(4-phthalimidophenyl)-1-propanone **64**

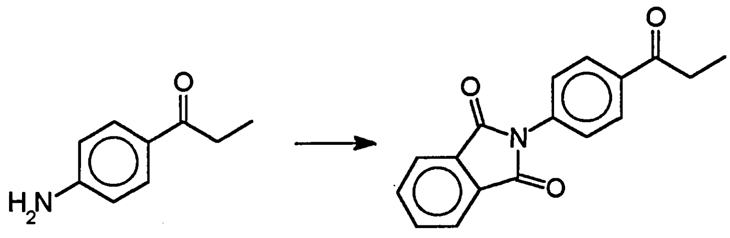


63 **64**

N-Phenylphthalimide 63 (2.00g, 8.98mmol), anhydrous aluminium chloride (3.6g, 27.1mmol) and propionyl chloride (2.49g, 27.0mmol) were dissolved in dry DCM and heated at reflux. Analysis by TLC (2:1 petrol / ethyl acetate) after 24 hours showed only the presence of starting material. Further amounts of anhydrous aluminium chloride (3.6g, 27.1mmol) and propionyl chloride (2.49g, 27.0mmol) were added. A further 48 hours heating at reflux failed to yield any product.

The same procedure as outlined above was repeated except that CS_2 was used as solvent instead of DCM. Identical results were obtained.

1-(4-Phthalimidophenyl)-1-propanone **64**



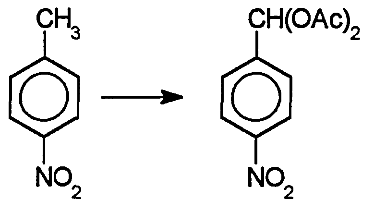
55 **64**

1-(4-Aminophenyl)-1-propanone **55** (0.50g, 3.36mmol) was dissolved in glacial acetic acid (10ml) prior to the addition of phthalic anhydride. After 24 hours at reflux, TLC analysis (2:1 petroleum ether / ethyl acetate) showed that no starting material remained. The product was isolated by pouring into rapidly stirred aqueous $NaHCO_3$ (100ml) from which the product crystallised. Filtration under vacuum and drying afforded the title compound as pale grey needle shaped crystals (0.71g, 75%) m.p. 206-208°C. (Found M^+, 279.0883. $C_{17}H_{13}NO_3$ requires M, 279.0895); ν_{max} (KBr disk)/cm^{-1} 2980 and 2937 C-H$_{(str)}$, 1744 and 1720 imide C=O$_{(str)}$ and 1687 ketone C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.25 (3H, t, *J*=7, CH_3), 3.05 (2H, q, *J*=7, CH_2), 7.65 (2H, d, *J*=9, aromatic), 7.85 (2H, dd, *J*=3 and 5, aromatic), 8.00 (2H, dd, *J*=3 and 5, aromatic) and 8.10 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.5 and 32.2, (aliphatic), 124.3, 126.5, 129.2, 131.9 and 135.0 (aromatic), 167.6 and 189.0 (C=O).

Attempted preparation of 4-nitropropiophenone

Method 1 (Oxidation of 4-nitrotoluene followed by Grignard)

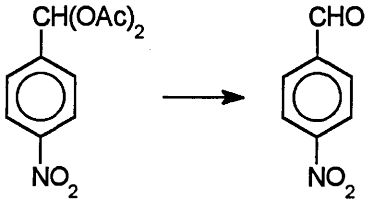
Part I (4-Nitrophenyl diacetate **66**)



65 **66**

4-Nitrotoluene **65** (20.0g, 0.146 mol), acetic anhydride (160ml) and conc. sulphuric acid (32ml) were cooled to 0°C in an ice bath. An ice cold solution of chromium trioxide (40.0g, 0.40 mol) in acetic anhydride (180ml) was added to the reaction at such a rate as to maintain the temperature at less than 10°C. Analysis by TLC (7:3 petrol / ethyl acetate) after 30 minutes showed no starting material. The reaction was poured into stirred crushed ice (600g) and made up to 2 litres with water. The title compound was isolated as a damp pale cream coloured fine crystalline solid by filtration.

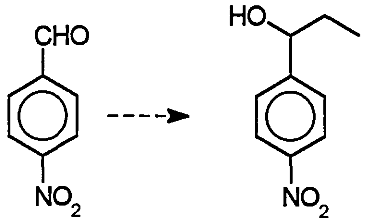
Part II (4-Nitrobenzaldehyde **67**)



66 **67**

The 4-nitrophenyl diacetate **66** was dissolved in ethanol (150ml), water (150ml) and conc. sulphuric acid (10ml) and then heated at reflux for 60 minutes. Analysis of a small sample by TLC (7:3 petrol / ethyl acetate) showed complete conversion of the starting material and so the reaction was allowed to cool to room temperature. Upon cooling needle shaped crystals formed which were filtered off under vacuum and washed with water. The wet solid was dissolved in DCM (2 x 100ml), dried with Na_2SO_4 and the solvent removed under reduced pressure afforded the title compound (16.3g, 74% overall from 4-nitrotoluene **65**).

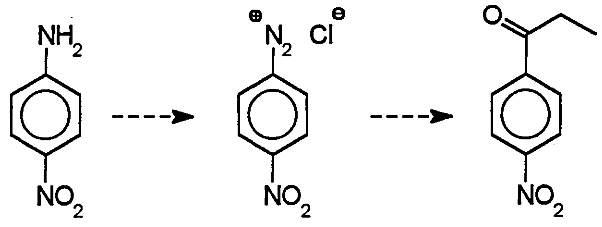
Part III (Attempted preparation of 1-(4-nitrophenyl)-1-propanol **68**)



67 **68**

Bromoethane (5.42g, 49.7mmol) was dissolved in THF (50ml) to which magnesium turnings (1.19g, 49.7mmol) and a crystal of iodine were added. After a vigorous exotherm the reaction mixture was heated at reflux for 30 minutes. 4-Nitrobenzaldehyde **67** (7.50g, 49.7mmol) dissolved in dry THF (100ml) was added at such a rate as to maintain a steady reflux. Upon addition a black discolouration developed throughout the reaction mixture. Analysis by TLC (7:3 petrol / ethyl acetate) showed only one component, the ^{1}H NMR spectrum of which was not consistent with that of the title compound.

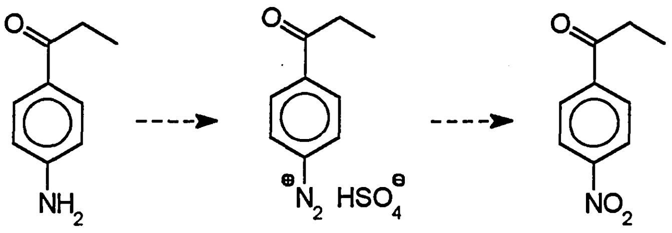
Method 2 (Diazonium from 4-nitroaniline **71**)



71 **72** **69**

Conc. HCl (11ml), water (15ml), ice (20g), 4-nitroaniline **71** (7.0g, 50mmol) and sodium nitrite (3.5g, 51mmol) were stirred at 0°C for 30 minutes. The reaction mixture was neutralised with a solution of sodium acetate (4.4g, 54mmol) in water (7ml). A solution of propanaldoxime (3.0g, 41mmol) and sodium acetate (33.0g, 0.402 mol) in water (36ml) at 10°C was prepared, to which copper sulphate (2.5g, 15.5mmol) and anhydrous sodium sulphite (0.20g, 1.94mmol) were added. The propanaldoxime solution was added to the diazonium solution with stirring over 10 minutes and stirred for a further 60 minutes room temperature. Stirring was stopped and the reaction allowed to stand for 3 hours prior to the addition of conc. HCl to pH 3. The reaction mixture was filtered under vacuum and the liquors refluxed with 2N HCl. Analysis by TLC (4:1 petrol / ethyl acetate) showed numerous products.

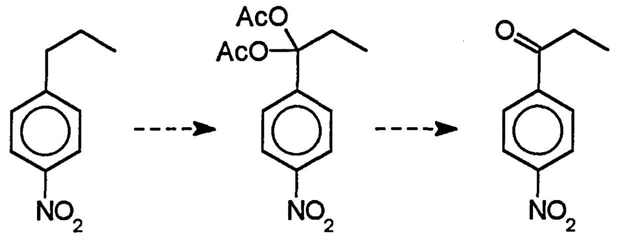
Method 3 (Diazonium from 4-aminopropiophenone **55**)



55 **73** **69**

Sodium nitrite (3.27g, 47mmol) and conc. sulphuric acid (6.5ml) were stirred together (evolution of brown nitrogen dioxide fumes) until a grey solid was produced. A slurry of 4-aminopropiophenone **55** (1.00g, 6.7mmol) in glacial acetic acid (28ml) was prepared and cooled to 0°C before being added to the stirred sodium nitrite / conc. sulphuric acid mixture. Next day analysis by TLC (4:1 petrol / ethyl acetate) showed mainly starting material amongst several products.

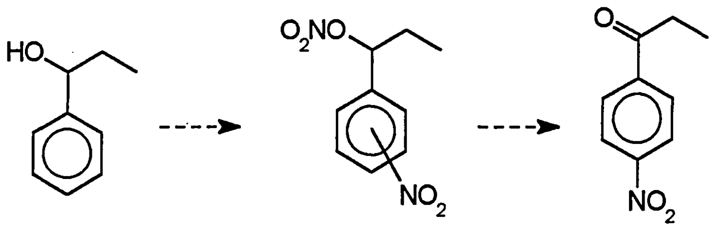
Method 4 Oxidation of 4-nitropropylbenzene



74 **75** **69**

4-Nitropropylbenzene **74** (1.00g, 6.06mmol) was dissolved in acetic anhydride (20ml) and cooled to -7°C in an ice / acetone bath prior to the slow addition of conc. sulphuric acid (2ml). The mixture was allowed to stir for 10 minutes before chromium trioxide (2.8g, 28mmol) dissolved in acetic anhydride (20ml) was added to the reaction mixture at such a rate that the temperature did not exceed 5°C. The reaction mixture was stirred for a further 30 minutes, after which analysis by TLC (4:1 petrol / ethyl acetate) showed that no starting material remained. The reaction was poured into stirred crushed ice (60g) and made up to 100mls with water. The product was extracted with DCM (2 x 30ml), washed with 10% Na_2CO_3 solution (20ml), water (20ml) and dried with Na_2SO_4. Removal of the solvent under reduced pressure afforded a brown liquid (0.6g). Analysis by TLC (4:1 petrol / ethyl acetate) showed two spots which were separated by flash chromatography (4:1 petrol / ethyl acetate). Analysis of each compound by ^1H NMR indicated that neither of which was the required product.

Method 5 (Nitration of 1-phenyl-1-propanol)



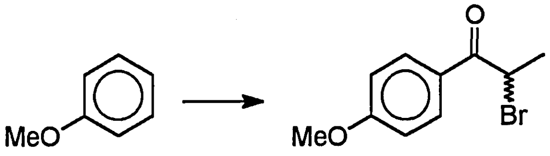
76 **77** **69**

Urea (1.23g, 19.8mmol) was dissolved in 96% nitric acid (27.5ml) by heating to 40°C. The reaction was then cooled to -7°C in an ice / acetone bath before the addition of 1-phenyl-1-propanol (5.00g, 36.8mmol) over 30 minutes. After a further 2 hours stirring analysis by TLC (4:1 petrol / ethyl acetate) showed complete conversion of starting material. The reaction was neutralised with aqueous NaOH, extracted with DCM (2 x 50ml), dried with $MgSO_4$ and the solvent removed under reduced pressure afforded a crude product of indeterminate composition. Several unsuccessful attempts at crystallising out the required product were made.

Racemic bromoketones

Method 1

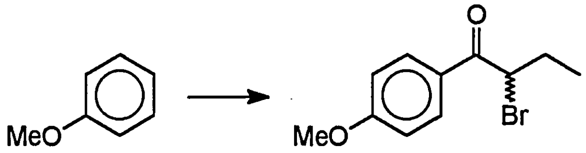
2-Bromo-1-(4-methoxyphenyl)-1-propanone 78



20 **78**

This compound was prepared from anisole **20** (5.00g, 46.3mmol) using the method described above for the preparation of **21** but using 2-bromopropanoyl bromide (13.0g, 60.2mmol), DCM (125ml) and anhydrous aluminium chloride (8.65g, 64.8mmol). The title compound was isolated as a white crystalline solid (6.95g, 62%) m.p. 65-66°C (lit., 66-67°C).[79] (Found M^+, 241.9921. $C_{10}H_{11}O_2{}^{79}Br$ requires M, 241.9942); ν_{max} (KBr disk)/cm^{-1} 3016, 2994 and 2934 $C\text{-}H_{(str)}$ and 1668 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.85 (3H, d, J=7, CH_3), 3.85 (3H, s, OCH_3), 5.25 (1H, q, J=7, CHBr), 6.95 (2H, d, J=9, aromatic) and 8.00 (2H, d, J=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.6 (aliphatic), 41.9 (CHBr), 55.8 (MeO), 114.3, 127.1, 131.6 and 164.3 (aromatic) and 192.3 (C=O).

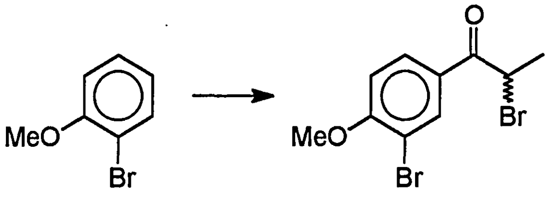
2-Bromo-1-(4-methoxyphenyl)-1-butanone 79



20 **79**

This compound was prepared from anisole **20** (5.00g, 46.3mmol) using the method described above for the preparation of **21** but using 2-bromobutanoyl bromide (13.8g, 60.2mmol), DCM (125ml) and anhydrous aluminium chloride (8.65g, 64.8mmol). The title compound was isolated as an off-white crystalline solid (10.0g, 84%) m.p. 51-53°C. (Found M$^+$, 256.0115. $C_{11}H_{13}O_2{}^{79}Br$ requires M, 256.0099); ν_{max} (KBr disk)/cm^{-1} 3019, 2990, 2971 and 2934 C-H$_{(str)}$ and 1671 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.10 (3H, t, *J*=7, CH$_3$), 2.20 (2H, m, CH$_2$), 3.90 (3H, s, OCH$_3$), 5.05 (1H, t, *J*=7, CHBr), 7.00 (2H, d, *J*=8, aromatic) and 8.05 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.4 and 28.6 (aliphatic), 49.1 (CHBr), 55.8 (MeO), 113.3, 129.1, 131.6 and 164.3 (aromatic) and 192.3 (C=O).

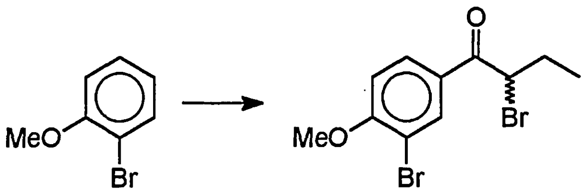
2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone **80**



39 **80**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using 2-bromopropionyl bromide (7.50g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mmol). The title compound was isolated as a white crystalline solid (6.53g, 76%) m.p. 86-88°C. (Found M$^+$, 319.9068. $C_{10}H_{10}O_2{}^{79}Br_2$ requires M, 319.9048); ν_{max} (KBr disk)/cm^{-1} 3019, 2991 and 2933 C-H$_{(str)}$ and 1669 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.85 (3H, d, *J*=7, CH$_3$), 3.95 (3H, s, OCH$_3$), 5.20 (1H, q, *J*=7, CHBr), 6.95 (1H, d, *J*=9, aromatic), 7.95 (H, dd, *J*=9, 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 20.4 (aliphatic), 41.5 (CHBr), 56.9 (MeO), 111.5, 112.5, 128.2, 130.5, 134.7 and 160.4 (aromatic) and 191.3 (C=O).

2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81**

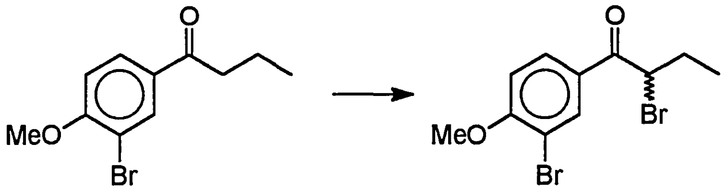


39 **81**

This compound was prepared from 2-bromoanisole **39** (5.00g, 26.7mmol) using the method described above for the preparation of **21** but using 2-bromobutanoyl bromide (7.98g, 34.7mmol), DCM (75ml) and anhydrous aluminium chloride (4.99g, 37.4mmol). The title compound was isolated as a white crystalline solid (6.46g, 72%) m.p. 86-88°C. (Found M$^+$, 333.9231. $C_{11}H_{12}O_2{}^{79}Br_2$ requires M, 333.9204); ν_{max} (KBr disk)/ cm^{-1} 3016, 2992 and 2939 C-H$_{(str)}$ and 1667 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.10 (3H, t, *J*=7, CH$_3$), 2.20 (2H, m, CH$_2$), 4.00 (3H, s, OCH$_3$), 5.00 (1H, t, *J*=8, CHBr), 6.95 (1H, d, *J*=9, aromatic), 7.95 (1H, dd, *J*=9 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.5 and 27.2 (aliphatic), 49.1 (CHBr), 56.9 (MeO), 111.6, 112.5, 128.7, 130.5, 134.6 and 160.4 (aromatic) and 191.2 (C=O).

Method 2

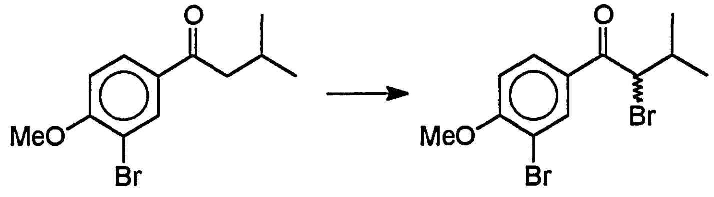
2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81**



40 **81**

1-(3-Bromo-4-methoxyphenyl)-1-butanone **40** (9.55g, 37.3mmol) was dissolved in dry chloroform (50ml) and dry ethyl acetate (50ml), through which nitrogen was bubbled through for 5 minutes prior to the addition of copper(II) bromide (16.64g, 74.6mmol). The reaction mixture was refluxed for 4 hours until TLC analysis (4:1 petrol / ethyl acetate) showed no starting material (no reaction with 2,4 dinitrophenylhydrazine spray). The reaction mixture was allowed to cool to room temperature before the copper salts were removed by filtration and washed with chloroform (100ml). The combined organic washes and filtrates were concentrated under reduced pressure, re-dissolved in ether (100ml), washed with water (50ml), saturated aqueous $NaHCO_3$ (2 x 50ml) and finally saturated sodium chloride solution (50ml). Drying (Na_2SO_4) and the solvent removed under reduced pressure to yield the title compound as a straw coloured solid (11.5g, 92%) m.p. 86-88°C. (Found M^+, 333.9231. $C_{11}H_{12}O_2{}^{79}Br_2$ requires M, 333.9204); ν_{max} (KBr disk)/ cm^{-1} 3016, 2992 and 2939 $C\text{-}H_{(str)}$ and 1669 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.10 (3H, t, *J*=7, CH_3), 2.20 (2H, m, CH_2), 4.00 (3H, s, OCH_3), 5.00 (1H, t, *J*=8, CHBr), 6.95 (1H, d, *J*=9, aromatic), 7.95 (1H, dd, *J*=9 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.5 and 27.2 (aliphatic), 49.1 (CHBr), 56.9 (MeO), 111.6, 112.5, 128.7, 130.5, 134.6 and 160.4 (aromatic) and 191.2 (C=O).

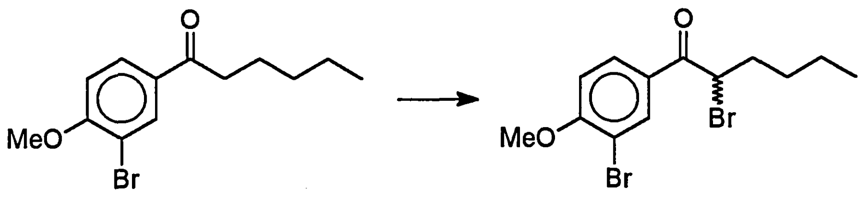
2-Bromo-1-(3-bromo-4-methoxyphenyl)-3-methyl-1-butanone **83**



41 **83**

This compound was prepared from 1-(3-bromo-4-methoxyphenyl)-3-methyl-1-butanone **41** (10.1g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid (10.7g, 82%). (Found M^+, 347.9392. $C_{12}H_{14}O_2{}^{79}Br_2$ requires M, 347.9361); ν_{max} (film)/cm^{-1} 3016, 2997 and 2930 $C\text{-}H_{(str)}$ and 1669 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (6H, d, *J*=7, $(C\underline{H}_3)_2CH$), 2.45 (1H, m, $(CH_3)_2C\underline{H}$), 4.00 (3H, s, $OC\underline{H}_3$), 4.85 (1H, d, *J*=7, $C\underline{H}Br$), 6.95 (1H, d, *J*=8, aromatic), 7.90 (H, dd, *J*=8, 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 21.0, 32.8 (aliphatic), 56.9 (MeO), 59.1 (CHBr), 112.6, 114.9, 130.3, 130.5, 134.6 and 161.4 (aromatic) and 191.2 (C=O).

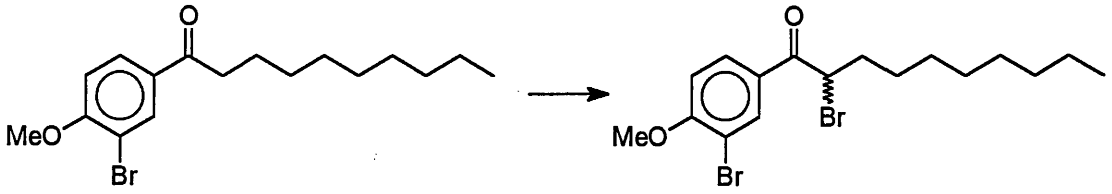
2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-hexanone **84**



42 **84**

This compound was prepared from 1-(3-bromo-4-methoxyphenyl)-1-hexanone **42** (10.6g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid which solidified (11.8g, 87%) m.p. 50-52°C. (Found M$^+$, 361.9501. $C_{13}H_{16}O_2{}^{79}Br_2$ requires M, 361.9517); ν_{max} (KBr disk)/cm^{-1} 3019, 2996 and 2932 C-H$_{(str)}$ and 1665 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.95 (3H, t, *J*=7, CH$_3$), 1.40 (4H, m, CH$_3$-(C<u>H</u>$_2$)$_2$-), 2.15 (2H, m, CHBrC<u>H</u>$_2$), 4.00 (3H, s, OCH$_3$), 5.05 (1H, t, *J*=7, CHBr), 6.95 (1H, d, *J*=8, aromatic), 7.95 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.2, 22.6, 30.0 and 33.5 (aliphatic), 47.3 (CHBr), 56.9 (MeO), 111.6, 112.5, 128.7, 130.5, 134.7 and 160.4 (aromatic) and 191.3 (C=O).

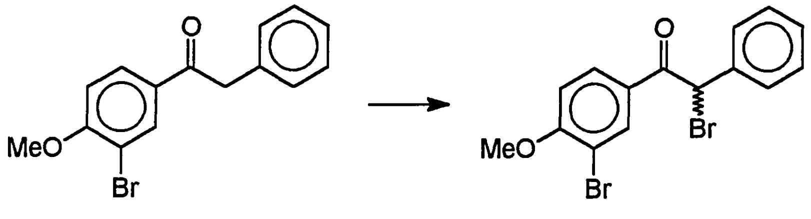
2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-decanone **85**



43 **85**

This compound was prepared from 1-(3-bromo-4-methoxyphenyl)-1-decanone **43** (12.7g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid which solidified (13.5g, 86%) m.p. 52-54°C. (Found M$^+$, 418.0129. $C_{17}H_{24}O_2{}^{79}Br_2$ requires M, 418.0143); ν_{max} (KBr disk)/cm^{-1} 3012, 2989 and 2935 C-H$_{(str)}$ and 1666 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.90 (3H, t, *J*=7, CH$_3$), 1.20- 1.55 (12H, m, CH$_3$-(C<u>H</u>$_2$)$_6$-), 2.15 (2H, m, CHBrC<u>H</u>$_2$), 4.00 (3H, s, OCH$_3$), 5.05 (1H, t, *J*=7, CHBr), 6.95 (1H, d, *J*=8, aromatic), 8.00 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.4, 22.9, 28.0, 29.0, 29.5, 29.6, 32.1 and 32.8, (aliphatic), 47.6 (CHBr), 56.5 (MeO), 111.3, 112.5, 128.8, 130.5, 134.6 and 160.4 (aromatic) and 191.5 (C=O).

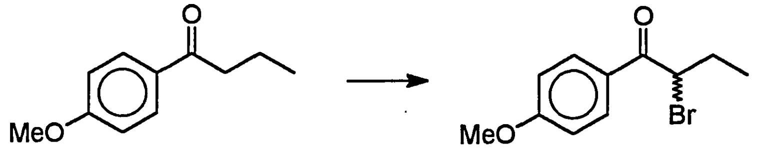
2-Bromo-1-(3-bromo-4-methoxyphenyl)-2-phenyl-1-ethanone **86**



44 **86**

This compound was prepared from 1-(3-bromo-4-methoxyphenyl)-2-phenyl-1-ethanone **44** (10.9g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid which solidified (11.2g, 81%) m.p. 116-118°C. (Found M$^+$, 369.9228. $C_{14}H_{12}O_2{}^{79}Br_2$ requires M, 369.9204); ν_{max} (KBr disk)/cm^{-1} 3009, 2992 and 2938 C-H$_{(str)}$ and 1669 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 3.95 (3H, s, OCH$_3$), 6.30 (1H, s, CHBr), 6.90 (1H, d, *J*=8, aromatic), 7.40 (3H, m, aromatic), 7.50 (2H, m, aromatic), 7.95 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic). δ_C (62.88 MHz; CDCl$_3$) 51.0 (CHBr), 56.9 (MeO), 111.6, 112.6, 128.2, 129.4, 130.8, 134.9, 136.2 and 160.4 (aromatic) and 189.1 (C=O).

2-Bromo-1-(4-methoxyphenyl)-1-butanone **79**

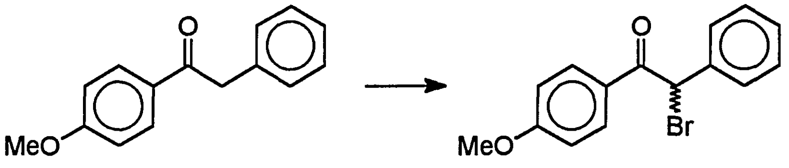


22 **79**

This compound was prepared from 1-(4-methoxyphenyl)-1-butanone **22** (6.64g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid which solidified (7.67g, 80%) m.p. 42-44°C. (Found M$^+$, 256.0115. $C_{11}H_{13}O_2{}^{79}Br$ requires M, 256.0099); ν_{max} (KBr disk)/cm^{-1} 3019, 2990, 2971 and 2934 C-H$_{(str)}$ and 1676 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.10 (3H, t, *J*=7, CH$_3$), 2.20 (2H, m, CH$_2$), 3.90 (3H, s, OCH$_3$), 5.05 (1H, t, *J*=7, CHBr), 7.00 (2H, d, *J*=8, aromatic) and 8.05 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.4 and

28.6 (aliphatic), 49.1 (CHBr), 55.8 (MeO), 113.3, 129.1, 131.6 and 164.3 (aromatic) and 192.3 (C=O).

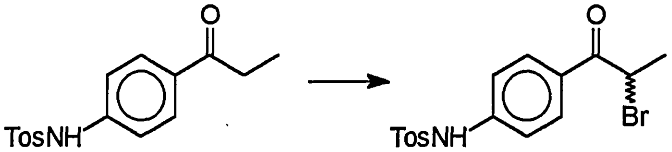
2-Bromo-1-(4-methoxyphenyl)-2-phenyl-1-ethanone **87**



26 **87**

This compound was prepared from 1-(4-methoxyphenyl)-2-phenyl-1-ethanone **26** (8.43g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. The title compound was isolated as a brown viscous liquid which solidified (8.96g, 82%) m.p. 136-138°C. (Found M$^+$, 292.0082. $C_{14}H_{13}O_2{}^{79}Br$ requires M, 292.0099); ν_{max} (KBr disk)/cm^{-1} 3020, 2985, 2971 and 2934 C-H$_{(str)}$ and 1669 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 3.80 (3H, s, OCH$_3$), 5.80 (1H, t, *J*=7, CHBr), 7.10 (2H, d, *J*=7, aromatic), 7.40 (5H, m, aromatic) and 8.20 (2H, d, *J*=7, aromatic); δ_C (62.88 MHz; CDCl$_3$) 50.6 (aliphatic), 55.1 (MeO), 113.9, 127.5, 129.0, 130.2, 130.5, 132.0 and 163.9 (aromatic) and 187.6 (C=O).

2-Bromo-1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **88**

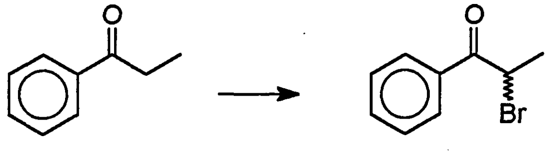


59 **88**

This compound was prepared from 1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **59** (11.3g, 37.3mmol) using the 'method 2' described above for the preparation of **81**. Purification by flash chromatography (2:1 petrol / ethyl acetate) afforded the title compound as a pale brown crystalline solid (8.96g, 54%) m.p. 182-184°C. (Found M$^+$, 381.0016. $C_{16}H_{16}NO_3SBr$ requires M, 381.0034); ν_{max} (KBr disk)/cm^{-1} 3230 and 3201 N-H$_{(str)}$, 2975, 2936 and 2872 C-H$_{(str)}$ and 1671 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 2.15 (3H, d, *J*=7, CHBrC$\underline{H}_3$), 2.70 (3H, s, ArCH$_3$), 5.90 (1H, q, *J*=7, CHBr), 7.65 (2H, d, *J*=8, aromatic), 7.75 (2H, d, *J*=8, aromatic), 8.15 (2H, d, *J*=8, aromatic), 8.25 (2H, d, *J*=8, aromatic) and 9.95 (1H, s, N-H); δ_C (62.88 MHz; CDCl$_3$) 20.3 and 21.3 (aliphatic), 42.7

(CHBr), 118.9, 127.9, 130.1, 130.6, 131.3, 137.6, 143.7 and 144.9 (aromatic) and 192.5 (C=O).

2-Bromo-1-phenyl-1-propanone **89**

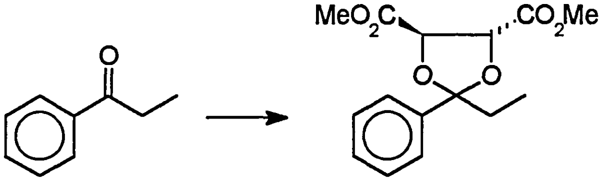


82 **89**

This compound was prepared from propiophenone **82** (5.00g, 37.3mmol) using 'method 2' described above for the preparation of **81**. Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (7.04g, 94%). (Found M$^+$, 199.9852. $C_8H_9O^{79}Br$ requires M, 199.9839); ν_{max} (film)/cm^{-1} 2984, 2972 and 2930 C-H$_{(str)}$ and 1675 C=O$_{(str)}$. δ_H (250 MHz; $CDCl_3$) 1.90 (3H, d, *J*=8, CH_3), 5.30 (1H, q, *J*=8, CHBr), 7.45 (2H, m, aromatic), 7.55 (1H, m, aromatic) and 8.00 (2H, m, aromatic). δ_C (62.88 MHz; $CDCl_3$) 20.2 (aliphatic), 62.8 (CHBr), 129.1, 129.5, 133.1 and 136.2 (aromatic) and 198.5 (C=O).

Preparation of acetals with dimethyl tartrate

Dimethyl (4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **90**

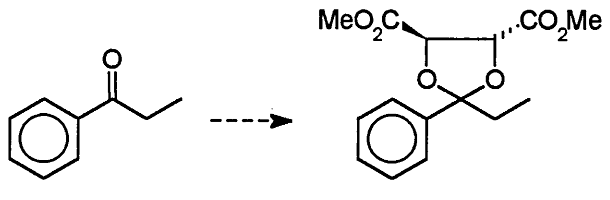


82 **90**

Propiophenone **82** (20.2g, 151mmol), dimethyl tartrate (29.5g, 165mmol) and trimethyl orthoformate (17.5g, 165mmol) were heated to ~50°C prior to the addition of methanesulphonic acid (0.77g, 8.0mmol). The reaction was then heated at 95°C for 5 hours during which time methanol and methyl formate were distilled off. The reaction mixture was allowed to cool before being poured into vigorously stirred saturated Na_2CO_3 solution (150ml) and extracted with DCM (2 x 100ml). The combined organic extracts were then washed with water (100ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a colourless liquid

(44.4g, 99%). (Found M$^+$, 294.1089. $C_{15}H_{18}O_6$ requires M, 294.1103); ν_{max} (film)/cm^{-1} 3009, 2973 and 2950 C-H$_{(str)}$, 1775 and 1742 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=8, CH_3), 1.95 (2H, q, *J*=8, CH_2), 3.50 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=7, 2 x CH-O), 7.25 (3H, m, aromatic) and 7.45 (2H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.2 and 34.1 (aliphatic), 35.8 and 36.0 (2 x OMe), 75.3 and 76.7 (2 x CH-O), 113.9 (O-C-O), 125.7, 128.3, 128.4 and 142.3 (aromatic), 167.7 and 168.2 (2 x C=O).

Dimethyl (4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **90**

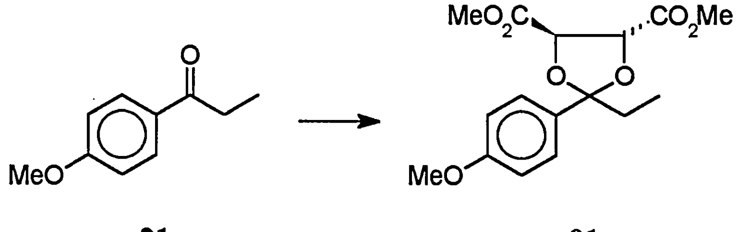


82 **90**

Propiophenone **28** (8.17g, 61.0mmol) and dimethyl tartrate (23.95g, 122mmol) in toluene (350ml) were heated to 100°C. Methanesulphonic acid (2.34g, 24.4mmol) was added and the reaction heated at reflux under a Dean Stark trap for 15 hours. A sample was analysed by ^{1}H NMR which showed a very low conversion of propiophenone **28** to product, furthermore the ^{1}H NMR indicated significant amounts of polymerisation / transesterification had taken place and therefore the experiment was abandoned at this stage.

4-Methoxyphenyl substituted alkyl acetals

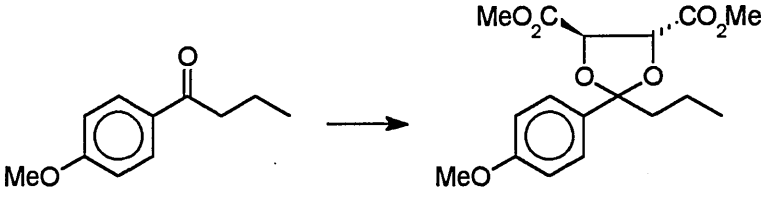
Dimethyl (4*R*,5*R*)-2-ethyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate (30)



21 **91**

1-(4-Methoxyphenyl)-1-propanone **21** (20.5g, 125mmol), dimethyl tartrate (23.3g, 131mmol) and trimethyl orthoformate (26.5g, 250mmol) were heated to ~50°C prior to addition of methanesulphonic acid (0.77g, 8.0mmol). The reaction was then heated at 95°C for 5 days, during which time methanol and methyl formate were distilled off. The reaction mixture was allowed to cool before being poured into vigorously stirred saturated Na_2CO_3 (150ml) solution and extracted with DCM (2 x 100ml). The combined organic extracts were then washed with water (100ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product as a pale brown liquid. Purification by vacuum distillation afforded the title compound as a colourless liquid (33.2g, 82%). (Found M^+, 324.1181. $C_{16}H_{20}O_7$ requires M, 324.1209); ν_{max} (film)/cm^{-1} 3005, 2982, 2959 and 2843 C-H$_{(str)}$, 1769 and 1736 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.10 (3H, t, *J*=7, CH_3), 2.15 (2H, q, *J*=7, CH_2), 3.75, 3.95 and 4.00 (3 x 3H, 3 x s, 3 x OCH_3), 4.95 and 5.00 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.00 (2H, d, *J*=9, aromatic) and 7.55 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 7.9 and 34.0 (aliphatic), 52.7 and 53.1 (2 x OMe [ester]), 55.5 (MeO [aryl]), 76.5 and 77.6 (2 x CH-O), 113.5 (O-C-O), 115.5, 127.7, 133.0 and 159.9 (aromatic) and 169.8 (2 x C=O).

<u>Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate (**92**)</u>

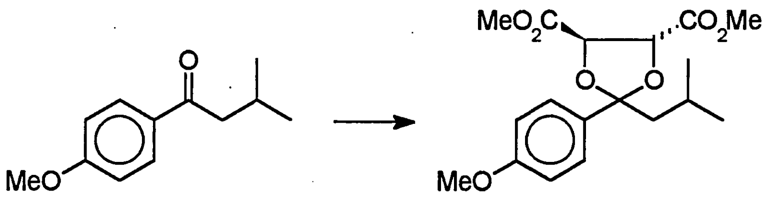


22 **92**

This compound was prepared from 1-(4-methoxyphenyl)-1-butanone **22** (22.3g, 125mmol) using the method described above for the preparation of **91**. Purification by vacuum distillation afforded the title compound as a colourless liquid (29.2g, 69%). (Found M^+, 338.1342. $C_{17}H_{22}O_7$ requires M, 338.1366); ν_{max} (film)/cm^{-1} 3006, 2979, 2944 and 2856 C-H$_{(str)}$, 1766 and 1736 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, CH_3), 1.35 (2H, m, $CH_3C\underline{H_2}$), 1.90 (2H, m, $CH_3CH_2C\underline{H_2}$), 3.55, 3.75 and 3.80 (3 x 3H, 3 x s, 3 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.80 (2H, d, *J*=9, aromatic) and 7.35 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.2, 16.9 and 43.1

(aliphatic), 52.5 and 52.9 (2 x OMe [ester]), 55.3 (MeO [aryl]), 76.4 and 77.6 (2 x CH-O), 113.4 (O-C-O), 115.0, 127.6, 133.2 and 159.9 (aromatic) and 169.7 (2 x C=O).

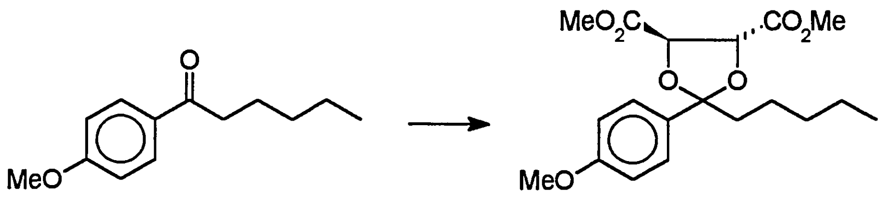
Dimethyl (4*R*,5*R*)-2-isobutyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate (**93**)



23 **93**

This compound was prepared from 1-(4-methoxyphenyl)-3-methyl-1-butanone **23** (24.0g, 125mmol) using the method described above for the preparation of **91**. Purification by vacuum distillation afforded the title compound as a colourless liquid (29.9g, 68%) Found M$^+$, 352.1516. $C_{18}H_{24}O_7$ requires M, 352.1522); ν_{max} (film)/cm^{-1} 3003, 2982, 2954 and 2849 C-H$_{(str)}$, 1769 and 1738 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (6H, 2 x d, *J*=7, $(CH_3)_2CH$), 1.70 (1H, m, CH_2CH), 1.85 (2H, d, *J*=6, CH_2), 3.50, 3.75 and 3.80 (3 x 3H, 3 x s, 3 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.80 (2H, d, *J*=9, aromatic) and 7.35 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 24.1, 25.4 and 49.2 (aliphatic), 52.6 and 53.0 (2 x OMe [ester]), 55.5 (MeO [aryl]), 76.5 and 77.9 (2 x CH-O), 113.5 (O-C-O), 115.5, 127.6, 133.4 and 159.8 (aromatic), 169.8 and 169.9 (2 x C=O).

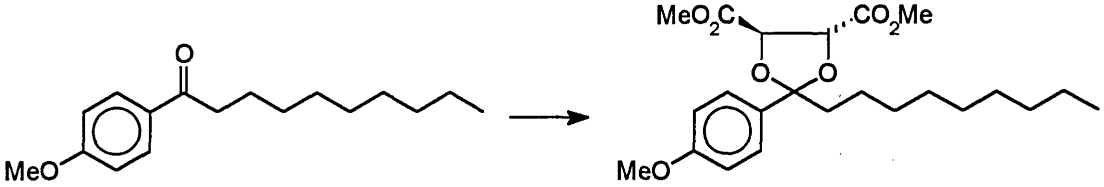
Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate (**94**)



24 **94**

This compound was prepared from 1-(4-methoxyphenyl)-1-hexanone **24** (25.8g, 125mmol) using the method described above for the preparation of **91**. Purification by vacuum distillation afforded the title compound as a colourless liquid (31.6g, 69%). (Found M$^+$, 366.1691. $C_{19}H_{26}O_7$ requires M, 366.1679); ν_{max} (film)/cm^{-1} 3004, 2979, 2949 and 2841 C-H$_{(str)}$, 1766 and 1741 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.80 (3H, t, *J*=7, CH$_3$), 1.20-1.45 (6H, m, CH$_3$-(C<u>H</u>$_2$)$_3$-), 1.95 (2H, m, CH$_3$-(CH$_2$)$_3$-C<u>H</u>$_2$), 3.55, 3.75 and 3.80 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.80 (2H, d, *J*=9, aromatic) and 7.35 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.3, 22.8, 23.3, 31.9 and 41.0 (aliphatic), 52.6 and 53.0 (2 x OMe [ester]), 55.5 (MeO [aryl]), 76.5 and 77.8 (2 x CH-O), 113.5 (O-C-O), 115.2, 159.9, 133.2 and 127.6 (aromatic) and 169.8 (2 x C=O).

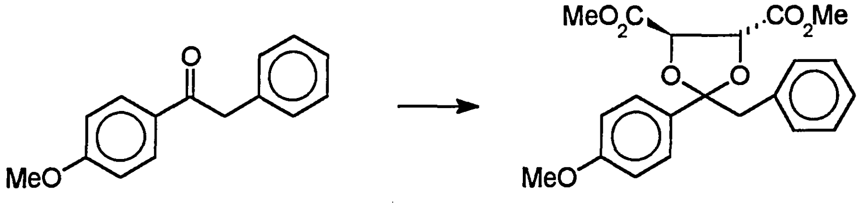
<u>Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-nonyl-1,3-dioxolane-4,5-dicarboxylate (95)</u>



25 **95**

This compound was prepared from 1-(4-methoxyphenyl)-1-decanone **25** (32.8g, 125mmol) using the method described above for the preparation of **91**. Purification by vacuum distillation afforded the title compound as a colourless liquid (44.3g, 84%). (Found M$^+$- CH$_3$O, 391.2118. $C_{23}H_{34}O_7$ requires M- CH$_3$O, 391.2121); ν_{max} (film)/cm^{-1} 3003, 2972, 2954 and 2841 C-H$_{(str)}$, 1771 and 1741 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.85 (3H, t, *J*=7, CH$_3$), 1.15-1.40 (14H, m, CH$_3$-(C<u>H</u>$_2$)$_7$-), 1.95 (2H, m, CH$_3$-(CH$_2$)$_7$-C<u>H</u>$_2$), 3.55, 3.75 and 3.85 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.75 and 4.85 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.80 (2H, d, *J*=9, aromatic) and 7.35 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.4, 22.9, 23.6, 29.5, 29.8, 32.1 and 41.1 (aliphatic), 52.6 and 52.9 (2 x OMe [ester]), 55.4 (MeO [aryl]), 76.4 (2 x CH-O), 113.5 (O-C-O), 115.2, 127.6, 133.2 and 159.9 (aromatic) and 169.8 (2 x C=O).

Dimethyl (4*R*,5*R*)-2-benzyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **96**

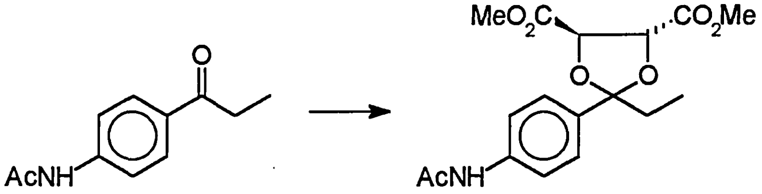


26 **96**

This compound was prepared from 1-(4-methoxyphenyl)-2-phenyl-1-ethanone **26** (28.3g, 125mmol) using the method described above for the preparation of **91**. Purification by crystallisation from methanol afforded the title compound as a colourless waxy solid (39.1g, 81%) m.p. 65-66°C. (Found M^+, 386.1370. $C_{21}H_{22}O_7$ requires M, 386.1366; ν_{max} (film)/cm^{-1} 3010, 3001, 2975 and 2843 C-$H_{(str)}$, 1768 and 1739 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 3.30 (2H, s, CH_2), 3.55, 3.80 and 3.85 (3 x 3H, 3 x s, 3 x OCH_3), 4.65 and 4.85 (2 x 1H, 2 x d, *J*=5, 2 x CH-O), 6.80 (2H, d, *J*=8, aromatic) and 7.10-7.30 (7H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 47.6 (aliphatic), 52.7 and 53.0 (2 x OMe [ester]), 55.4 (MeO [aryl]), 76.7 and 77.7 (2 x CH-O), 113.3 (O-C-O), 114.5, 126.9, 127.9, 131.3, 132.9, 135.3 and 159.9 (aromatic) and 169.7 (2 x C=O).

4-Acetamidophenyl substituted acetals

Dimethyl (4*R*,5*R*)-2-ethyl-2-(4-acetamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **98**

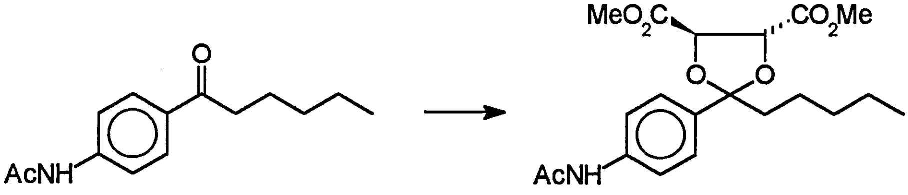


46 **98**

This compound was prepared from 1-(4-acetamidophenyl)-1-propanone **46** (5.00g, 26.2mmol) using the method described above for the preparation of **91**. Purification by flash chromatography (2:1 petroleum ether / ethyl acetate) afforded the title compound as a brown viscous colourless oil (4.23g, 46%). (Found M^+, 351.1324. $C_{17}H_{21}NO_7$ requires M, 351.1318; ν_{max} (film)/cm^{-1} 3108 and 3061 N-$H_{(str)}$, 2994, 2973 and 2936 C-

$H_{(str)}$, 1742 and 1732 ester $C=O_{(str)}$ and 1666 amide $C=O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=8, CH_3), 1.90 (2H, q, *J*=8, CH_2), 2.10 (3H, s, $COCH_3$), 3.55 and 3.80 (2 x 3H, 2 x s, 2 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=5, 2 x CH-O), 7.35 (2H, d, *J*=8, aromatic), 7.45 (2H, d, *J*=8, aromatic) and 8.00 (1H, s, N-H); δ_C (62.88 MHz; $CDCl_3$) 15.2, 24.3 and 33.9 (aliphatic), 52.8 and 53.2 (2 x OMe), 76.3 (2 x CH-O), 115.3 (O-C-O), 119.3, 126.6, 136.3 and 138.8 (aromatic) and 169.8 (3 x C=O).

Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate **99**

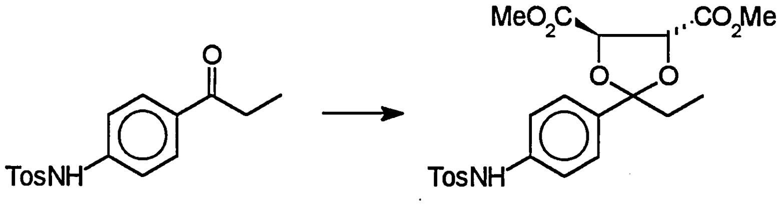


49 **99**

This compound was prepared from 1-(4-acetamidophenyl)-1-hexanone **49** (6.11g, 26.2mmol) using the method described above for the preparation of **91**. Purification by flash chromatography (2:1 petroleum ether / ethyl acetate) afforded the title compound as a brown viscous colourless oil (4.53g, 44%). (Found M^+, 393.1789. $C_{20}H_{27}NO_7$ requires M, 393.1788); ν_{max} (film)/cm^{-1} 3101 and 3053 $N-H_{(str)}$, 2999, 2969 and 2929 $C-H_{(str)}$, 1742 and 1732 ester $C=O_{(str)}$ and 1666 amide $C=O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.80 (3H, t, *J*=7, CH_3), 1.20-1.40 (6H, m, CH_3-$(\underline{CH_2})_3$-), 1.90 (2H, m, CH_3-$(CH_2)_3$-$\underline{CH_2}$), 2.10 (3H, s, $COCH_3$), 3.55 and 3.80 (2 x 3H, 2 x s, 2 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.35 (2H, d, *J*=8, aromatic), 7.45 (2H, d, *J*=8, aromatic) and 7.90 (1H, s, N-H); δ_C (62.88 MHz; $CDCl_3$) 13.9, 22.5, 23.0, 24.1, 31.7 and 40.6 (aliphatic), 52.3 and 52.7 (2 x OMe), 76.3 (2 x CH-O), 114.8 (O-C-O), 119.3, 126.6, 136.3 and 138.8 (aromatic) and 169.6 (3 x C=O).

p-Toluenesulphonamidophenyl substituted acetals

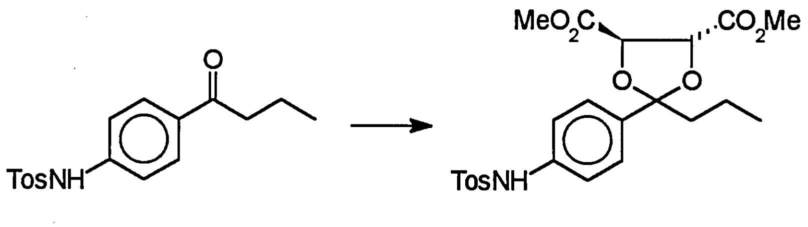
Dimethyl (4*R*,5*R*)-2-ethyl-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **100**



59 **100**

This compound was prepared from 1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **59** (10.0g, 33.0mmol) using the method described above for the preparation of **91**. Purification by (re)crystallisation from dry methanol afforded the title compound as a pale brown crystalline solid (12.7g, 83%) m.p. 136-138°C. (Found M$^+$, 463.1323. $C_{22}H_{25}NO_8S$ requires M, 463.1301); ν_{max} (KBr disk)/cm^{-1} 3288 N-H$_{(str)}$, 2994, 2986, 2930 and 2885 C-H$_{(str)}$ and 1742 and 1732 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.85 (3H, t, *J*=7, CH$_2$C<u>H</u>$_3$), 1.95 (2H, q, *J*=7, CH$_3$C<u>H$_2$</u>) 2.40 (3H, s, ArCH$_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH$_3$), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.05 (2H, d, *J*=9, aromatic), 7.15 (1H, s, N-H), 7.25 (2H, d, *J*=8, aromatic), 7.35 (2H, d, *J*=8, aromatic) and 7.65 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl$_3$) 7.9, 21.9 and 33.9 (aliphatic), 52.6 and 53.2 (2 x OMe), 76.5 and 77.7 (2 x CH-O), 115.1 (O-C-O), 120.9, 127.6, 130.0, 136.4, 137.0, 137.8 and 144.3 (aromatic) and 169.7 (2 x C=O).

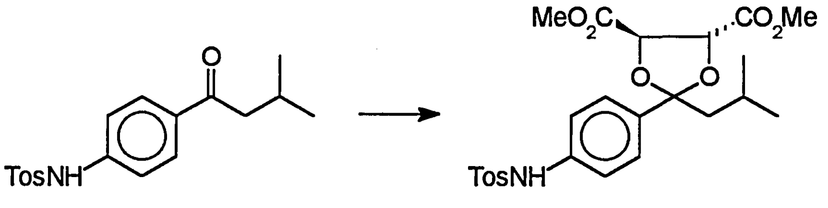
Dimethyl (4*R*,5*R*)-2-(4-*p*-toluenesulphonamidophenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate **101**



60 **101**

This compound was prepared from 1-(4-*p*-toluenesulphonamidophenyl)-1-butanone **60** (10.5g, 33.0mmol) using the method described above for the preparation of **91**. Purification by (re)crystallisation from dry methanol afforded the title compound as a white crystalline solid (14.2g, 90%) m.p. 115-116°C. (Found M$^+$, 477.1440. $C_{23}H_{27}NO_8S$ requires M, 477.1458); ν_{max} (KBr disk)/cm^{-1} 3285 N-H$_{(str)}$, 2999, 2986, 2931 and 2884 C-H$_{(str)}$ and 1745 and 1730 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, $CH_2C\underline{H_3}$), 1.30 (2H, m, *J*=8, $CH_3C\underline{H_2}$) 1.90 (2H, m, $CH_3CH_2C\underline{H_2}$) 2.40 (3H, s, $ArCH_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (1H, s, N-H), 7.00 (2H, d, *J*=6, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (2H, d, *J*=9, aromatic) and 7.65 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.2, 16.9, 21.8 and 42.9 (aliphatic), 52.6 and 53.2, (2 x OMe), 76.4 (2 x CH-O), 114.3 (O-C-O), 144.8, 120.9, 127.6, 129.9 and 136.9 (aromatic) and 169.6 (2 x C=O).

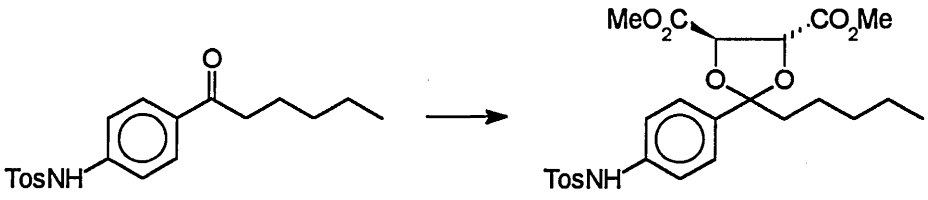
Dimethyl (4*R*,5*R*)-2-isobutyl-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **102**



61 **102**

This compound was prepared from 1-(4-*p*-toluenesulphonamidophenyl)-3-methyl-1-butanone **61** (10.9g, 33.0mmol) using the method described above for the preparation of **91**. Purification by (re)crystallisation from dry methanol afforded the title compound as a white crystalline solid (14.3g, 88%) m.p. 105-107°C. (Found M$^+$, 491.1618. $C_{24}H_{29}NO_8S$ requires M, 491.1614); ν_{max} (KBr disk)/cm^{-1} 3281 N-H$_{(str)}$, 2997, 2984 and 2931 C-H$_{(str)}$ and 1741 and 1732 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (6H, 2 x d, *J*=7, $(C\underline{H_3})_2CH$), 1.65 (1H, m, $CH_2C\underline{H}$), 1.85 (2H, d, *J*=6, CH_2), 2.35 (3H, s, $ArCH_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (1H, s, N-H), 7.00 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (2H, d, *J*=9, aromatic) and 7.65 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; $CDCl_3$) 21.8, 24.0 and 49.0 (aliphatic), 52.5 and 53.1 (2 x OMe), 76.4 and 77.3 (2 x CH-O), 115.1 (O-C-O), 120.7, 127.4, 127.6, 129.9, 136.4, 137.3, 137.9 and 144.2 (aromatic) and 169.8 (2 x C=O).

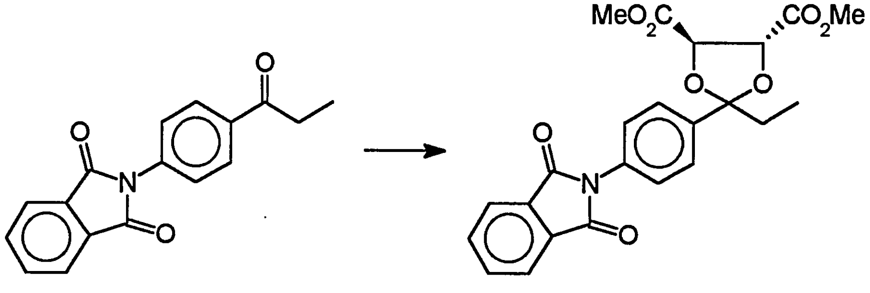
Dimethyl (4*R*,5*R*)-2-(4-*p*-toluenesulphonamidophenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate **103**



62 **103**

This compound was prepared from 1-(4-*p*-toluenesulphonamidophenyl)-1-hexanone **62** (11.6g, 33.0mmol) using the method described above for the preparation of **91**. Purification by (re)crystallisation from dry methanol afforded the title compound as a pale brown solid (11.7g, 70%) m.p. 108-110°C. (Found M$^+$, 505.1769. $C_{25}H_{31}NO_8S$ requires M, 505.1770); ν_{max} (film)/cm^{-1} 3288 N-H$_{(str)}$, 2989, 2976 and 2872 C-H$_{(str)}$, 1739 and 1725 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, CH_3), 1.25 (6H, m, CH_3-($C\underline{H}_2)_3$-), 1.90 (2H, m, CH_3-($CH_2)_3$-$C\underline{H}_2$), 2.40 (3H, s, $ArCH_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.75 and 4.80 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.90 (1H, s, N-H), 7.05 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (2H, d, *J*=9, aromatic) and 7.65 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; $CDCl_3$) 13.7, 21.9, 28.0, 32.8, 37.2 and 37.5 (aliphatic), 52.6 and 53.2 (2 x OMe), 76.4 (2 x CH-O), 114.8 (O-C-O), 120.9, 127.6, 129.9, 136.9 and 144.3 (aromatic) and 169.6 (2 x C=O).

Attempted synthesis of dimethyl (4*R*,5*R*)-2-(4-phthalimidophenyl)-2-ethyl-1,3-dioxolane-4,5-dicarboxylate **174**

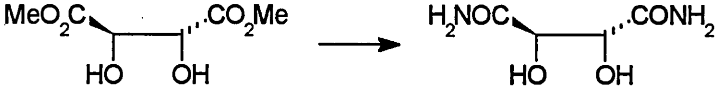


64 **174**

We attempted to prepare dimethyl (4*R*,5*R*)-2-(4-phthalimidophenyl)-2-ethyl-1,3-dioxolane-4,5-dicarboxylate **174** from 1-(4-phthalimidophenyl)-1-propanone **64** (1.00g, 3.6mmol), dimethyl tartrate (0.67g 3.8mmol), trimethyl orthoformate (0.76g, 7.2mmol) and methanesulphonic acid (1 drop) using the same method as for the preparation of **91**. Unfortunately we were unable to separate the crude title compound from the starting material by flash chromatography (2:1 petrol / ethyl acetate). Further attempts at preparation or purification were unsuccessful.

Other chiral auxiliaries

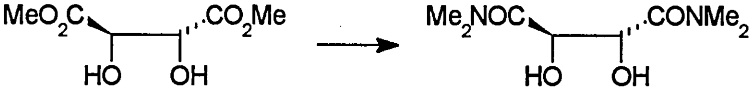
(2*R*,3*R*)-2,3-Dihydroxybutanediamide **104**



Dimethyl tartrate **104**

Dimethyl tartrate (10.0g, 56.2mmol) was dissolved in .880 ammonia (100ml) and stirred for 24 hours at room temperature after which time TLC analysis (2:1 petrol : ethyl acetate) indicated complete conversion of the starting material. Removal of water, methanol and excess ammonia under reduced pressure gave the title compound as a white crystalline solid (8.25g, 99%) m.p. 193-195°C (lit., 195-196°C).[79] (Found M$^+$, 148.0471. $C_4H_8N_2O_4$ requires M, 148.0484); ν_{max} (KBr disk)/cm^{-1} 3456-3434 N-H$_{(str)}$, 3223 O-H$_{(str)}$, 2945-2908 C-H$_{(str)}$ and 1676 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 4.15 (2H, s, 2 x CH-O), 5.55 (2H, bs, 2 x OH), 7.25 (2H, s, NH_2), 7.30 (2H, s, NH_2); δ_C (62.88 MHz; $CDCl_3$) 75.8 (2 x CH-O) and 178.4 (2 x C=O).

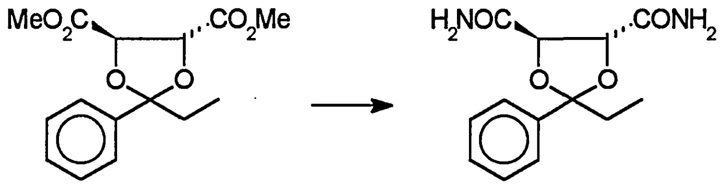
N,N,N',N'-Tetramethyl-(2*R*,3*R*)-2,3-dihydroxybutanediamide **105**



Dimethyl tartrate **105**

Dimethylamine was distilled and dried over KOH from a 40% w / v aqueous solution (100ml) and collected at -78°C. This was then added to a stirred solution of dimethyl tartrate (20.0g, 0.112 mol) in anhydrous methanol (100ml) which had been cooled to -78°C. The reaction was allowed to warm to -5°C and maintained at this temperature for 3 days after which time analysis by TLC (2:1 petrol / ethyl acetate) indicated complete conversion of the starting di-ester. The reaction mixture was allowed to warm to room temperature, then a small sample was removed for crystallisation on a watch glass. The remaining solution was concentrated under reduced pressure before it was seeded. The crystallisation was allowed to proceed at 0°C for an hour before isolation of the title compound as a white crystalline solid (14.5g, 64%) m.p. 187-189°C.[42] (Found M$^+$, 204.1130. $C_8H_{16}N_2O_4$ requires M, 204.1110); ν_{max} (KBr disk)/cm^{-1} 3395 O-H$_{(str)}$, 2996, and 2938 C-H$_{(str)}$ and 1645 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 2.95 (6H, s, 2 x CH_3), 3.05 (6H, s, 2 x CH_3), 4.20 (2H, s, 2 x OH), 4.60 (2H, s, 2 x CH-O); δ_C (62.88 MHz; $CDCl_3$) 36.4 (2 x *N*-methyl), 37.2 (2 x *N*-methyl), 70.0 (2 x CH-O) and 171.1 (2 x C=O).

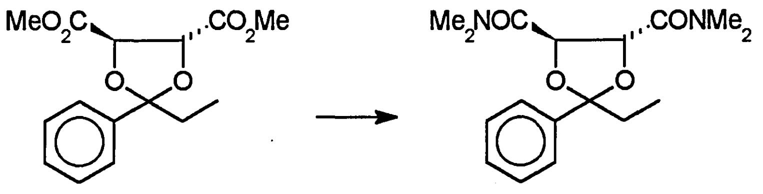
(4*R*,5*R*)-2-Ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxamide **106**



90 **106**

Dimethyl (4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **90** (5.0g, 17.0mmol) was dissolved in .880 ammonia (50ml) and stirred for 24 hours at room temperature after which time analysis by TLC (1:1 petrol / ethyl acetate) showed no starting material. Removal of water, methanol and excess ammonia under reduced pressure afforded the title compound as a white crystalline solid (4.5g, 99%) m.p. 101-103°C. (Found M$^+$, 264.1127. $C_{13}H_{16}N_2O_4$ requires M, 264.1110); ν_{max} (film)/cm^{-1} 3465 N-H$_{(str)}$, 2974, 2937, 2909 and 2878 C-H$_{(str)}$ and 1704-1672 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J*=7, $CH_2C\underline{H_3}$), 2.00 (2H, q, *J*=7, $C\underline{H_2}CH_3$), 4.50 and 4.60 (2 x 1H, 2 x d, *J*=8, 2 x CH-O), 6.50, 6.70, 6.80 and 7.15 (4 x 2H, 4 x s, 4 x NH_2), 7.20-7.50 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.1 and 34.2 (aliphatic), 78.2 (2 x CH-O), 114.8 (O-C-O), 125.7, 128.8 and 141.1 (aromatic), 171.9 and 172.9 (2 x C=O).

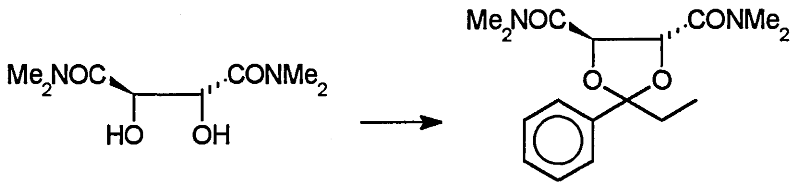
N,N,N',N'-Tetramethyl-(4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxamide **107**



90 **107**

Dimethylamine was distilled and dried over KOH from a 40% w / v aqueous solution (20ml) and collected at -78°C. This was added to a stirred solution of dimethyl (4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **90** (5.00g, 17.0mmol) in dry methanol (13ml) which had been cooled to -78°C. The reaction was allowed to warm to -5°C and maintained at this temperature for 3 days after which time analysis by TLC (2:1 petrol / ethyl acetate) indicated complete conversion of the starting material. Removal of methanol and excess dimethylamine gave the title compound as a white crystalline solid (5.4g, 99%) m.p. 67-70°C. (Found M$^+$, 320.1752. $C_{17}H_{24}N_2O_4$ requires M, 320.1736); ν_{max} (KBr disk)/cm^{-1} 2966-2880 C-H$_{(str)}$ and 1646-1662 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.85 (3H, t, *J*=7, CH$_2$CH$_3$), 1.90 (2H, q, *J*=7, CH$_2$CH$_3$), 2.80, 2.95, 3.15 and 3.25 (4 x 3H, 4 x s, 4 x CH$_3$), 5.10 and 5.20 (2 x 1H, 2 x d, *J*=7, CH-O), 7.20-7.40 (5H, m, aromatic); δ_C (62.88 MHz; CDCl$_3$) 8.1 and 34.1 (aliphatic), 35.7, 35.9 and 37.3 (4 x *N*-methyl), 75.3 and 76.7 (2 x CH-O), 113.9 (O-C-O), 125.7, 128.2, 128.4 and 142.3 (aromatic), 167.6 and 168.2 (2 x C=O).

N,N,N',N'-Tetramethyl-(4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxamide **107**

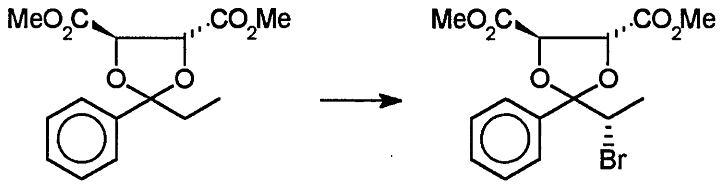


105 **107**

This compound was prepared from propiophenone (5.00, 37.5mmol) and *N,N,N',N'*-tetramethyl-(2*R*,3*R*)-2,3-dihydroxybutanediamide **105** (10.00g, 49.0mmol), using the method described above for the preparation of **91**. Purification by flash chromatography (ethyl acetate) afforded the title compound as a pale yellow solid (8.8g, 74%) m.p. 67-70°C. (Found M$^+$, 320.1752. $C_{17}H_{24}N_2O_4$ requires M, 320.1736); ν_{max} (KBr disk)/cm^{-1} 2966-2880 C-H$_{(str)}$ and 1646-1662 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, CH_2CH_3), 1.90 (2H, q, *J*=7, CH_2CH_3), 2.80, 2.95, 3.15 and 3.25 (4 x 3H, 4 x s, 4 x CH_3), 5.10 and 5.20 (2 x 1H, 2 x d, *J*=7, CH-O), 7.20-7.40 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 8.1 and 34.1 (aliphatic), 35.7, 35.9 and 37.3 (4 x *N*-methyl), 75.3 and 76.7 (2 x CH-O), 113.9 (O-C-O), 125.7, 128.2, 128.4 and 142.3 (aromatic), 167.6 and 168.2 (2 x C=O).

Bromination of dimethyl tartrate acetals

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate 108

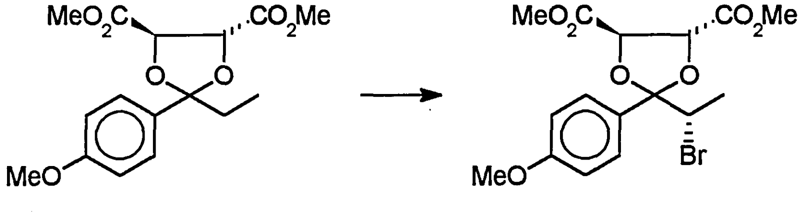


90 **108**

Dimethyl (4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **90** (5.00g, 17.0mmol) was dissolved in dry CCl_4 (40ml) prior to the addition of hydrogen chloride saturated dry CCl_4 (5ml). The reaction was maintained at -6°C in an ice / acetone bath during the dropwise addition of bromine (2.85g, 17.6mmol) in CCl_4 (10ml). When analysis by TLC (4:1 petrol / ethyl acetate) showed no starting material (2,4-dinitrophenylhydrazine spray), the reaction was worked up by slow addition to DCM (50ml) slurried anhydrous potassium carbonate (10g). The slurry was stirred for 10 minutes before water (50ml) was slowly added to give a two phase system, from which the lower organic layer containing the title compound was separated and the aqueous layer re-extracted with DCM (2 x 50ml). The combined organic extracts were then washed with water (50ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a colourless / straw coloured viscous liquid (4.69, 74%, (*S*):(*R*) 12:1). (Found M$^+$, 372.0208. $C_{15}H_{17}O_6{}^{79}Br$ requires M, 372.0209); ν_{max} (film)/cm^{-1} 3001, 2975, 2951 and 2843 C-H$_{(str)}$, 1768 and 1739 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.65 (3H, d, *J*=7, CH_3), 3.55 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.40 (1H, q, *J*=7, CHBr), 4.85 and 5.00 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.35 (3H, m, aromatic) and 7.55 (2H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.8 (aliphatic), 52.8, 52.9 and 55.3 (CHBr and 2 x OMe), 77.3 and 78.2 (2 x CH-O), 113.5 (O-C-O), 127.3, 128.0, 129.4 and 137.4 (aromatic), 168.7 and 169.0 (2 x C=O).

4-Methoxyphenyl substituted bromoacetals

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **109**

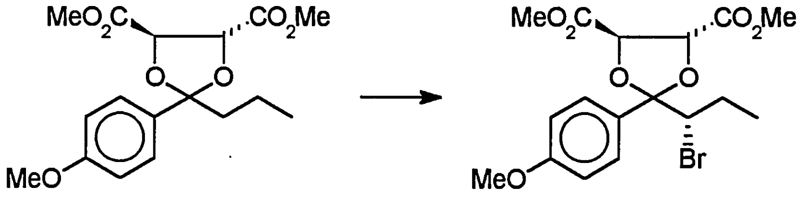


91 **109**

The dimethyl (4*R*,5*R*)-2-ethyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **91** (20.0g, 61.7mmol) was dissolved in CCl_4 (100ml) prior to the addition of hydrogen chloride saturated dry CCl_4 (50ml). The reaction was maintained at -6°C in a ice / acetone bath during the addition of bromine (9.8g, 61.0mmol) in CCl_4 (190ml) over 2 hours whilst vigorously stirred. When analysis by TLC (4:1 petrol / ethyl acetate) showed no starting material (2,4 dinitrophenylhydrazine spray), the reaction was worked up by slow addition to DCM (150ml) slurried anhydrous potassium carbonate (20g). The slurry was stirred for 10 minutes before water (100ml) was added to give a two phase which was separated, the aqueous layer was re-extraction with DCM (2 x 100ml). The combined organic extracts were then washed with water (100ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a colourless / straw coloured viscous liquid (24.1g, 97%, (*S*):(*R*) 19:1). (Found M^+, 402.0346. $C_{16}H_{19}O_7{}^{79}Br$ requires M, 402.0314); ν_{max} (film)/cm^{-1} 3002, 2976, 2952 and 2849 $C\text{-}H_{(str)}$, 1766 and 1739 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.60 (3H, d, *J*=7, CH_3), 3.55, 3.80 and 3.85 (3 x 3H, 3 x s, 3 x OCH_3), 4.35 (1H, q, *J*=7, CHBr), 4.85 and 4.90 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (2H, d, *J*=9, aromatic) and 7.45 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.9 (aliphatic), 52.8 and 53.2 (CHBr and 2 x OMe [ester]), 55.5

(MeO [aryl]), 77.3 and 78.2 (2 x CH-O), 113.4 (O-C-O), 113.6, 128.8, 129.3 and 160.5 (aromatic), 169.2 and 168.9 (2 x C=O).

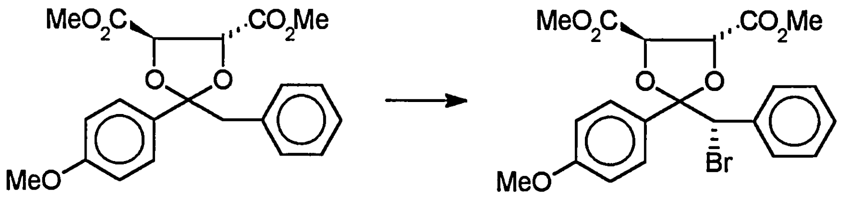
Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **110**



92 **110**

This compound was prepared from dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate **92** (20.9g, 61.7mmol) using the method described above for the preparation of **109**. The title compound was isolated as a colourless viscous oil (23.4g, 91%, (*S*):(*R*) 19:1). (Found M^+, 416.0486. $C_{17}H_{21}O_7{}^{79}Br$ requires M, 416.0471); ν_{max} (film)/cm^{-1} 3015, 2992, 2961 and 2855 $C\text{-}H_{(str)}$, 1772 and 1746 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, *J*=7, CH_3), 1.60 (1H, m, 0.5 x $C\underline{H_2}CH_3$), 1.95 (1H, m, 0.5 x $C\underline{H_2}CH_3$), 3.55, 3.80 and 3.85 (3 x 3H, 3 x s, 3 x $OC\underline{H_3}$), 4.15 (1H, dd, *J*=11 and 2, $C\underline{H}Br$), 4.85 and 4.90 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (2H, d, *J*=9, aromatic) and 7.45 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.9 and 26.4 (aliphatic), 52.8 and 53.2 (2 x OMe [ester]), 55.5 (MeO [aryl]), 62.7 (CHBr), 77.3 (2 x CH-O), 113.5 (O-C-O), 113.6, 128.8, 129.7 and 160.4 (aromatic), 168.9 and 169.2 (2 x C=O).

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromo-1-phenylmethyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **111**

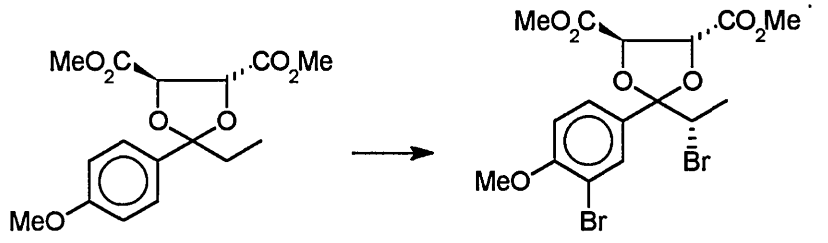


96 **111**

This compound was prepared from dimethyl (4*R*,5*R*)-2-benzyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **96** (23.8g, 61.7mmol) using the method described above for the preparation of **109**. The title compound was isolated as a colourless viscous oil (26.1g, 91%, (*S*):(*R*) 12:1). (Found M$^+$, 464.0458. $C_{21}H_{21}O_7{}^{79}Br$ requires M, 464.0471); ν_{max} (film)/cm^{-1} 3012, 2989, 2962 and 2842 C-H$_{(str)}$, 1767 and 1735 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 3.70, 3.80 and 3.85 (3 x 3H, 3 x s, 3 x OCH_3), 4.65 and 4.85 (2 x 1H, 2 x d, *J*=5, 2 x CH-O), 6.70 (1H, s, CHBr), 6.80 (2H, d, *J*=8, aromatic) and 7.10-7.30 (7H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 52.8 and 53.2 (CHBr and 2 x OMe [ester]), 55.5 (MeO [aryl]), 77.3 and 78.2 (2 x CH-O), 113.6 (O-C-O), 116.8, 126.6, 127.0, 127.4, 127.5, 134.1, 139.5 and 157.2 (aromatic), 169.2 and 168.9 (2 x C=O).

3-Bromo-4-methoxyphenyl substituted bromoacetals

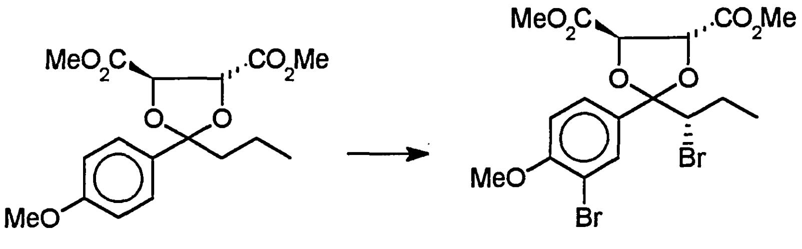
Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 112



91 **112**

The dimethyl (4*R*,5*R*)-2-ethyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **91** (177.1g, 0.546mol) was dissolved in CCl_4 (1100ml) prior to the addition of a small portion hydrogen chloride saturated dry CCl_4 (5ml). The reaction was maintained at -6°C during the dropwise addition of bromine (179.17g, 1.12mol) in CCl_4 (900ml) over 2 hours. After the addition the reaction was allowed to warm to room temperature. When analysis by TLC (4:1 petrol / ethyl acetate) showed no starting material (2,4 dinitrophenylhydrazine spray), the reaction was worked up by slow addition to DCM (400ml) slurried anhydrous potassium carbonate (100g). The slurry was stirred for 30 minutes before water (750ml) was slowly added to give a two phase system from which the lower organic layer was separated and the aqueous layer re-extracted with DCM (2 x 300ml). The combined organic extracts were then washed with water (500ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a colourless viscous liquid which solidified upon standing (236.5g, 90%, (*S*):(*R*) 19:1) m.p. 80-82°C. (Found M$^+$, 479.9432. $C_{16}H_{18}O_7{}^{79}Br_2$ requires M, 479.9419); ν_{max} (KBr disk)/cm^{-1} 3007, 2982, 2955 and 2845 C-H$_{(str)}$, 1769 and 1740 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.75 (3H, d, *J*=7, CH$_3$), 3.75, 4.00 and 4.05 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.45 (1H, q, *J*=7, CHBr), 4.95 and 5.05 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.00 (1H, d, *J*=9, aromatic), 7.60 (1H, dd, *J*=9 and 2, aromatic) and 7.85 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 20.8 (aliphatic), 52.7, 53.0 and 53.3 (CHBr and 2 x OMe [ester]), 56.6 (MeO [aryl]), 77.2 and 78.4 (2 x CH-O), 111.2 (aromatic), 112.9 (O-C-O), 128.2, 130.8, 132.5, 132.6 and 156.7 (aromatic), 169.1 and 168.7 (2 x C=O).

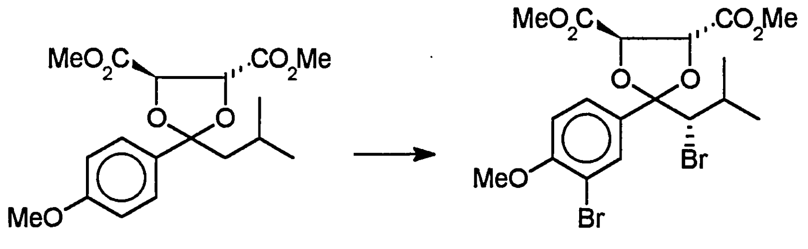
Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromopropyl]-1,3-dioxolane-4,5-dicarboxylate **113**



92 **113**

This compound was prepared from dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate **92** (84.5g, 0.25mmol) using the method described above for the preparation of **112** using CCl$_4$ (500ml), hydrogen chloride saturated dry CCl$_4$ (2ml) and bromine (82.0g, 0.512mol) in CCl$_4$ (400ml). The title compound was isolated as a colourless viscous oil (112.6g, 91%, (*S*):(*R*) 19:1). (Found M$^+$, 493.9589. $C_{17}H_{20}O_7{}^{79}Br_2$ requires M, 493.9576); ν_{max} (film)/cm^{-1} 3000, 2975 and 2949 C-H$_{(str)}$, 1765 and 1742 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.05 (3H, t, *J*=7, CH$_2$CH$_3$), 1.60 (1H, m, 0.5 x C$\underline{H}_2$CH$_3$), 2.00 (1H, m, 0.5 x C$\underline{H}_2$CH$_3$), 3.65, 3.85 and 3.95 (3 x 3H, 3 x s, 3 x OC$\underline{H}_3$), 4.10 (1H, dd, *J*=2 and 11, CHBr), 4.80 and 4.90 (2 x 1H, 2 x d, *J*=5, 2 x CH-O), 6.85 (1H, d, *J*=8, aromatic), 7.45 (1H, dd, *J*=8 and 2, aromatic) and 7.70 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.9 and 26.3 (aliphatic), 52.9 and 53.3 (2 x OMe [ester]), 56.5 (MeO [aryl]), 62.2 (CHBr), 77.3 (2 x CH-O), 111.2 (aromatic), 112.9 (O-C-O), 128.1, 131.2, 132.4 and 156.6 (aromatic), 169.0 and 168.7 (2 x C=O).

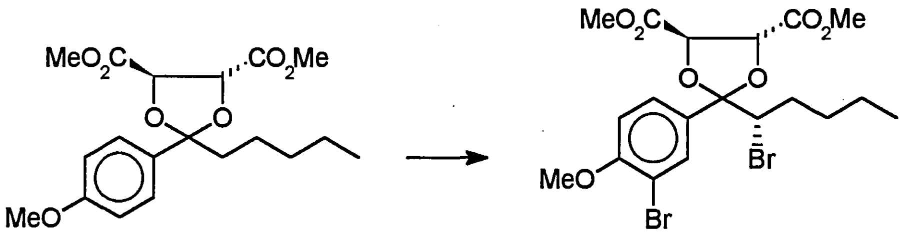
Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromo-2-methylpropyl]-1,3-dioxolane-4,5-dicarboxylate **114**



93 **114**

This compound was prepared from dimethyl (4*R*,5*R*)-2-isobutyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **93** (88.0g, 0.25mol) using the method described for the preparation of **112**. The title compound was isolated as a colourless viscous oil (120.9g, 95%, (*S*):(*R*) 12:1). (Found M$^+$, 507.9750. $C_{18}H_{22}O_7{}^{79}Br_2$ requires 507.9732); ν_{max} (film)/cm^{-1} 3001, 2972, 2945 and 2835 C-H$_{(str)}$, 1766 and 1737 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.95 (6H, 2 x d, *J*=7, (C<u>H</u>$_3$)$_2$CH), 1.80 (1H, m, (CH$_3$)$_2$C<u>H</u>), 3.60, 3.80 and 3.90 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.25 (1H, d, *J*=2, CHBr), 4.85 and 4.95 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (1H, d, *J*=9, aromatic), 7.45 (1H, dd, *J*=9 and 2, aromatic) and 7.70 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 17.9, 23.5 and 29.2 (aliphatic), 53.3 (2 x OMe [ester]), 56.6 (MeO [aryl]), 68.2 (CHBr), 79.1 (2 x CH-O), 111.6 (aromatic), 113.3 (O-C-O), 127.4, 130.4, 131.9, 134.7 and 156.7 (aromatic) and 168.9 (2 x C=O).

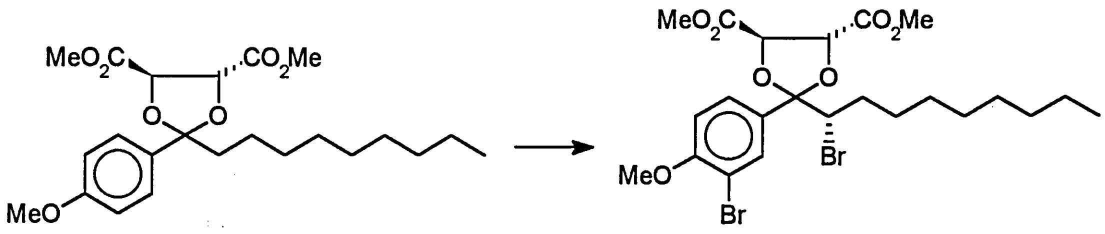
Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromopentyl]-1,3-dioxolane-4,5-dicarboxylate **115**



94 **115**

This compound was prepared from dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate **94** (91.5g, 250mmol) using the method described above for the preparation of **112**. The title compound was isolated as a colourless viscous oil (119.0g, 91%, (*S*):(*R*) 12:1). (Found M$^+$, 521.9862. $C_{19}H_{24}O_7{}^{79}Br_2$ requires M, 521.9889); ν_{max} (film)/cm^{-1} 3000, 2974, 2945, and 2832 C-H$_{(str)}$, 1762 and 1731 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.85 (3H, t, *J*=7, CH$_3$), 1.30 (2H, m, $CH_3C\underline{H}_2$), 1.60 (3H, m, $CH_3CH_2C\underline{H}_2$ and 0.5 x $C\underline{H}_2CHBr$), 1.90 (1H, m, 0.5 x $C\underline{H}_2CHBr$) 3.65, 3.85 and 3.95 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.20 (1H, dd, *J*=2 and 11, CHBr), 4.85 and 4.95 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.85 (1H, d, *J*=9, aromatic), 7.50 (1H, dd, *J*=9 and 2, aromatic) and 7.75 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.2, 22.2, 30.1 and 32.6 (aliphatic), 53.3 (2 x OMe [ester]), 56.6 (MeO [aryl]), 60.1 (CHBr), 79.1 (2 x CH-O), 111.2 (aromatic), 113.0 (O-C-O), 128.3, 131.2, 132.6 and 156.6 (aromatic) and 168.8 (2 x C=O).

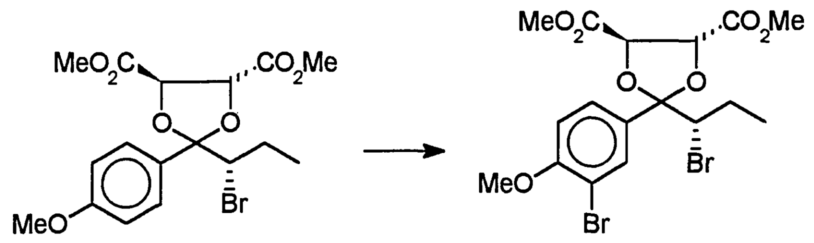
Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromononyl]-1,3-dioxolane-4,5-dicarboxylate **116**



95 **116**

This compound was prepared from dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-nonyl-1,3-dioxolane-4,5-dicarboxylate **95** (105.5g, 0.25mol) using the method described above for the preparation of **112**. The title compound was isolated as a colourless viscous oil (141.8g, 98%, (*S*):(*R*) 10:1). (Found M$^+$, 578.0511. $C_{23}H_{32}O_7{}^{79}Br_2$ requires M, 578.0515); ν_{max} (film)/cm^{-1} 3001, 2974, 2955 and 2839 C-H$_{(str)}$, 1764 and 1736 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.85 (3H, t, *J*=6, CH$_3$), 1.25 (10H, m, $CH_3\text{-}(C\underline{H}_2)_5\text{-}$), 1.65 (2H, m, $C\underline{H}_2CH_2CHBr$), 1.85 (2H, m, $C\underline{H}_2CHBr$) 3.65, 3.85 and 3.90 (3 x 3H, 3 x s, 3 x OCH$_3$), 4.20 (1H, dd, *J*=2 and 11, CHBr), 4.85 and 4.90 (2 x 1H, 2 x d, *J*=7, 2 x CH-O), 6.85 (1H, d, *J*=9, aromatic), 7.45 (1H, dd, *J*=9, 2, aromatic) and 7.70 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; CDCl$_3$) 14.1, 22.7, 24.6, 26.3, 29.4, 29.7, 31.8 and 35.3 (aliphatic), 53.3 (2 x OMe [ester]), 56.6 (MeO [aryl]), 60.1 (CHBr), 79.1 (2 x CH-O), 111.2 (aromatic), 113.0 (O-C-O), 128.3, 131.2, 132.6 and 156.6 (aromatic) and 168.8 (2 x C=O).

Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromopropyl]-1,3-dioxolane-4,5-dicarboxylate **113**

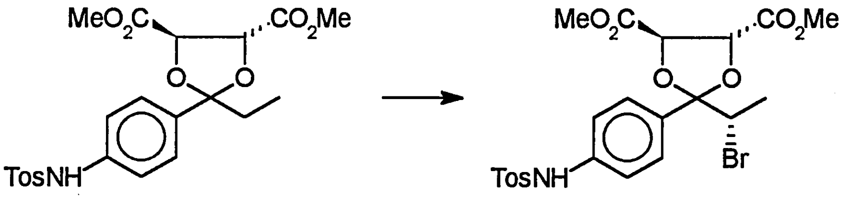


110 **113**

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **110** [(*S*):(*R*) 19:1](1.5g, 3.60mmol) was stirred in CCl_4 (10ml) at room temperature prior to the addition of bromine (0.575g, 3.60mmol). When analysis by ^1H NMR showed complete conversion of the starting material the reaction was worked up by slow addition to DCM (20ml) slurried anhydrous potassium carbonate (5g). The slurry was stirred for 30 minutes before water (25ml) was slowly added to give a two phase system from which the lower organic layer was separated and the aqueous layer re-extracted with DCM (2 x 15ml). The combined organic extracts were then washed with water (20ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a colourless viscous liquid (1.62g. 91%, (*S*):(*R*) 19:1). (Found M^+, 493.9589. $C_{17}H_{20}O_7{}^{79}Br_2$ requires M, 493.9576); ν_{max} (film)/cm^{-1} 3000, 2975, 2949, $C\text{-}H_{(str)}$, 1765 and 1742 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, t, *J*=7, CH_2CH_3), 1.60 (1H, m, 0.5 x $C\underline{H}_2CH_3$), 2.00 (1H, m, 0.5 x $C\underline{H}_2CH_3$), 3.65, 3.85 and 3.95 (3 x 3H, 3 x s, 3 x $OC\underline{H}_3$), 4.10 (1H, dd, *J*=2 and 11, CHBr), 4.80 and 4.90 (2 x 1H, 2 x d, *J*=5, 2 x CH-O), 6.85 (1H, d, *J*=8, aromatic), 7.45 (1H, dd, *J*=8 and 2, aromatic) and 7.70 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.9 and 26.3 (aliphatic), 52.9 and 53.3 (2 x OMe [ester]), 56.5 (MeO [aryl]), 62.2 (CHBr), 77.3 (2 x CH-O), 111.2 (aromatic), 112.9 (O-C-O), 128.1, 131.2, 132.4 and 156.6 (aromatic), 169.0 and 168.7 (2 x C=O).

p-Toluenesulphonamidophenyl substituted bromoacetals

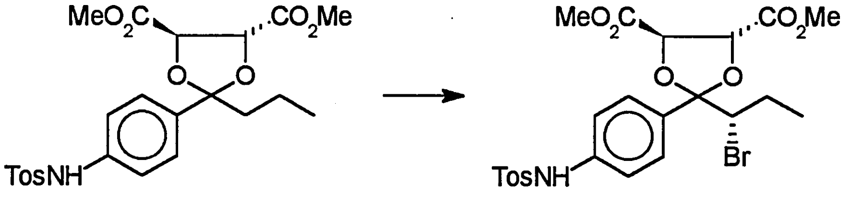
Dimethyl (4*R*,5*R*)-2-[(1*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **117**



100 **117**

The dimethyl (4*R*,5*R*)-2-ethyl-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **100** (6.02g, 13.0mmol) was dissolved in dry DCM (60ml) prior to the addition of hydrogen chloride saturated dry DCM (5ml). The reaction was maintained at -6°C using an ice / acetone bath during the addition of bromine (2.08g, 13.0mmol) in dry DCM (10ml). When analysis by TLC (2:1 petrol / ethyl acetate) showed no starting material (2,4 dinitrophenylhydrazine spray), the reaction was worked up by slow addition to DCM (100ml) slurried anhydrous potassium carbonate (15g). The slurry was stirred for 10 minutes before water (100ml) was added to give a two phase system, separated and the aqueous layer re-extracted with DCM (2 x 75ml). The combined organic extracts were then washed with water (50ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the product as a straw coloured viscous liquid which partially solidified. Purification by flash chromatography (2:1 petrol / ethyl acetate) followed by (re)crystallisation from dry methanol gave the pure title compound as a pale brown crystalline solid (5.64g, 80%, (*S*):(*R*) 10:1) m.p. 121-123°C. (Found M^+, 541.0422. $C_{22}H_{24}NO_8S^{79}Br$ requires M, 541.0406); ν_{max} (KBr disk)/cm^{-1} 3292 N-H$_{(str)}$, 2998, 2986 and 2955 C-H$_{(str)}$ and 1740 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, d, *J*=7, CHBrC$\underline{H}_3$), 2.35 (3H, s, $ArCH_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.30 (1H, q, *J*=7, CHBr), 4.80 and 4.90 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.70 (1H, s, N-H), 7.05 (2H, d, *J*=8, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.40 (2H, d, *J*=8, aromatic) and 7.70 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.8 and 21.8 (aliphatic), 52.7 and 53.3 (CHBr and 2 x OMe), 78.2 (2 x CH-O), 113.3 (O-C-O), 120.2, 127.6, 128.6, 130.0, 133.8, 136.4, 137.9 and 144.4 (aromatic), 168.9 and 169.1 (2 x C=O).

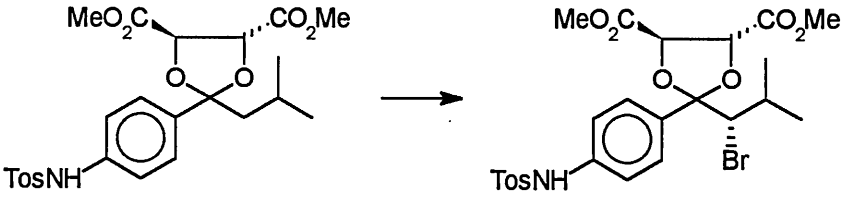
Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **118**



101 **118**

This compound was prepared from dimethyl (4*R*,5*R*)-2-(4-*p*-toluenesulphonamidophenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate **101** (6.20g, 13.0mmol) using the method described above for the preparation of **117**. Purification by flash chromatography (2:1 petrol / ethyl acetate) followed by (re)crystallisation from dry methanol gave the pure title compound as a pale brown crystalline solid (4.77g, 66%, (*S*):(*R*) 10:1) m.p. 136-138°C. (Found M^+, 555.0575. $C_{23}H_{26}NO_8S^{79}Br$ requires M, 555.0563); ν_{max} (KBr disk)/cm^{-1} 3299 N-H$_{(str)}$, 2996, 2981 and 2945 C-H$_{(str)}$ and 1735 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.95 (3H, t, *J*=7, CH$_2$C<u>H$_3$</u>), 1.55 (1H, m, 0.5 x C<u>H$_2$</u>CH$_3$), 1.90 (1H, m, 0.5 x C<u>H$_2$</u>CH$_3$), 2.35 (3H, s, ArCH$_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH$_3$), 4.10 (1H, dd, *J*=11 and 2, C<u>H</u>Br), 4.80 and 4.90 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.05 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.40 (2H, d, *J*=8, aromatic), 7.55 (1H, s, N-H) and 7.70 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.9, 21.8 and 26.3 (aliphatic), 52.7 and 53.3 (2 x OMe), 62.2 (CHBr), 78.2 (2 x CH-O), 113.3 (O-C-O), 119.1, 120.2, 127.6, 128.6, 130.0, 130.9, 134.2, 136.4, 137.9 and 144.3 (aromatic), 168.9 and 169.1 (2 x C=O).

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromo-2methylpropyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **119**

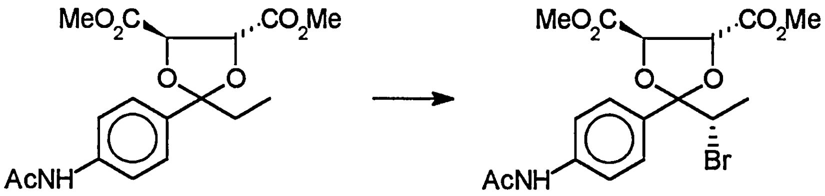


102 **119**

This compound was prepared from dimethyl (4*R*,5*R*)-2-isobutyl-2-(4-*p*-toluenesulphonamidophenyl),3-dioxolane-4,5-dicarboxylate **102** (6.38g, 13.0mmol) using the method described above for the preparation of **117**. Purification by flash chromatography (2:1 petrol / ethyl acetate) followed by crystallisation from dry methanol gave the pure title compound as a pale brown crystalline solid (1.70g, 23%, (*S*):(*R*) 8:1) m.p. 122-125°C. (Found M$^+$, 569.0724. $C_{24}H_{28}NO_8S^{79}Br$ requires M, 569.0719); ν_{max} (KBr disk)/cm^{-1} 3290 N-H$_{(str)}$, 2995, 2980 and 2949 C-H$_{(str)}$ and 1735 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (6H, dd, $(C\underline{H}_3)_2CH$), 1.60 (1H, m, $(CH_3)_2C\underline{H}$), 2.35 (3H, s, $ArCH_3$), 3.45 and 3.85 (2 x 3H, 2 x s, 2 x OCH_3), 4.25 (1H, d, *J*=2, CHBr), 4.80 and 4.90 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.05 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.35 (2H, d, *J*=9, aromatic), 7.70 (2H, d, *J*=8, aromatic) and 7.80 (1H, s, N-H); δ_C (62.88 MHz; $CDCl_3$) 17.8, 21.8, 23.4 and 29.1 (aliphatic), 52.7 and 53.2 (2 x OMe), 68.2 (CHBr), 78.2 (2 x CH-O), 113.6 (O-C-O), 120.6, 127.6, 127.9, 130.0, 135.2, 136.4, 137.9 and 144.4 (aromatic), 168.6 and 169.3 (2 x C=O).

4-Acetamidophenyl substituted bromoacetals

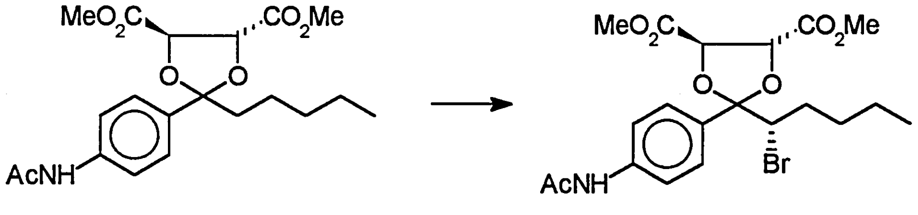
Attempted preparation dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-acetamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **120**



98 **120**

We attempted to prepare this compound from dimethyl (4*R*,5*R*)-2-ethyl-2-(4-acetamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **98** (1.30g, 3.7mmol) dissolved in dry DCM (15ml) prior to the addition of small sample hydrogen chloride saturated dry DCM (3ml). The reaction was maintained at -6°C in a ice / acetone bath during the addition of bromine (0.69g, 4.3mmol) in dry DCM (3ml). When analysis by TLC (4:1 petrol / ethyl acetate) showed no starting material (2,4 dinitrophenylhydrazine spray), the reaction was worked up by slow addition to DCM (50ml) slurried anhydrous potassium carbonate (10g). The slurry was stirred for 10 minutes before water (50ml) was added to give a two phase system which was separated and the aqueous layer then re-extracted with DCM (2 x 25ml). The combined organic extracts were then washed with water (25ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude title compound as a straw coloured viscous liquid. Purification by flash chromatography (4:1 petrol / ethyl acetate + a trace of triethylamine) was attempted but the title compound decomposed to the corresponding bromoketone.

Attempted preparation dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopentyl]-2-(4-acetamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **121**

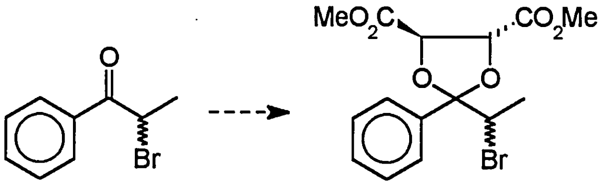


99 **121**

The attempted preparation of this compound was from dimethyl (4*R*,5*R*)-2-pentyl-2-(4-acetamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **99** (1.45g, 3.7mmol) using the method as described above for the preparation of **120**. The expected product from this reaction decomposed to the corresponding bromoketone during the work-up procedure.

Attempted preparation of racemic bromoacetals from bromoketones

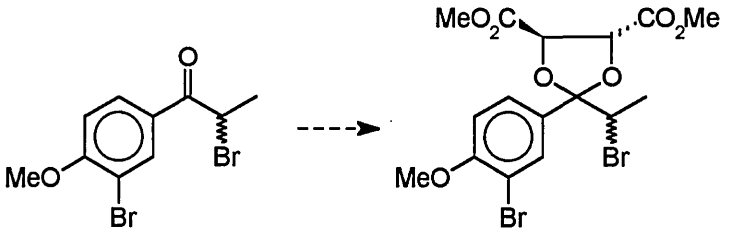
Attempted preparation of racemic dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108**



89 **108**

Racemic 2-bromo-1-phenyl-1-propanone **89** (1.00g, 4.7mmol), dimethyl tartrate (1.67g, 9.4mmol), trimethyl orthoformate (1.00g, 9.4mmol) were heated to ~50°C prior to the addition of methanesulphonic acid (1 drop). The reaction was then heated at 95°C for 5 hours during which time methanol and methyl formate were distilled off. Analysis by TLC (4:1 petrol / ethyl acetate) after 5 hours showed only starting material and none of the expected product. Further heating with additional amounts of trimethyl orthoformate, dimethyl tartrate and methanesulphonic acid failed to produce any product as indicated by TLC analysis.

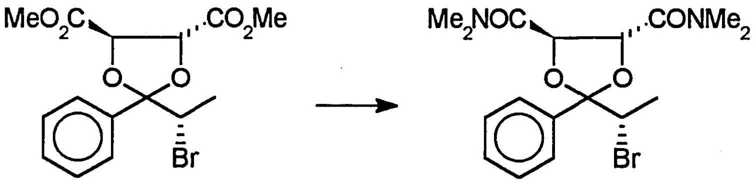
Attempted preparation of dimethyl (4*R*,5*R*)-2-[1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **112**



80 **112**

Racemic 2-bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone **80** (1.00g, 3.10mmol), dimethyl tartrate (3.31g, 18.6mmol), dimethyl sulphite (1.26g, 11.5mmol) and trifluoromethanesulphonic acid (0.47g, 3.72mmol) in dry DCM (10ml) were stirred at room temperature for 5 hours during which time no reaction was observed by TLC (4:1 petrol / ethyl acetate).

N,*N*,*N'*,*N'*-Tetramethyl-(4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxamide **122**

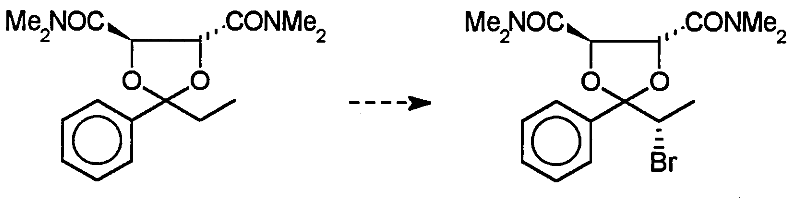


108 **122**

Dimethylamine was distilled and dried over KOH from a 40% w / v aqueous solution (20ml) and collected at -78°C. This was added to a stirred solution of dimethyl (4*R*,5*R*)-2-[(1*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (1.03g, 2.76mmol) in dry methanol (7ml) which had been cooled to -78°C. The reaction was allowed to warm to -5°C and maintained at this temperature for 3 days after which time analysis by TLC (2:1 petrol / ethyl acetate) indicated complete conversion of the starting material. Removal of methanol and excess dimethylamine gave the title compound as a white viscous gum (1.05g, 95%). (Found M$^+$, 398.0418. $C_{17}H_{23}{}^{79}BrN_2O_4$ requires M, 398.0412); ν_{max} (KBr disk)/cm^{-1} 2969-2872 C-H$_{(str)}$ and 1672-1643 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.60 (3H, d, *J*=7, CHBrC$\underline{H}_3$), 2.85, 3.00, 3.20 and 3.25 (4 x 3H, 4 x s, 4 x *N*-CH_3), 4.35 (1H, q, *J*=7, CHBr), 5.20 and 5.30 (2 x 1H, 2 x d, *J*=7, CH-O), 7.30-7.45 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.9 (aliphatic), 35.7, 35.9 and 37.3 (4 x *N*-methyl), 53.2 (CHBr), 77.3 and 78.7 (2 x CH-O), 113.9 (O-C-O), 125.7, 128.2, 128.4 and 142.3 (aromatic), 169.6 and 171.2 (2 x C=O).

Attempted bromination of an acetal containing a modified chiral auxiliaries

Attempted preparation of *N,N,N',N'*-tetramethyl-(4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxamide 122

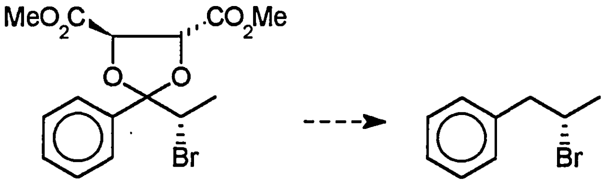


107 **122**

N,N,N',N'-Tetramethyl-(4*R*,5*R*)-2-ethyl-2-phenyl-1,3-dioxolane-4,5-dicarboxamide **107** (1.00g, 3.13mmol) was dissolved in dry DCM (10ml) and cooled to -6°C before bromine (0.50g, 3.13mmol) dissolved in dry DCM (3ml) and HCl saturated DCM (2ml) were added. Analysis by TLC (2:1 petrol : ethyl acetate) indicated no reaction after 3 hours and therefore more HCl saturated DCM (2ml) was added. The reaction was stirred overnight at room temperature during which time the bromine colour disappeared indicating that a reaction had taken place. The reaction was worked up by slow addition to DCM (15ml) slurried anhydrous potassium carbonate (2g). The slurry was stirred for 10 minutes before water (10ml) was slowly added to give a two phase system, from which the lower organic layer was separated and the aqueous layer re-extracted with DCM (2 x 15ml). The combined organic extracts were then washed with water (15ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield a straw coloured viscous liquid. Analysis by ^1H NMR indicated that we produced 2-bromopropiophenone **89**.

Hydrogenolysis of the 1,3-dioxolane ring

Attempted preparation of (*S*)-2-bromo-1-phenylpropane **123*S***



108 **123*S***

Method 1 (Balloon / sonic bath)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.75g, 2.01mmol) and catalyst [5% Pd on carbon] (0.05g) in methanol (5ml) were sonicated for 7.5 hours under an atmosphere of hydrogen gas then allowed to stand over night. Analysis by TLC (9:1 petrol / ethyl acetate) showed only starting material which was recovered.

Method 2 (Hydrogenator)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.25g, 0.67mmol) and catalyst [5% Pd on carbon] (25 mg) were stirred in methanol (5ml). The reaction mixture was then hydrogenated for 8.5 hours. Analysis by TLC (9:1 petrol / ethyl acetate) showed only the presence of starting material which was recovered.

Method 3 (Balloon / HCl)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.50g, 1.34mmol) and catalyst [5% Pd on carbon] (0.025g) were stirred in super dry methanol (5ml) which had been saturated with dry hydrogen chloride gas. A balloon filled with hydrogen gas was attached and the reaction heated at reflux overnight. Analysis ^{1}H NMR showed only starting material.

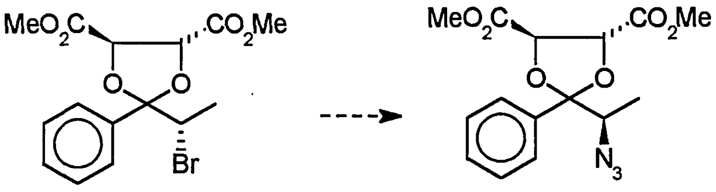
Method 4 (Transfer hydrogenolysis using cyclohexene)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.25g, 0.67mmol), catalyst [10% $Pd(OH)_2$ on carbon] (0.065g) and cyclohexene (3ml) were stirred in ethanol (5ml). The reaction was heated at reflux for 24 hours prior to analysis by TLC (9:1 petrol / ethyl acetate) which showed only starting material.

Method 5 (Transfer hydrogenolysis using ammonium formate)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.60g, 1.61mmol), catalyst [5% Pd on carbon] (40 mg) and ammonium formate (2.0g, 32mmol) were stirred in methanol (5ml) and heated at reflux overnight. Analysis by TLC (9:1 petrol / ethyl acetate) showed several spots. DCM (50ml) was added and the catalyst filtered off. The DCM solution was dried with $MgSO_4$ and the solvent removed under reduced pressure to afford a colourless viscous liquid. Purification by flash chromatography (9:1 petrol / ethyl acetate) and analysis by ^1H NMR indicated that we had prepared the acetal **90** and recovered some starting material **108**.

Attempted azide displacement of bromine from bromoacetal



108 **124**

Method 1

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (1.00g, 2.7mmol) and sodium azide (0.35g, 5.4mmol) were dissolved in dry DMF (5ml). The reaction was stirred for 24 hours at room temperature after which time analysis by TLC (4:1 petrol / ethyl acetate) indicated no reaction. The mixture was then heated at 55°C for 48 hours, again analysis by TLC indicated no reaction. Water (1.5ml) was added and the reaction heated to 65°C for a further 48 hours, again analysis by TLC indicated no reaction. The temperature was increased to 90°C which resulted in the formation of a black intractable solid.

Method 2

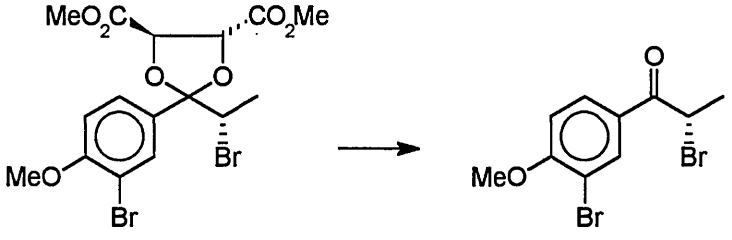
Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (1.00g, 2.7mmol) and sodium azide (0.52g, 8.0mmol) were dissolved in *N*-methyl-2-

pyrollidinone (NMP) (5ml) and heated at reflux. Analysis by TLC (4:1 petrol / ethyl acetate) after 6 hours showed numerous spots, however isolation of a product, for which we were able to deduce a structure proved very difficult.

Preparation of enantiomerically enriched bromoketones

3-Bromo-4-methoxyphenyl substituted bromoketones

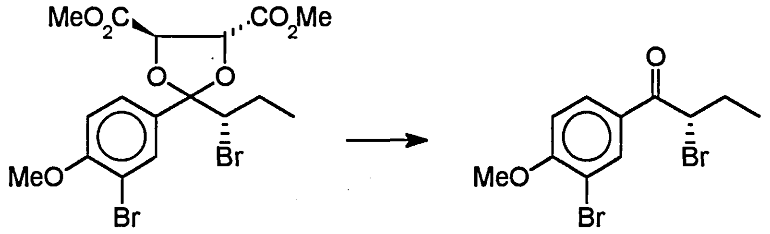
(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone (**80*S***)



112 **80**(*S*)

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **112** (38.8g, 80.6mmol) was dissolved in methanesulphonic acid (400ml) and stirred for 5 minutes prior to the dropwise addition of water (3.8g, 0.211mol) over 5 minutes. Analysis by gas chromatography after 1 hour indicated that almost complete conversion had taken place. The reaction mixture was slowly poured onto stirred crushed ice (600g) / ether (300ml), separated and the aqueous layer re-extracted with ether (2 x 150ml). The combined ether extracts were then washed with water (200ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude title compound as a viscous liquid or low melting solid. Purification by (re)crystallisation from methanol afforded the title compound as a white crystalline solid (13.5g, 52%, >98% e.e. as determined by ^1H NMR in the presence $Eu(hfc)_3$) m.p. 108-110°C. (Found M^+, 319.9068. $C_{10}H_{10}O_2{}^{79}Br_2$ requires M, 319.9048); ν_{max} (KBr disk)/cm^{-1} 3019, 2991, and 2933 C-$H_{(str)}$ and 1669 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.85 (3H, d, *J*=7, $CHBrC\underline{H_3}$), 3.95 (3H, s, OCH_3), 5.20 (1H, q, *J*=7, $C\underline{H}BrCH_3$), 6.95 (1H, d, *J*=9, aromatic), 7.95 (H, dd, *J*=9 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.4 (aliphatic), 41.5 (CHBr), 56.9 (MeO), 111.5, 112.5, 128.2, 130.5, 134.7 and 160.4 (aromatic) and 191.3 (C=O).

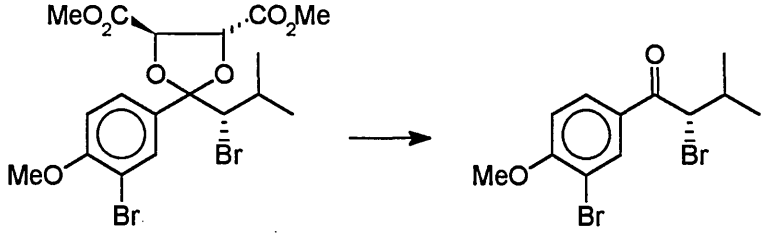
(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81*S***



113 **81(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **113** (39.9g, 80.6mmol) using the method described above for the preparation of **80*S***. Purification by (re)crystallisation from methanol afforded the title compound as a white crystalline solid (13.5g, 50%, >98% e.e.) m.p. 82-84°C. (Found M$^+$, 333.9231. $C_{11}H_{12}O_2{}^{79}Br_2$ requires M, 333.9204); ν_{max} (KBr disk)/cm^{-1} 3016, 2992 and 2939 C-H$_{(str)}$ and 1666 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.10 (3H, t, *J*=7, CH_3), 2.20 (2H, m, $CH_3\underline{CH_2}$), 4.00 (3H, s, OCH_3), 5.00 (1H, t, *J*=8, CHBr), 6.95 (1H, d, *J*=9, aromatic), 7.95 (1H, dd, *J*=9 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.5 and 27.2 (aliphatic), 49.1 (CHBr), 56.9 (MeO), 111.6, 112.5, 128.7, 130.5, 134.6 and 160.4 (aromatic) and 191.2 (C=O).

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-3-methyl-1-butanone **83*S***

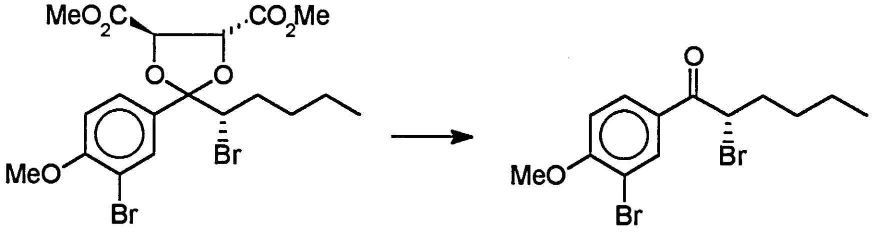


114 **83(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromo-2-methylpropyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **114** (4.10g, 8.06mmol) using the method described above for the preparation of **80(*S*)** but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid which failed to crystallise from methanol (1.97g, 70%, 71% e.e.). (Found M$^+$, 347.9392. $C_{12}H_{14}O_2{}^{79}Br_2$ requires M, 347.9361); ν_{max} (film)/cm^{-1} 3016, 2997 and

2930 C-H$_{(str)}$ and 1669 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (6H, d, *J*=7, (C<u>H</u>$_3$)$_2$CH), 2.45 (1H, m, (CH_3)$_2$C<u>H</u>), 4.00 (3H, s, OCH_3), 4.85 (1H, d, *J*=7, CHBr), 6.95 (1H, d, *J*=8, aromatic), 7.90 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 21.0 and 32.8 (aliphatic), 56.9 (MeO), 59.1 (CHBr), 112.6, 114.9, 130.3, 130.5, 134.6 and 161.4 (aromatic) and 191.2 (C=O).

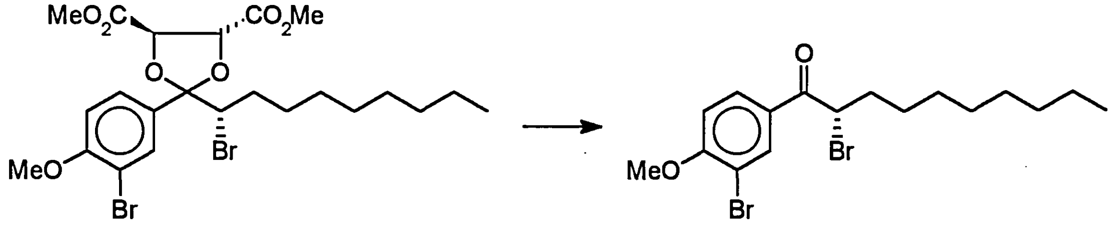
<u>(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-hexanone **84(*S*)**</u>



115 **84(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopentyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **115** (4.22g, 8.06mmol) using the method described above for the preparation of **80**(*S*) but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). Purification by flash chromatography (4:1 petrol / ethyl acetate) followed by (re)crystallisation from methanol afforded the title compound as a white crystalline solid (1.96g, 67%, 66% e.e.) m.p. 58-60°C. (Found M$^+$, 361.9501. $C_{13}H_{16}O_2{}^{79}Br_2$ requires M, 361.9517); ν_{max} (KBr disk)/cm^{-1} 3019, 2996 and 2932 C-H$_{(str)}$ and 1665 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J*=7, CH_3), 1.40 (4H, m, 2 x CH_3-(C<u>H</u>$_2$)$_2$-), 2.15 (2H, m, CHBrC<u>H</u>$_2$), 4.00 (3H, s, OCH_3), 5.05 (1H, t, *J*=7, CHBr), 6.95 (1H, d, *J*=8, aromatic), 7.95 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.2, 22.6, 30.0 and 33.5 (aliphatic), 47.3 (CHBr), 56.9 (MeO), 111.6, 112.5, 128.7, 130.5, 134.7 and 160.4 (aromatic) and 191.3 (C=O).

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-decanone **85(*S*)**

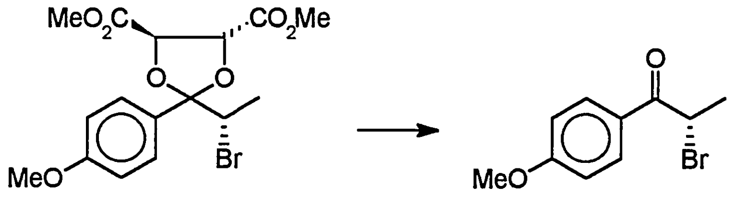


116 **85(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromononyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **116** (4.67g, 8.06mmol) using the method described above for the preparation of **80**(*S*) but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). Purification by flash chromatography (4:1 petrol / ethyl acetate) followed by (re)crystallisation from methanol afforded the title compound as a white crystalline solid (1.45g, 43%, >98% e.e.) m.p. 58-59°C. (Found M^+, 418.0129. $C_{17}H_{24}O_2{}^{79}Br_2$ requires M, 418.0143); ν_{max} (KBr disk)/cm^{-1} 3012, 2989 and 2935 $C\text{-}H_{(str)}$ and 1669 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.20- 1.55 (12H, m, CH_3-($C\underline{H}_2$)$_6$-), 2.15 (2H, m, $CHBrC\underline{H}_2$), 4.00 (3H, s, OCH_3), 5.05 (1H, t, *J*=7, CHBr), 6.95 (1H, d, *J*=8, aromatic), 8.00 (H, dd, *J*=8 and 2, aromatic) and 8.20 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.4, 22.9, 28.0, 29.0, 29.5, 29.6, 32.1 and 32.8, (aliphatic), 47.6 (CHBr), 56.5 (MeO), 111.3, 112.5, 128.8, 130.5, 134.6 and 160.4 (aromatic) and 191.5 (C=O).

4-Methoxyphenyl substituted bromoketones

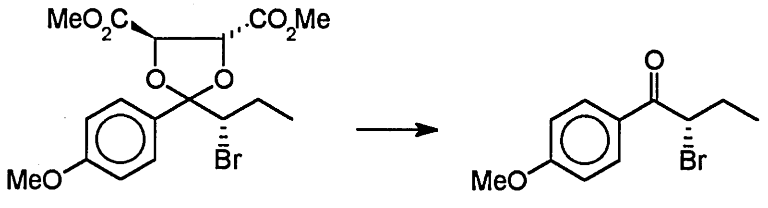
(*S*)-2-Bromo-1-(4-methoxyphenyl)-1-propanone 78(*S*)



109 **78(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **109** (3.24g, 8.06mmol) using the method described above for the preparation of **80**(*S*) but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). Purification by (re)crystallisation from methanol afforded the title compound as a white crystalline solid (1.13g, 58%, 80% e.e.) m.p. 63-64°C (lit., m.p. racemic 66-67°C).[33] (Found M$^+$, 241.9921. $C_{10}H_{11}O_2{}^{79}Br$ requires M, 241.9942); ν_{max} (KBr disk)/cm^{-1} 3016, 2994 and 2934 C-H$_{(str)}$ and 1666 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.85 (3H, d, *J*=7, CH$_3$), 3.85 (3H, s, OCH$_3$), 5.25 (1H, q, *J*=7, C<u>H</u>Br), 6.95 (2H, d, *J*=9, aromatic) and 8.00 (2H, d, *J*=9, aromatic); δ_C (62.88 MHz; CDCl$_3$) 20.6 (aliphatic), 41.9 (CHBr), 55.8 (MeO), 114.3, 127.1, 131.6 and 164.3 (aromatic) and 192.3 (C=O).

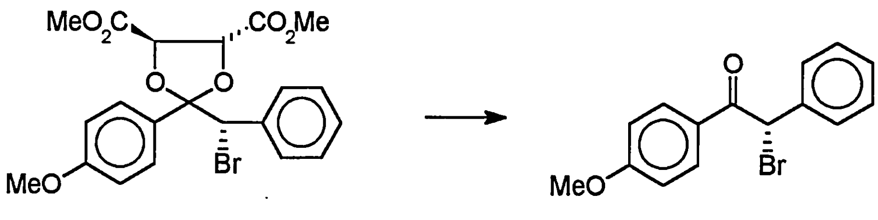
<u>(*S*)-2-Bromo-1-(4-methoxyphenyl)-1-butanone **79(*S*)**</u>



110 **79(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **110** (3.24g, 8.06mmol) using the method described above for the preparation of **79(*S*)** but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). The crude title compound was obtained as a white crystalline solid (1.34g, 65%, 92% e.e.) m.p. 51-53°C. (Found M$^+$, 256.0115. $C_{11}H_{13}O_2{}^{79}Br$ requires M, 256.0099); ν_{max} (KBr disk)/cm^{-1} 3019, 2990, 2971 and 2934 C-H$_{(str)}$ and 1676 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.10 (3H, t, *J*=7, CH$_3$), 2.20 (2H, m, CH$_2$), 3.90 (3H, s, OCH$_3$), 5.05 (1H, t, *J*=7, CHBr), 7.00 (2H, d, *J*=8, aromatic) and 8.05 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.4 and 28.6 (aliphatic), 49.1 (CHBr), 55.8 (MeO), 113.3, 129.1, 131.6 and 164.3 (aromatic) and 192.3 (C=O).

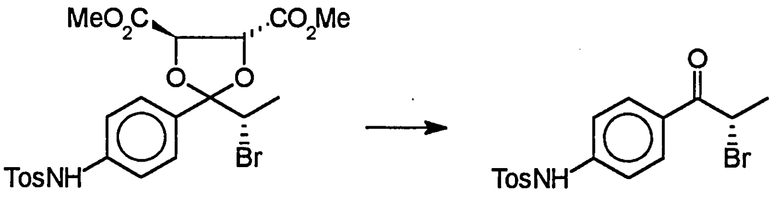
<u>(*S*)-2-Bromo-1-(4-methoxyphenyl)-2-phenyl-1-ethanone **87(*S*)**</u>



111 **87(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromo-1-phenylmethyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **111** (3.75g, 8.06mmol) using the method described above for the preparation of **80**(*S*) but using methanesulphonic acid (40ml) and water (0.38g, 21.1mmol). Purification by (re)crystallisation from methanol afforded the title compound as a white crystalline solid of indeterminate enantiomeric excess (1.06g, 45%, N / A% e.e.) m.p. 136-138°C. (Found M$^+$, 292.0082. $C_{14}H_{13}O_2{}^{79}Br$ requires M, 292.0099); ν_{max} (KBr disk)/cm^{-1} 3020, 2985, 2971 and 2934 C-H$_{(str)}$ and 1669 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 3.80 (3H, s, OCH_3), 5.80 (1H, t, *J*=7, CHBr), 7.10 (2H, d, *J*=7, aromatic), 7.40 (5H, m, aromatic) and 8.20 (2H, d, *J*=7, aromatic); δ_C (62.88 MHz; $CDCl_3$) 50.6 (aliphatic), 55.1 (MeO), 113.9, 127.5, 129.0, 130.2, 130.5, 132.0 and 163.9 (aromatic) and 187.6 (C=O).

Attempted preparation of (*S*)-2-bromo-1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **88**(*S*)

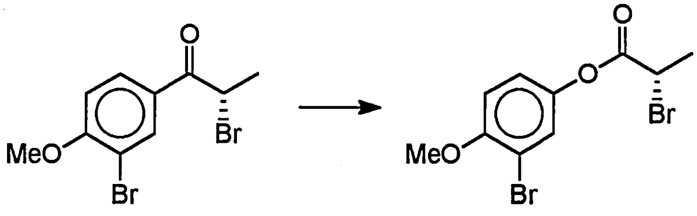


117 **88**(*S*)

We attempted to prepare (*S*)-2-bromo-1-(4-*p*-toluenesulphonamidophenyl)propan-1-one **88**(*S*) from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **117** (1.00g, 1.85mmol) using the method described above for the preparation of **80**(*S*) but using methanesulphonic acid (10ml) and water (0.07g, 3.89mmol). After 2 hours analysis by TLC (2:1 petrol / ethyl acetate) indicated that some starting material remained, so another aliquot of water (0.07g, 3.89mmol) was added. After a further 2 hours analysis by TLC showed no starting material and the reaction was worked-up as described above in the preparation of **80**(*S*). Analysis by ^1H NMR spectroscopy indicated that under these conditions the acetal group was hydrolysed, but unfortunately partial hydrolysis of the sulphonamide group also occurred.

Preparation of aryl (*S*)-2-bromoalkyl esters

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)**



80(*S*) **128(*S*)**

Method 1

(*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone **80(*S*)** (0.100g, 0.31mmol) was dissolved in dry DCM (5ml) to which di-sodium hydrogen phosphate (Na_2HPO_4) (0.300g, 2.1mmol), urea / hydrogen peroxide addition product (0.06g, 0.62mmol) and trifluoroacetic anhydride (3ml) were added. The reaction was monitored by ^{1}H NMR spectroscopy for 4 days with no sign of reaction, another portion of urea / hydrogen peroxide addition product (0.12g, 1.24mmol) was added. No sign of reaction was observed after a further 4 days.

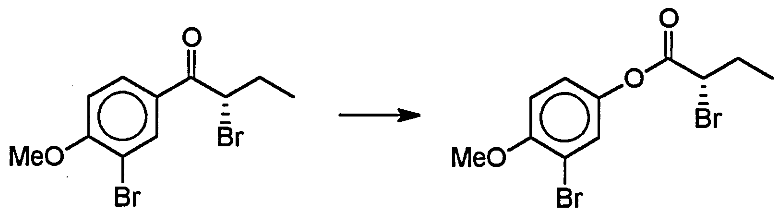
Method 2

(*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone **80(*S*)** (0.100g, 0.31mmol) was dissolved in 1,2 dichloroethane (5ml) to which di-sodium hydrogen phosphate (Na_2HPO_4) (0.300g, 2.1mmol) and 3-chloroperoxybenzioc acid (MCPBA; 57-86% w/w) (0.600g) were added. The reaction was heated at reflux for 48 hours after which time analysis by ^{1}H NMR indicated complete conversion of the starting material **80(*S*)** had taken place. The reaction mixture was poured into a solution of water (10ml) and saturated aqueous $NaHCO_3$ (10ml). The layers were separated and the aqueous phase re-extracted with DCM (2 x 15ml). The combined organic extracts were washed with 10% w/w aqueous $NaHCO_3$ (15ml) and water (15ml) prior to drying with $MgSO_4$. The solvent was removed under reduced pressure to give the crude product as a pale brown viscous liquid which was purified by flash chromatography (19:1 petrol / ethyl acetate) to yield the title compound (3.31g, 79%).

Method 3

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-propanone **80**(*S*) (4.00g, 12.4mmol) was dissolved in chloroform (125ml) to which di-sodium hydrogen phosphate (Na_2HPO_4) (4.00g, 28.2mmol) and 3-chloroperoxybenzioc acid (MCPBA; 57-86% w/w) (9.40g) were added. The reaction was followed by ^{1}H NMR analysis until complete conversion of the starting material had taken place (approx. 48 hours). The reaction mixture was poured into a solution of water (75ml) and saturated aqueous $NaHCO_3$ (75ml). The layers were separated and the aqueous phase re-extracted with DCM (2 x 125ml). The combined organic extracts were then washed with 10% w/w aqueous $NaHCO_3$ (50ml) and water (50ml) prior to drying with $MgSO_4$. The solvent was removed under reduced pressure to give the crude product as a pale brown liquid which was then purified by flash chromatography (19:1 petrol / ethyl acetate) to yield the title compound (4.10g, 98%). Found M$^+$, 335.9018. $C_{10}H_{10}O_3{}^{79}Br_2$ requires M, 335.8997); ν_{max} (film)/cm^{-1} 2981, 2969 and 2920 C-H$_{(str)}$ and 1765 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.95 (3H, t, *J*=7, CH_3), 3.90 (3H, s, OCH_3), 4.10 (1H, q, *J*=7, CHBr), 6.90 (1H, d, *J*=8, aromatic), 7.10 (1H, dd, *J*=8, 2, aromatic) and 7.40 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 24.1(aliphatic), 45.4 (CHBr), 56.6 (MeO), 112.2, 121.2, 126.4, 128.6, 148.2 and 153.5 (aromatic) and 169.4 (C=O).

3-Bromo-4-methoxyphenyl (*S*)-2-bromobutanoate **129**(*S*)

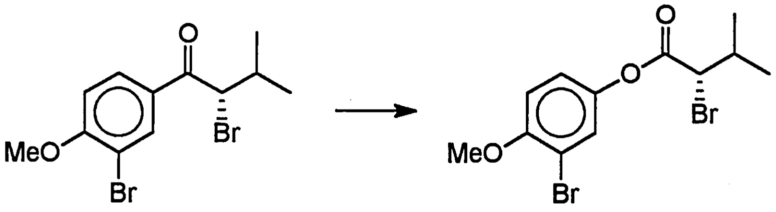


81(*S*) **129**(*S*)

This compound was prepared from (*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81**(*S*) (4.17g, 12.4mmol) using 'method 3' described above for the preparation of **128**(*S*). Purification by flash chromatography (19:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (3.67g, 87%). (Found M$^+$, 349.9139. $C_{11}H_{12}O_3{}^{79}Br_2$ requires M, 349.9153); ν_{max} (film)/cm^{-1} 2979 and 2925 C-H$_{(str)}$ and 1769 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J*=7, CH_3), 2.20 (2H, m, CH_2), 3.90 (3H, s,

OCH_3), 4.35 (1H, t, *J*=7, CHBr), 6.90 (1H, d, *J*=8, aromatic), 7.10 (1H, dd, *J*=8, 2, aromatic) and 7.35 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.0 and 24.4 (aliphatic), 54.0 (CHBr), 56.6 (MeO), 112.2, 121.2, 126.6, 144.2 and 154.5 (aromatic) and 168.7 (C=O).

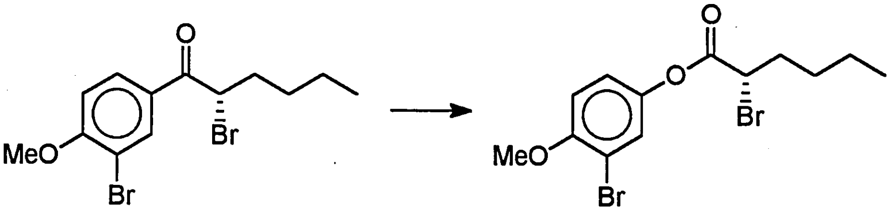
3-Bromo-4-methoxyphenyl (*S*)-2-bromo-3-methylbutanoate **130**(*S*)



82(*S*) **130**(*S*)

This compound was prepared from (*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-3-methyl-1-butanone **82**(*S*) (4.34g, 12.4mmol) using 'method 3' described above for the preparation of **128**(*S*). Purification by flash chromatography (19:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (3.18g, 70%). (Found M^+, 363.9302. $C_{12}H_{14}O_3{}^{79}Br_2$ requires M, 363.9310); ν_{max} (film)/cm^{-1} 2991 and 2962, C-H$_{(str)}$ and 1761 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.15 (6H, d, *J*=7, $(C\underline{H}_3)_2CH$), 2.35 (1H, m, $(CH_3)_2C\underline{H}$), 3.90 (3H, s, OCH_3), 4.20 (1H, d, *J*=8, CHBr), 6.90 (1H, d, *J*=9, aromatic), 7.10 (1H, dd, *J*=9 and 2, aromatic) and 7.40 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.4 and 32.6 (aliphatic). 54.0 (CHBr), 56.9 (MeO), 112.2, 121.2, 126.4, 128.6, 144.2 and 154.5 (aromatic) and 168.3 (C=O).

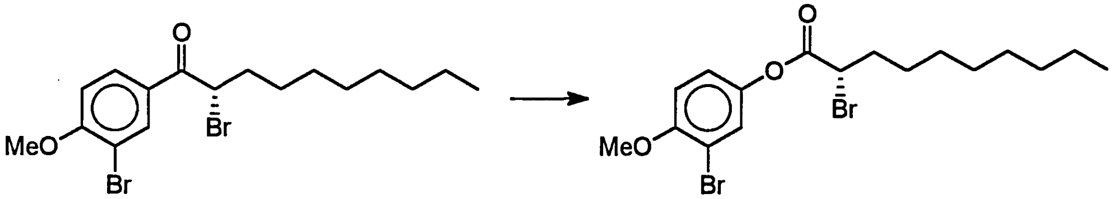
3-Bromo-4-methoxyphenyl (*S*)-2-bromohexanoate **131**(*S*)



84(*S*) **131**(*S*)

This compound was prepared from (*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-1-hexanone **84**(*S*) (4.51g, 12.4mmol) using 'method 3' described above for the preparation of **128**(*S*). Purification by flash chromatography (19:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (4.01g, 85%). (Found M$^+$, 377.9459. $C_{13}H_{16}O_3{}^{79}Br_2$ requires M, 377.9466); ν_{max} (film)/cm^{-1} 2983 and 2920 C-H$_{(str)}$ and 1771 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J*=7, CH_3), 1.40 (4H, m, CH_3-($C\underline{H}_2$)$_2$-), 2.15 (2H, m, CHBrC$\underline{H}_2$), 3.85 (3H, s, OCH_3), 4.40 (1H, t, *J*=8, CHBr), 6.90 (1H, d, *J*=8, aromatic), 7.05 (1H, dd, *J*=8 and 2, aromatic) and 7.35 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.1, 21.3, 27.9 and 34.7 (aliphatic), 45.6 (CHBr), 56.8 (MeO), 111.9, 112.2, 121.2, 126.4, 144.2 and 154.5 (aromatic) and 168.7 (C=O).

3-Bromo-4-methoxyphenyl (*S*)-2-bromodecanoate **132**(*S*)

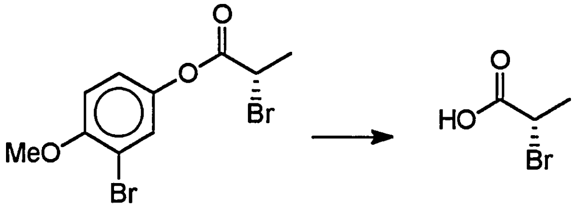


85(*S*) **132**(*S*)

This compound was prepared from (*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)-1-decanone **85**(*S*) (5.21g, 12.4mmol) using 'method 3' described above for the preparation of **128**(*S*). Purification by flash chromatography (19:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (4.43g, 82%). (Found M$^+$, 434.0071. $C_{17}H_{24}O_3{}^{79}Br_2$ requires M, 434.0092); ν_{max} (film)/cm^{-1} 2985, 2959 and 2929 C-H$_{(str)}$ and 1752 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_3), 1.20-1.65 (12H, m, CH_3-($C\underline{H}_2$)$_6$-), 2.15 (2H, m, CHBrC$\underline{H}_2$), 3.90 (3H, s, OCH_3), 4.40 (1H, t, *J*=7, CHBr), 6.90 (1H, d, *J*=8, aromatic), 7.10 (1H, dd, *J*=8 and 2, aromatic) and 7.35 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 14.4, 22.9, 27.6, 29.1, 29.4, 29.6, 32.1 and 35.0 (aliphatic), 45.6 (CHBr), 56.9 (MeO), 112.2, 121.2, 126.4, 128.6, 144.2 and 154.5 (aromatic) and 168.8 (C=O).

Preparation of (*S*)-2-bromo carboxylic acids

(*S*)-2-Bromopropanoic acid 133(*S*)



128(*S*) **133(*S*)**

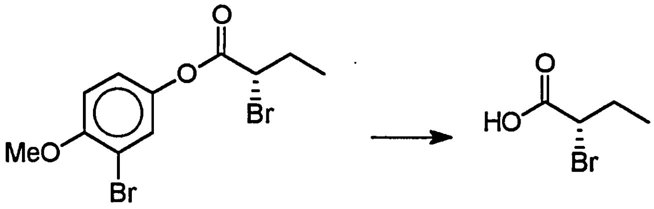
Method 1

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.50g, 1.48mmol) was dissolved in THF (25ml) and water (15ml) to which a mixture of lithium hydroxide monohydrate (0.126g, 3.0mmol) and hydrogen peroxide (27% w/w in water) (0.756g, 6.0mmol) was added in one portion. Analysis by TLC after 5 minutes (4:1 petrol / ethyl acetate) showed no starting material. The reaction was worked up by addition of saturated sodium thiosulphate solution (25ml) and 10% w/w aqueous $NaHCO_3$ (25ml) and extracted with DCM (2 x 15ml) to remove the 3-bromo-4-methoxyphenol. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with DCM (2 x 25ml). These organic extracts were combined, dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product.

Method 2

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.300g, 0.89mmol) was dissolved in THF (3ml) and water (3ml) to which was added lithium hydroxide monohydrate (0.040g, 0.95mmol). Analysis by TLC after 5 minutes (4:1 petrol / ethyl acetate) showed no starting material. The reaction was then worked up by addition of 10% w/w aqueous $NaHCO_3$ (20ml) and extracted with DCM (2 x 15ml) to remove the 3-bromo-4-methoxyphenol. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with DCM (2 x 25ml). These organic extracts were combined, dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a pale brown viscous liquid (0.098g, 72%). (Found M^+, 151.9482. $C_3H_5O_2{}^{79}Br$ requires M, 151.9473); ν_{max} (film)/cm^{-1} 3200-2630 O-H$_{(str)}$, 2980 and 2922 C-H$_{(str)}$ and 1728 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.80 (3H, d, *J*=7, CH_3), 4.20 (1H, q, *J*=7, CHBr) and 9.05 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 21.5 (aliphatic), 40.0 (CHBr) and 175.0 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester **138**(S) for which analysis by chiral GC determined the enantiomeric excess to be 96%.

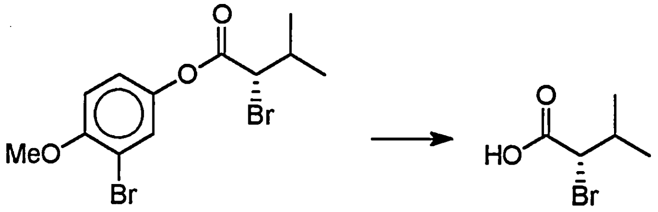
(*S*)-2-Bromobutanoic acid **134**(*S*)



129(*S*) **134**(*S*)

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromobutanoate **129**(*S*) (0.313g, 0.89mmol) using 'method 2' described above for the preparation of **133**(*S*). This yielded the title compound as a pale brown viscous liquid (0.089g, 60%). (Found M^+, 165.9638. $C_4H_7O_2{}^{79}Br$ requires M, 165.9629); ν_{max} (film)/cm^{-1} 3210-2630 O-$H_{(str)}$, 2983 and 2929 C-$H_{(str)}$ and 1725 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, *J*=8, CH_3), 2.05 (2H, m, CH_2), 4.15 (1H, t, *J*=7, CHBr) and 9.00 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 11.8 and 28.1 (aliphatic), 46.9 (CHBr) and 176.0 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester **139**(*S*) for which analysis by chiral GC determined the enantiomeric excess to be 94%.

(*S*)-2-Bromo-3-methylbutanoic acid **135**(*S*)

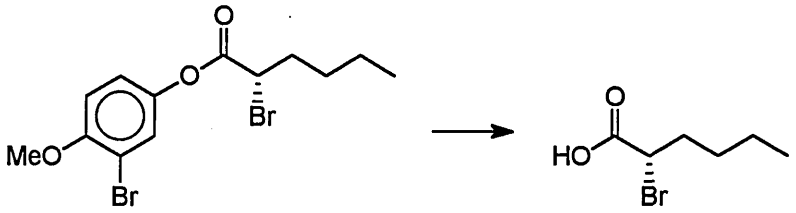


130(*S*) **135**(*S*)

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromo-3-methylbutanoate **130**(*S*) (0.326g, 0.89mmol) using 'method 2' described above for the preparation of **133**(*S*). This yielded the title compound as a pale brown viscous liquid

(0.101g, 63%). (Found M$^+$, 179.9772. $C_5H_9O_2{}^{79}Br$ requires M, 179.9786); ν_{max} (film)/ cm^{-1} 3205-2625 O-H$_{(str)}$, 2979 and 2928 C-H$_{(str)}$ and 1732 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.00 (3H, d, *J*=7, CH$_3$), 1.05 (3H, d, *J*=7, CH$_3$), 2.25 (1H, m, CH), 4.05 (1H, d, *J*=7, CHBr) and 9.00 (1H, bs, OH); δ_C (62.88 MHz; CDCl$_3$) 20.0, 20.3 and 32.4 (aliphatic), 54.2 (CHBr) and 176.4 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester **140(*S*)**, unfortunately it was insufficiently pure to permit analysis by chiral GC or ^{1}H NMR in the presence of Eu(hfc)$_3$.

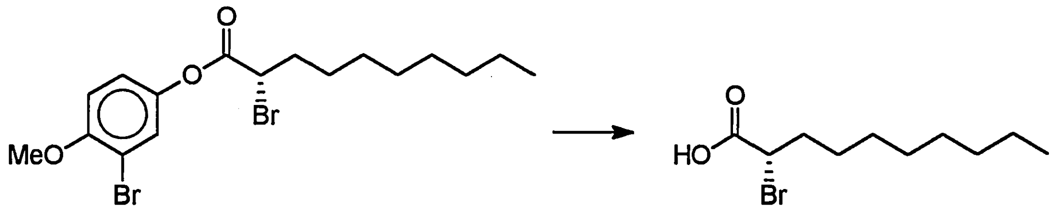
(*S*)-2-Bromohexanoic acid 136(*S*)



131(*S*) **136(*S*)**

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromohexanoate **131(*S*)** (0.338g, 0.89mmol) using 'method 2' described above for the preparation of **128(*S*)**. This yielded the title compound as a pale brown viscous liquid (0.101g, 68%). (Found M$^+$, 193.9956. $C_6H_{11}O_2{}^{79}Br$ requires M, 193.9942); ν_{max} (film)/cm^{-1} 3190-2600 O-H$_{(str)}$, 2983 and 2934 C-H$_{(str)}$ and 1729 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.90 (3H, t, *J*=7, CH$_3$), 1.20-1.50 (4H, m, CH$_3$(C<u>H</u>$_2$)$_2$), 2.05 (2H, m, C<u>H</u>$_2$CHBr), 4.25 (1H, t, *J*=7, CHBr) and 9.80 (1H, bs, OH); δ_C (62.88 MHz; CDCl$_3$) 14.0, 22.2, 29.6 and 34.6 (aliphatic), 45.6 (CHBr) and 176.6 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester **141(*S*)**, unfortunately it was insufficiently pure to permit analysis by chiral GC or ^{1}H NMR in the presence of Eu(hfc)$_3$.

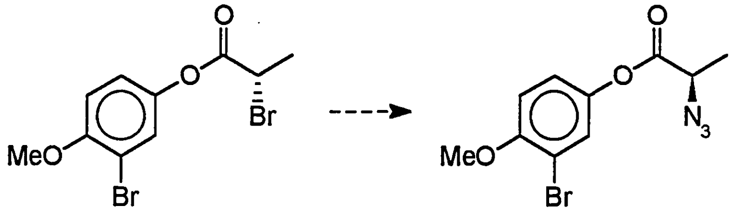
(*S*)-2-Bromodecanoic acid **137(*S*)**



132(*S*) **137(*S*)**

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromodecanoate **132(*S*)** (0.388g, 0.89mmol) using 'method 2' described above for the preparation of **128(*S*)**. This yielded the title compound as a pale brown viscous liquid (0.134g, 55%). (Found M$^+$, 250.0560. $C_{10}H_{19}O_2{}^{79}Br$ requires M, 250.0568); ν_{max} (film)/cm^{-1} 3200-2600 O-H$_{(str)}$, 2982 and 2925 C-H$_{(str)}$ and 1726 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 0.90 (3H, t, *J*=7, CH$_3$), 1.20-1.50 (12H, m, CH$_3$-(C$\underline{H}_2$)$_6$-), 2.05 (2H, m, C$\underline{H}_2$CHBr), 4.25 (1H, t, *J*=7, C$\underline{H}$Br) and 7.60 (1H, bs, OH); δ_C (62.88 MHz; CDCl$_3$) 14.4, 22.9, 29.1, 27.6, 29.6, 32.1, 35.2 and 46.1 (aliphatic), 53.2 (CHBr) and 170.9 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester **142(*S*)**, unfortunately it was insufficiently volatile to allow analysis by chiral GC, but analysis by ^{1}H NMR in the presence of Eu(hfc)$_3$ showed the enantiomeric excess to be 88%.

Attempted preparation of 3-Bromo-4-methoxyphenyl (*R*)-2-azidopropanoate **143(*R*)**



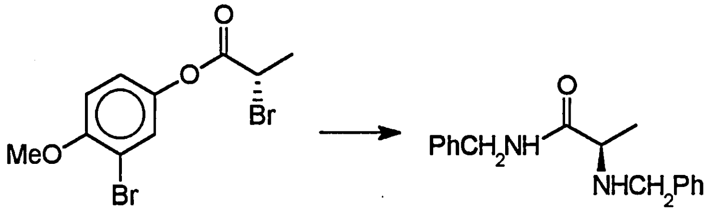
128(*S*) **143(*S*)**

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.50g, 1.48mmol) and sodium azide (0.481g, 7.4mmol) were dissolved in dry DMF (2ml) and heated at 50°C for 40 hours. Analysis by TLC (2:1 petrol / ethyl acetate) showed no starting material, but analysis by ^{1}H NMR indicated displacement of the aryl functionality.

Preparation of 2-substituted amides

Preparation of benzylamides

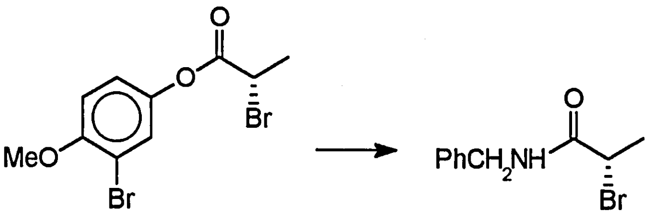
(*R*)-*N*-benzyl-2-(benzylamino)propanamide **144(*R*)**



128(*S*) **144(*R*)**

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.70g, 2.07mmol) was dissolved in dry toluene (15ml) to which anhydrous potassium carbonate (0.31g, 2.28mmol) and benzylamine **165** (0.46g, 4.55mmol) were added. The mixture was heated at reflux for 26 hours before TLC analysis (4:1 petrol / ethyl acetate) confirmed that no starting material remained. The reaction mixture was dissolved in DCM (25ml), washed with 2N NaOH (10ml) and then extracted with dilute 2N HCl (2 x 25ml). The acid extract was made alkaline with saturated aqueous Na_2CO_3 solution (50ml) and the product extracted into DCM (2 x 50ml). The combined final organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a white crystalline solid (0.311g, 56%) m.p. 82-84°C. (Found M^+, 268.1589. $C_{17}H_{20}NO$ requires M, 268.1576); ν_{max} (KBr disk)/cm^{-1} 3285-3115 N-H$_{(str)}$, 3040, 2969 and 2874 C-H$_{(str)}$, 1662 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.35 (3H, d, *J*=7, CH_3), 1.95 (1H, bs, $CH_2N\underline{H}CH$), 3.30 (1H, q, *J*=7, $COC\underline{H}CH_3$), 3.75 (2H, s, $ArC\underline{H}_2NHCH$), 4.45 (2H, d, *J*=6, $ArC\underline{H}_2NHCO$), 7.20-7.50 (10H, m, aromatic) and 7.60 (1H, s, CONH); δ_C (62.88 MHz; $CDCl_3$) 23.1 (aliphatic), 44.3 and 44.8 ($ArCH_2$), 127.9, 129.0 and 138.0 (aromatic) and 170.1 (C=O).

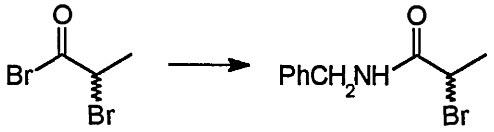
(*S*)-*N*-benzyl-2-bromopropanamide **145(*S*)**



128(*S*) **145(*S*)**

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.250g, 0.74mmol) was dissolved in THF (5ml) prior to the addition of benzylamine (0.087g, 0.81mmol) and stirring overnight at room temperature. Analysis by TLC (4:1 petrol / ethyl acetate) showed no starting material. Ethyl acetate (50ml) was added and the mixture washed with 2N HCl (2 x 15ml) and 2N NaOH (2 x 15ml). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as an off-white crystalline solid (0.130g, 73%) m.p. 87-90°C. (Found M^+, 241.0121. $C_{10}H_{12}NO^{79}Br$ requires M, 241.0102); ν_{max} (KBr disk)/cm^{-1} 3267 N-H$_{(str)}$, 3082, 2985, 2969 and 2922 C-H$_{(str)}$, 1650 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.95 (3H, d, *J*=8, CHBrC<u>H</u>$_3$), 4.45 (3H, m, CHBr and ArCH$_2$), 6.65 (1H, bs, N-H) and 7.20-7.40 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.1 (aliphatic), 44.3 and 44.8 (CHBr and ArCH$_2$), 127.9, 129.0 and 138.0 (aromatic) and 170.1 (C=O).

Racemic *N*-benzyl-2-bromopropanamide 145

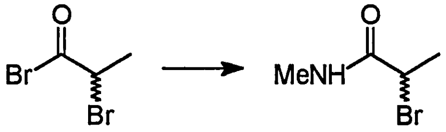


2-bromopropanoyl bromide **145**

Benzylamine **165** (1.00g, 9.35mmol) was dissolved in DCM (25ml) to which anhydrous Na_2CO_3 (3.36g, 32mmol) and 2-bromopropanoyl bromide (2.00g, 9.26mmol) were added. The reaction was stirred at room temperature until analysis by TLC (4:1 petrol / ethyl acetate) indicated complete conversion of starting material, then DCM (50ml) was added and the mixture washed with 2N HCl (2 x 15ml) and 2N NaOH (2 x 15ml). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a crystalline solid (1.18g, 53%) m.p. 87-90°C. (Found M^+, 241.0099. $C_{10}H_{12}NO^{79}Br$ requires M, 241.0102); ν_{max} (KBr disk)/cm^{-1} 3267 N-H$_{(str)}$, 3082,2985, 2969 and 2922 C-H$_{(str)}$ and 1650 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.95 (3H, d, *J*=8, CHBrC<u>H</u>$_3$), 4.45 (3H, m, CHBr and ArCH$_2$), 6.65 (1H, bs, N-H) and 7.20-7.40 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 23.1 (aliphatic), 44.3 and 44.8 (CHBr and Ar<u>C</u>H$_2$), 127.9, 129.0 and 138.0 (aromatic) and 170.1 (C=O).

Racemic *N*-methyl-2-bromoamides

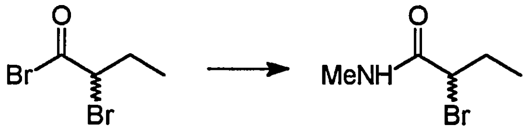
N-Methyl-2-bromopropanamide 146



2-bromopropanoyl bromide **146**

Racemic 2-bromopropanoyl bromide (3.00g, 13.9mmol) was dissolved in THF (50ml) to which anhydrous Na_2CO_3 (5.0g, 47.2mmol) and 40% w/w aqueous methylamine solution (1.10g, 14.7mmol) were added. The reaction was stirred at room temperature overnight and then ethyl acetate (75ml) was added and the mixture washed with 2N HCl (2 x 50ml) and 2N NaOH (2 x 25ml). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the title compound as a white crystalline solid (1.43g, 62%) m.p. 31-33°C. (Found M^+, 164.9785. $C_4H_8NO^{79}Br$ requires M, 164.9789); ν_{max} (film)/cm^{-1} 3290-3100 N-$H_{(str)}$, 2969-2879 C-$H_{(str)}$, 1650 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.80 (3H, d, *J*=8, CHBrC$\underline{H}_3$), 2.80 (3H, d, *J*=5, N-CH_3), 4.40 (1H, q, *J*=8, CHBr) and 7.10 (1H, bs, N-H).δ_C (62.88 MHz; $CDCl_3$) 22.0 (aliphatic), 25.6 (N-Me), 46.4 (CHBr) and 169.8 (C=O).

N-Methyl-2-bromobutanamide 147

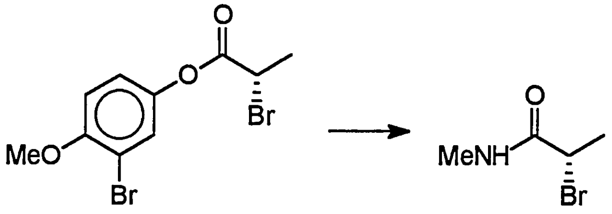


2-bromobutanoyl bromide **146**

This compound was prepared from 2-bromobutanoyl bromide (3.20g, 13.9mmol) using the method described above for the preparation of **147**. The title compound was isolated as an off-white crystalline solid (1.38g, 55%) m.p. 49-52°C. (Found M^+, 178.9951. $C_5H_{10}NO^{79}Br$ requires M, 178.9946); ν_{max} (KBr disk)/cm^{-1} 3290-3100 N-$H_{(str)}$, 2969-2874 C-$H_{(str)}$, 1657 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J*=7, CH_2C$\underline{H}_3$), 2.00 (2H, m, CH_3C$\underline{H}_2$), 2.80 (3H, d, *J*=5, N-CH_3), 4.25 (1H, t, *J*=7, CHBr) and 7.10 (1H, bs, N-H); δ_C (62.88 MHz; $CDCl_3$) 11.3 (aliphatic), 26.0 (N-Me), 29.4 (aliphatic), 52.4 (CHBr) and 169.5 (C=O).

Chiral (*S*)-*N*-methyl-2-bromoamides

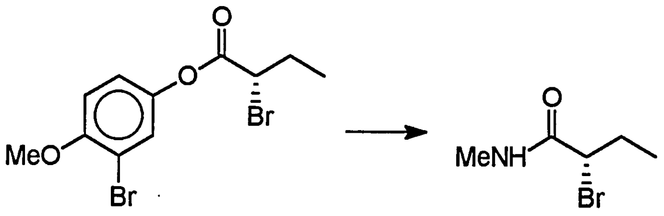
(*S*)-*N*-Methyl-2-bromopropanamide 146(*S*)



128(*S*) **146(*S*)**

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate **128(*S*)** (0.250g, (0.74mmol) was dissolved in THF (5ml) prior to the addition of 40% w/w aqueous methylamine solution (0.81mmol) followed by stirring overnight. Analysis by TLC (2:1 petrol / ethyl acetate) indicated complete conversion of starting material. Ethyl acetate (25ml) was added and the mixture washed with 2N HCl (2 x 10ml) and 2N NaOH (2 x 10ml). The organic layer was dried with $MgSO_4$ and the solvent removed under reduced pressure to give the crude (S)-*N*-methyl-2-bromoamide. Purification by flash chromatography (2:1 petrol / ethyl acetate) afforded the title compound as a white crystalline solid (0.081g, 66%, >95% e.e.) m.p. 31-33°C. (Found M^+, 164.9782. $C_4H_8NO^{79}Br$ requires M, 164.9789); ν_{max} (KBr disk)/cm^{-1} 3290-3100 $N\text{-}H_{(str)}$, 2969-2879 $C\text{-}H_{(str)}$, 1650 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.80 (3H, d, *J*=8, $CHBrC\underline{H_3}$), 2.80 (3H, d, *J*=5, $N\text{-}CH_3$), 4.40 (1H, q, *J*=8, CHBr) and 7.10 (1H, bs, N-H); δ_C (62.88 MHz; $CDCl_3$) 22.7 (aliphatic), 27.0 (N-Me), 44.0 (CHBr) and 171.1 (C=O).

(*S*)-*N*-Methyl-2-bromobutanamide 147(*S*)

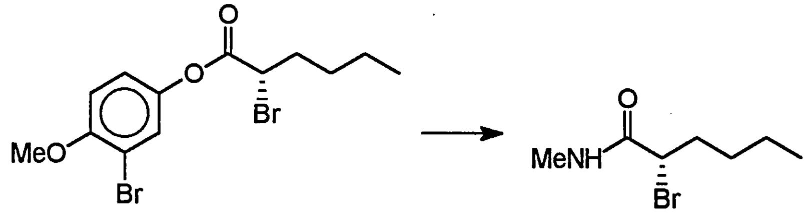


129(*S*) **147(*S*)**

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromobutanoate **129(*S*)** (0.260g, (0.74mmol) using the method described above for the preparation of **146(*S*)**. Purification by flash chromatography (2:1 petrol / ethyl acetate) afforded the title compound as an off-white crystalline solid (0.074g, 58%, >95% e.e.) m.p. 49-52°C.

(Found M^+, 178.9951. $C_5H_{10}NO^{79}Br$ requires M, 178.9946); ν_{max} (KBr disk)/cm^{-1} 3290-3100 N-$H_{(str)}$, 2969-2874 C-$H_{(str)}$, 1657 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.95 (3H, t, *J*=7, CH_3CH_2), 2.00 (2H, m, CH_3CH_2), 2.80 (3H, d, *J*=5, N-CH_3), 4.25 (1H, t, *J*=7, CHBr) and 7.10 (1H, bs, N-H); δ_C (62.88 MHz; $CDCl_3$) 12.0 (aliphatic), 27.2 (N-Me), 29.6 (aliphatic), 54.0 (CHBr) and 169.5 (C=O).

(*S*)-*N*-Methyl-2-bromohexanamide **148(*S*)**



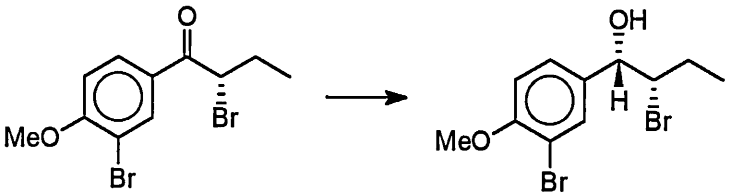
131(*S*) **148(*S*)**

This compound was prepared from 3-bromo-4-methoxyphenyl (*S*)-2-bromohexanoate **131(*S*)** (0.281g, 0.74mmol) using the method described above for the preparation of **146(*S*)**. Purification by flash chromatography (2:1 petrol / ethyl acetate) afforded the title compound as a pale brown viscous liquid (0.086g, 56%, 60% e.e.). (Found M^+, 207.0252. $C_7H_{14}NO^{79}Br$ requires M, 207.0259); ν_{max} (film)/cm^{-1} 3290-3100 N-$H_{(str)}$, 2975-2865 C-$H_{(str)}$, 1659 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, t, *J*=7, CH_2CH_3), 1.40 (4H, m, CH_3-$(CH_2)_2$-), 2.05 (1H, m, 0.5 x CH_2CHBr), 2.15 (1H, m, 0.5 x CH_2CHBr), 2.75 (3H, d, *J*=5, N-CH_3), 4.35 (1H, dd, *J*=7, CHBr) and 6.50 (1H, bs, N-H); δ_C (62.88 MHz; $CDCl_3$) 14.3 and 21.2 (aliphatic), 25.6 (N-Me), 28.8 and 35.1 (aliphatic), 50.2 (CHBr) and 169.4 (C=O).

Preparation of bromohydrins

Enantiomerically pure bromohydrin

(1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol **149(1*S*,2*S*)**



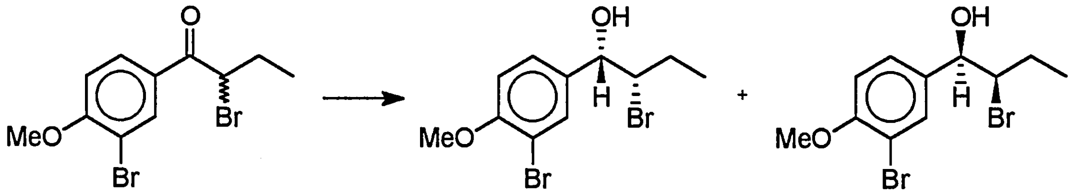
81(*S*) **149(1*S*,2*S*)**

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81**(*S*) (0.250g, 0.74mmol) was dissolved in bench methanol (20ml) and cooled to -78°C prior to the addition of sodium borohydride (0.028g, 0.74mmol). Analysis by TLC (4:1 petrol / ethyl acetate) of an acidified sample after 5 minutes showed a complete disappearance of starting material. The reaction mixture was neutralised with 2N HCl (20ml) and extracted with ether (3 x 25ml). The combined organic extracts were washed with water (25ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product as a colourless liquid. Purification by flash chromatography (4:1 petrol / ethyl acetate) gave the title compound as a colourless liquid (0.170g, 68%). (Found M^+, 335.9353. $C_{11}H_{14}O_2{}^{79}Br_2$ requires M, 335.9361); ν_{max} (film)/cm^{-1} 3620 O-$H_{(str)}$, 3026, 2993 and 2927 C-$H_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, t, *J*=8, $CH_2C\underline{H}_3$), 1.75 (2H, m, $CHBrC\underline{H}_2CH_3$), 2.65 (1H, bs, OH), 3.90 (3H, s, OCH_3), 4.15 (1H, m, CHBr), 4.65 (1H, d, *J*=7, $C\underline{H}OH$), 6.90 (1H, d, *J*=8, aromatic) 7.25 (1H, d, *J*=8, 2, aromatic) and 7.55 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.7 and 28.6 (aliphatic), 56.6 (MeO), 67.8 (CHBr), 76.5 (CH-OH), 112.1, 127.2, 131.8, 134.1 and 156.1 (aromatic).

Diastereomerically pure bromohydrin

(1*R*,2*R*) and (1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol

149(1*R*,2*R*) and (149(1*S*,2*S*)

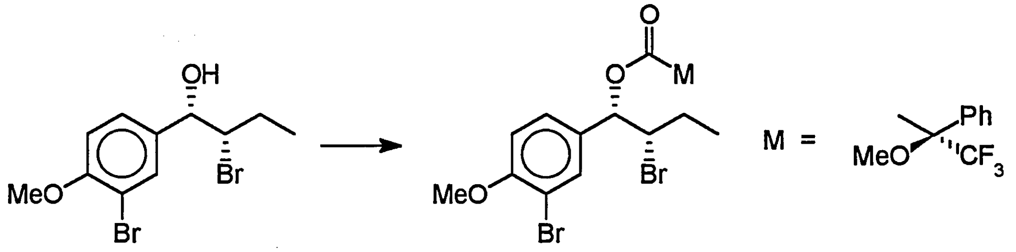


81 **149**(1*S*,2*S*) **149**(1*R*,2*R*)

These compounds were prepared from 2-bromo-1-(3-bromo-4-methoxyphenyl)-1-butanone **81** (0.250g, 0.74mmol) using the method described above for the preparation of **149**(1*S*,2*S*). Purification by flash chromatography (4:1 petrol / ethyl acetate) gave the title compound as a colourless liquid (0.170g, 76%). (Found M^+, 335.9366. $C_{11}H_{14}O_2{}^{79}Br_2$ requires M, 335.9361); ν_{max} (film)/cm^{-1} 3630 O-$H_{(str)}$, 3028, 2999 and 2920 C-$H_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.05 (3H, t, *J*=8, $CH_2C\underline{H}_3$), 1.75 (2H, m, $CHBrC\underline{H}_2CH_3$), 2.65 (1H, bs, OH), 3.90 (3H, s, OCH_3), 4.15 (1H, m, CHBr), 4.65 (1H, d, *J*=7, C<u>H</u>OH), 6.90 (1H, d, *J*=8, aromatic) 7.25 (1H, d, *J*=8, 2, aromatic) and 7.55 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.7 and 28.6 (aliphatic), 56.6 (MeO), 67.8 (CHBr), 76.5 (CH-OH), 112.1, 127.2, 131.8, 134.1 and 156.1 (aromatic).

Preparation of Mosher's esters of bromohydrins

(1*S*,2*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)butyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 150(1*S*,2*S*)

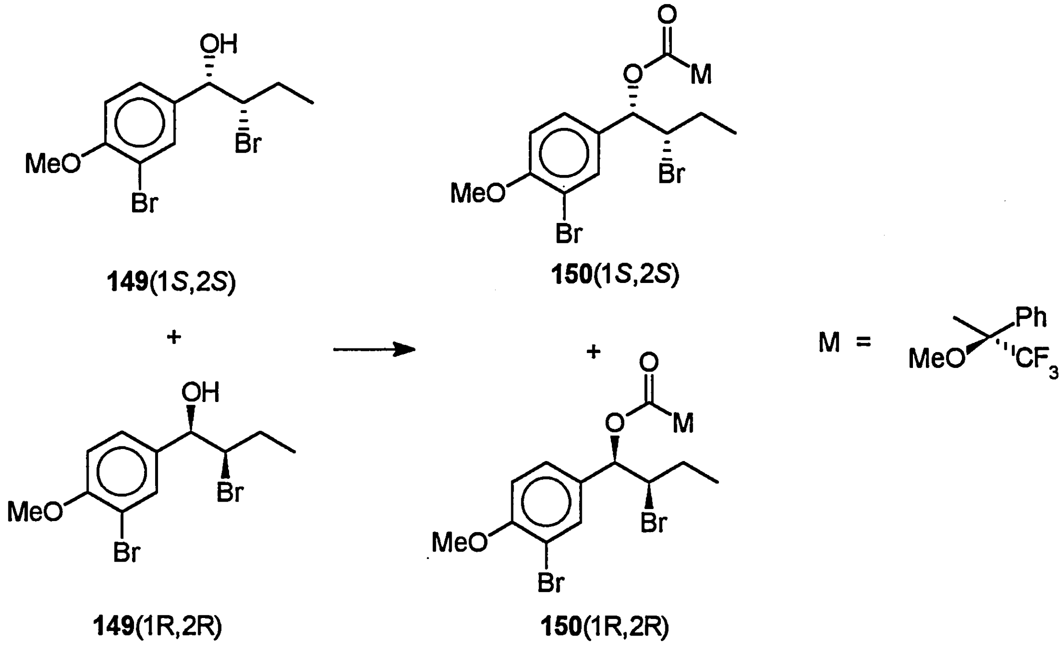


149(1*S*,2*S*) **150**(1*S*,2*S*)

The (1*S*,2*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol **150**(1*S*,2*S*) (0.164g, 0.485mmol) was dissolved in DCM (20ml) to which (*R*)-Mosher's acid (0.142g, 0.61mmol), DCC (0.131g, 0.61mmol) and DMAP (~5 mg) were added. The reaction was stirred at room temperature and monitored by TLC (4:1 petrol / ethyl acetate) until no starting material was observed. The reaction mixture was washed with 2N HCl (20ml), then 2N NaOH (20ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to yield the crude product. Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a colourless viscous liquid (0.193g, 72%). (Found M^+, 551.9772. $C_{21}H_{21}O_4{}^{79}Br_2F_3$ requires M, 551.9759); ν_{max} (film)/cm^{-1} 3021, 2983 and 2937 C-$H_{(str)}$ and 1745 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.00 (3H, t, *J*=7, $CH_2C\underline{H}_3$), 1.65 (2H, m, $C\underline{H}_2CH_3$), 3.45 (3H, s, OCH_3), 3.90 (3H, s, $ArOCH_3$), 4.15 (1H, m, CHBr), 6.00 (1H, d, *J*=8, CH-O), 6.85 (1H, *J*=8, aromatic) and 7.25-7.65 (9H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 12.1 and 27.9 (aliphatic), 55.9 (CHBr), 56.6 and 58.0 (2 x MeO), 79.8 (CH-O), 84.9 (q#, <u>C</u>-CF_3), 112.0, 112.2, 125.9, 127.9, 128.5, 128.7, 129.8, 130.0, 132.1, 132.5 and 156.8 (aromatic) and 162.5 (C=O, [1*S*,2*S*]).

[#] appearance similar to a quartet.

(1*R*,2*R*) and (1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **150(1*R*,2*R*)** and **150(1*S*,2*S*)**

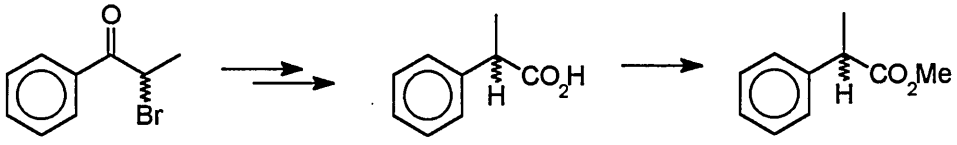


These compounds were prepared from a 1:1 mixture of (1*R*,2*R*)-2-bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol **149(**1*R*,2*R*) and (1*S*,2*S*)-2-bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol **149(**1*S*,2*S*) (0.164g, 0.485mmol) (0.164g, 0.485mmol) using the method described above for the preparation of **150(**1*S*,2*S*). Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded a mixture of the title compounds as a colourless viscous liquid (0.193g, 72%). (Found M$^+$, 551.9772. $C_{21}H_{21}O_4{}^{79}Br_2F_3$ requires M, 551.9759); ν_{max} (film)/cm^{-1} 3026, 2982 and 2934 C-H$_{(str)}$ and 1748 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.00 (3H, t, *J*=7, $CH_2C\underline{H}_3$), 1.65 (2H, m, $C\underline{H}_2CH_3$), 3.45 (1.5H, s, 0.5 x OCH_3), 3.65 (1.5H, s, 0.5 x OCH_3), 3.90 (3H, s, $ArOCH_3$), 4.15 (1H, m, CH_3 $CH_2C\underline{H}Br$), 5.90 (0.5H, d, *J*=8, 0.5 x C$\underline{H}$-O), 6.00 (0.5H, d, *J*=8, 0.5 x CH-O), 6.80 (0.5H, *J*=8, aromatic), 6.85 (0.5H, *J*=8, aromatic) and 7.25-7.65 (9H, m, aromatic); δ_C (62.88 MHz; CDCl$_3$) 12.1, 14.4, 21.2 and 27.9 (aliphatic), 55.9 (CHBr), 56.6 and 58.0 (2 x MeO), 79.8 (CH-O), 84.9 (q#, $\underline{C}$-CF$_3$), 112.0, 112.2, 125.9, 127.9, 128.5, 128.7, 129.8, 130.0, 132.1, 132.5 and 156.8 (aromatic), 162.5 (C=O, [1*S*,2*S*]) and 171.4 (C=O, [1*R*,2*R*])

appearance similar to a quartet.

Rearrangement of racemic 2-bromopropiophenone

2-Phenylpropanoic acid 151

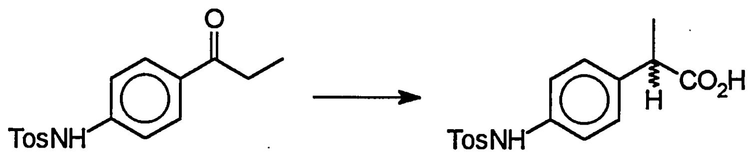


89 **151**

Anhydrous zinc bromide (21.2g, 94.1mmol) was added to dry methanol (5.6g, 175mmol) and stirred under a nitrogen atmosphere for 5 minutes. 2-Bromopropiophenone **89** (2.00g, 9.4mmol) was added and the reaction mixture was heated at reflux for 4 hours. The reaction was allowed to cool to room temperature before the addition of water (20ml) and extraction with DCM (2 x 20ml). The combined DCM extracts were washed with water (40ml), dried with Na_2SO_4 and the solvent removed under reduced pressure to give the crude ester. The crude ester was hydrolysed under alkaline conditions with 2N NaOH (30ml), methanol (50ml) and water (50ml) at reflux overnight. The reaction was allowed to cool before extraction with DCM (2 x 50ml). The aqueous layer was acidified to pH 2 with conc. HCl and extracted with DCM (2 x 50ml). The combined organic extracts were dried with Na_2SO_4 and the solvent removed under reduced pressure to give the crude acid which was treated with diazomethane to give the title compound as a colourless viscous liquid (0.60g, 39%). (Found M^+, 164.0832. $C_{10}H_{12}O_2$ requires M, 164.0837); ν_{max} (film)/cm^{-1} 3010, 2978 and 2949 $C\text{-}H_{(str)}$ and 1746 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, d, *J*=7, $CHC\underline{H}_3$), 3.70 (3H, s, OCH_3), 3.80 (1H, q, *J*=7, $C\underline{H}CH_3$), 7.35 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.0 and 41.8 (aliphatic), 52.1 (MeO), 125.0, 126.9, 128.1 and 145.2 (aromatic) and 172.0 (C=O).

Rearrangement with iodobenzene diacetate

2-(4-*p*-Toluenesulphonamidophenyl)propanoic acid 152

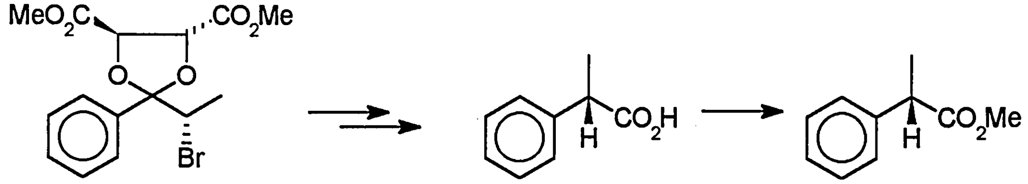


59 **152**

To a stirred solution of 1-(4-*p*-toluenesulphonamidophenyl)-1-propanone **59** (1.00g, 3.3mmol) and iodobenzene diacetate (1.28g, 4mmol) in trimethyl orthoformate (10ml), conc. sulphuric acid (0.64g) was added slowly at room temperature. The reaction was heated at 60°C until complete conversion of starting material was observed by TLC analysis (2:1 petrol / ethyl acetate). The reaction mixture was then quenched with water and extracted with ethyl acetate (2 x 20ml). The combined organic extracts were washed with water (20ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to give the crude methyl ester. The crude ester was added to 2N HCl (25ml) and heated at reflux until analysis by TLC (4:1 petrol / ethyl acetate) showed complete conversion of the ester. The reaction was allowed to cool to room temperature before being made alkaline (~ pH 9) with 2N sodium hydroxide and then extracted with ethyl acetate (2 x 20ml). The aqueous layer was acidified with conc. hydrochloric acid and extracted with ethyl acetate (2 x 20ml). The combined organic extracts were washed with water (20ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to give the title compound as a pale brown crystalline solid (0.49g, 47%) m.p. 80-81°C. (Found M^+, 319.0882. $C_{16}H_{17}NO_4S$ requires M, 319.0878); ν_{max} (film)/cm^{-1} 3293 $N\text{-}H_{(str)}$, 3210-2625 $O\text{-}H_{(str)}$, 3003, 2970 and 2945 $C\text{-}H_{(str)}$ and 1716 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, d, *J*=7, $CH\underline{H_3}$), 2.20 (3H, s, $ArCH_3$), 3.65 (1H, q, *J*=7, $C\underline{H}CH_3$), 7.00 (2H, d, *J*=8, aromatic), 7.05 (2H, d, *J*=8, aromatic), 7.10 (2H, d, *J*=8, aromatic), 7.65 (2H, d, *J*=8, aromatic), 8.10 (1H, s, N-H) and 10.70 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 18.4, 21.9 and 44.9 (aliphatic), 121.7, 127.6, 128.8, 130.1, 136.2, 136.4, 136.8 and 144.3 (aromatic) and 180.3 (C=O).

Rearrangement of bromoacetal diesters using $AgBF_4$

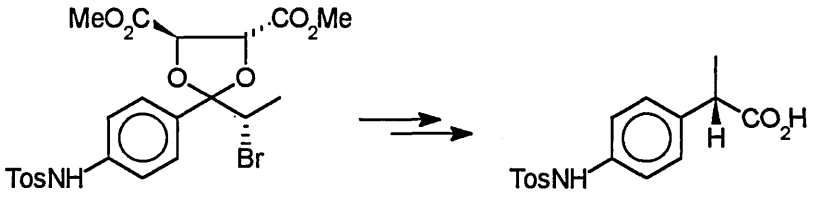
(*S*)-2-Phenylpropanoic acid 151(*S*)



108 **151(*S*)**

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (1.00g, 2.70mmol) was dissolved in 1,2-dichloromethane (10ml) to which silver tetrafluoroborate (0.73g, 3.75mmol) and water (0.073g, 4.05mmol) were added. The reaction was stirred overnight at room temperature after which TLC (4:1 petrol / ethyl acetate) indicated complete conversion of the starting material. The reaction was poured into water (25ml) and extracted with DCM (2 x 25ml), dried (Na_2SO_4) and the solvent removed under reduced pressure to give a solid (~0.50g). The solid was heated at reflux for 4 hours with acetic acid (2.5ml), conc. HCl (3ml) and water (23ml), then cooled to room temperature before being extracted with DCM (2 x 25ml). The combined organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to give the title compound as a colourless oil contaminated with acetic acid. Treatment with diazomethane gave the crude methyl ester which was purified by flash chromatography (9:1 petrol / ethyl acetate) to give the methyl ester as a viscous oil (0.31g, 71%, 78% e.e.). (Found M^+, 164.0848. $C_{10}H_{12}O_2$ requires M, 164.0837); ν_{max} (film)/cm^{-1} 3012, 2979 and 2946 $C\text{-}H_{(str)}$ and 1748 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, d, *J*=7, $CHC\underline{H}_3$), 3.70 (3H, s, OCH_3), 3.80 (1H, q, *J*=7, $C\underline{H}CH_3$), 7.35 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.0 and 41.8 (aliphatic), 52.1 (MeO), 125.0, 126.9, 128.1 and 145.2 (aromatic) and 172.0 (C=O).

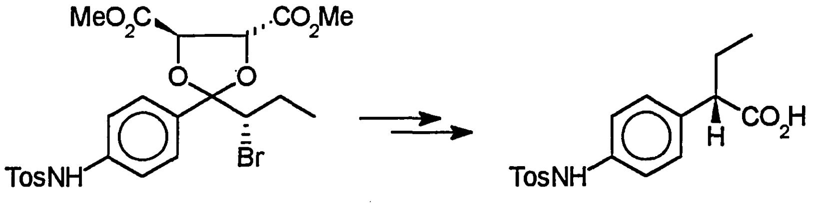
<u>(*S*)-2-(4-*p*-Toluenesulphonamidophenyl)propanoic acid **152(*S*)**</u>



117 **152(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **117** (1.46g, 2.70mmol) using the method described above for the preparation of **151*S*** except that the crude title compound was not treated with diazomethane. The crude title compound was isolated as an off-white crystalline solid (0.40g, 46%) m.p. 80-81°C. (Found M^+, 319.0882. $C_{16}H_{17}NO_4S$ requires M, 319.0878); ν_{max} (film)/cm^{-1} 3295 $N\text{-}H_{(str)}$, 3230-2610 $O\text{-}H_{(str)}$, 3006, 2972 and 2951 $C\text{-}H_{(str)}$ and 1712 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, d, *J*=7, $CHC\underline{H}_3$), 2.20 (3H, s, $ArCH_3$), 3.65 (1H, q, *J*=7, $C\underline{H}CH_3$), 7.00 (2H, d, *J*=8, aromatic), 7.05 (2H, d, *J*=8, aromatic), 7.10 (2H, d, *J*=8, aromatic), 7.65 (2H, d, *J*=8, aromatic), 8.15 (1H, s, N-H) and 11.20 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 18.4, 21.9 and 44.9 (aliphatic), 121.7, 127.6, 128.8, 130.1, 136.2, 136.4, 136.8 and 144.3 (aromatic) and 180.3 (C=O).

(*S*)-2-(4-*p*-Toluenesulphonamidophenyl)butanoic acid **153(*S*)**

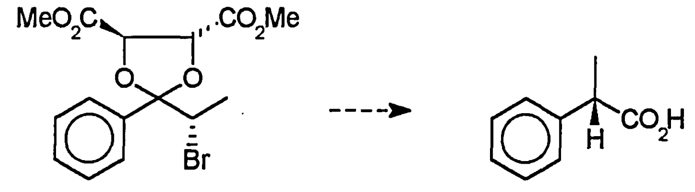


118 **153(*S*)**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **118** (0.150g, 0.27mmol) using the method described above for the preparation of **151(*S*)** except that the crude title compound was not treated with diazomethane. The crude title compound was isolated as a pale brown coloured viscous liquid (0.03g, 34%). (Found M^+, 333.1052. $C_{17}H_{19}NO_4S$ requires M, 333.1035); ν_{max} (film)/cm^{-1} 3290 N-$H_{(str)}$, 3200-2600 O-$H_{(str)}$, 3010, 2972 and 2946 C-$H_{(str)}$ and 1716 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J*=7, $CH_2C\underline{H_3}$), 1.80 (1H, m, ½ $CH\underline{H_2}CH_3$), 2.00 (1H, m, ½ $CH\underline{H_2}CH_3$), 2.20 (3H, s, $ArCH_3$), 3.45 (1H, q, *J*=7, $C\underline{H}CH_2CH_3$), 7.00 (2H, d, *J*=8, aromatic), 7.05 (2H, d, *J*=8, aromatic), 7.10 (2H, d, *J*=8, aromatic), 7.65 (2H, d, *J*=8, aromatic), 8.35 (1H, s, N-H), 10.2 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 12.8, 21.6, 25.9 and 49.4 (aliphatic), 120.4, 128.7, 129.0, 129.9, 133.3, 133.6, 137.8 and 145.1 (aromatic) and 177.6 (C=O).

Rearrangement of bromoacetal 108 with $ZnBr_2$

Attempted preparation of (*S*)-2-phenylpropanoic acid **151(*S*)**

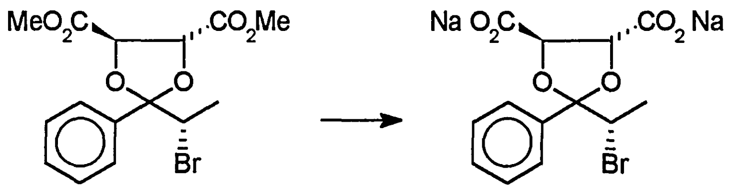


108 **151(*S*)**

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (1.00g, 2.68mmol) was dissolved in dry toluene (20ml) to which was added anhydrous zinc bromide (0.30g, 1.34mmol) and the atmosphere purged with nitrogen before the reaction was heated to reflux. After 24 hours at reflux the reaction was poured into water (20ml) and extracted with DCM (2 x 20ml). The combined organic extracts were dried with Na_2SO_4 and the solvent removed under reduced pressure to give a brown viscous oil (0.75g). The brown oil was dissolved in acetic acid (2.5ml), conc. HCl (3ml) and water (23ml) and heated at reflux for 4 hours, before being allowed to cool to room temperature. The crude carboxylic acid produced was extracted with DCM (2 x 20ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to give a brown oil (~0.6g) contaminated with acetic acid. The crude carboxylic acid was treated with diazomethane to give the crude methyl ester, which was purified by flash chromatography (9:1 petrol / ethyl acetate) to give the title compound as a colourless viscous liquid (0.23g, 52%, 0% e.e.). (Found M^+, 164.0842. $C_{10}H_{12}O_2$ requires M, 164.0837); ν_{max} (film)/cm^{-1} 3010, 2978 and 2942 $C\text{-}H_{(str)}$ and 1746 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, d, *J*=7, $CHC\underline{H}_3$), 3.70 (3H, s, OCH_3), 3.80 (1H, q, *J*=7, $C\underline{H}CH_3$), 7.35 (5H, m, aromatic); δ_C (62.88 MHz; $CDCl_3$) 20.0 and 41.8 (aliphatic), 52.1 (MeO), 125.0, 126.9, 128.1 and 145.2 (aromatic) and 172.0 (C=O).

Preparation of bromoacetal di-sodium salt

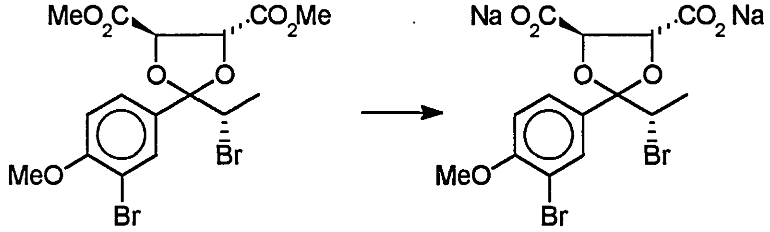
Disodium (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate 156



108 **156**

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **108** (0.97g, 2.6mmol) was dissolved in dry methanol (5ml) prior to the addition of NaOH (0.21g, 5.3mmol) and water (0.05g, 2.6mmol). The reaction was stirred at room temperature and monitored by ^1H NMR spectroscopy until complete conversion of the starting material was observed where upon the solvent was removed under reduced pressure. The title compound was obtained as an off-white hygroscopic crystalline solid (0.96g, 95%, 78% d.e.) m.p. 57-59°C. ν_{max} (KBr disk)/cm^{-1} 3001-2981 C-H$_{(str)}$, 1580, 1440 and 1422 $CO_{2\,(str)}$; δ_H (250 MHz; DMSO-d6) 1.70 (3H, d, *J*=7, CH_3), 3.90 and 4.25 (2 x 1H, 2 x d, *J*=9, 2 x CH-O), 4.65 (1H, d, *J*=7, CHBr), 7.25 (3H, d, *J*=8, aromatic) and 7.75 (2H, d, *J*=8, aromatic); δ_C (62.88 MHz; DMSO-d6) 20.8 (aliphatic), 51.3 (CHBr), 82.3 and 83.2 (2 x CH-O), 118.5 (O-C-O), 126.3, 128.0, 129.4, 142.4 (aromatic), 174.0 and 173.7 (2 x C=O).

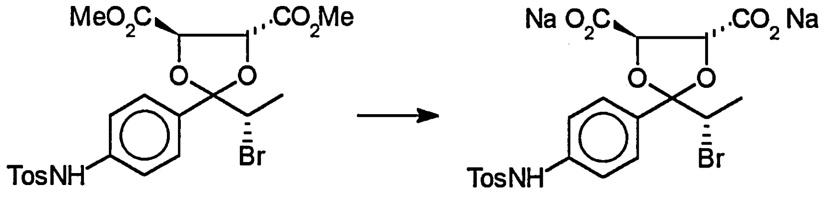
Disodium (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **157**



112 **157**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **112** (1.25g, 2.6mmol) using the method described above for the preparation of **156**. The title compound was isolated as an off-white hygroscopic crystalline solid (1.15g, 89%, 71% d.e.) m.p. 55-58°C. (ν_{max} (film)/cm^{-1} 3021-2965, C-H$_{(str)}$, 1575, 1436 and 1429 $CO_{2\,(str)}$; δ_H (250 MHz; DMSO-d6) 1.60 (3H, t, *J*=7, $CHBrCH_3$), 3.90 (3H, s, OCH_3), 4.35 (1H, q, *J*=7, $CHBr\ CH_3$), 4.45 and 4.65 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.90 (1H, d, *J*=8, aromatic), 7.45 (1H, dd, *J*=8 and 2, aromatic) and 7.70 (1H, d, *J*=2, aromatic); δ_C (62.88 MHz; DMSO-d6) 20.9 (aliphatic), 52.8 (CHBr), 56.4 (MeO), 77.3 and 78.2, (2 x CH-O), 113.4 (O-C-O), 113.6, 127.0, 128.8, 129.3 and 160.5 (aromatic), 171.2 and 170.9 (2 x C=O).

Disodium (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **158**

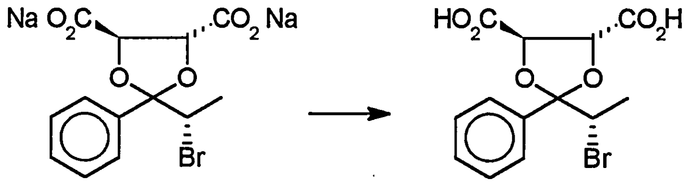


117 **158**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **117** (1.41g, 2.6mmol) using the method described above for the preparation of **156**. The title compound was isolated as an off-white hygroscopic crystalline solid (1.13g, 78%, d.e. N / A) m.p. 80-82°C. (ν_{max} (KBr disk)/cm^{-1} 3292 N-H$_{(str)}$, 3021-2965, C-H$_{(str)}$, 1575 and 1436 CO$_{2(str)}$; δ_H (250 MHz; DMSO-d6) 1.55 (3H, t, *J*=7, CHBrC$\underline{H_3}$), 2.35 (3H, s, ArCH$_3$), 4.30 (1H, q, *J*=7, C$\underline{H}$Br), 4.50 and 4.65 (2 x 1H, 2 x s, 2 x CH-O), 7.10 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.40 (2H, d, *J*=9, aromatic), 7.70 (2H, d, *J*=8, aromatic), 7.85 (1H, s, N-H); δ_C (62.88 MHz; DMSO-d6) 20.9 and 21.8 (aliphatic), 52.9 (CHBr), 113.5 (O-C-O), 120.3, 127.6, 128.6, 130.1, 133.3, 136.2, 138.1 and 144.5 (aromatic), 169.0 and 171.8 (2 x C=O).

Preparation of bromoacetal diacids

(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylic acid **159**

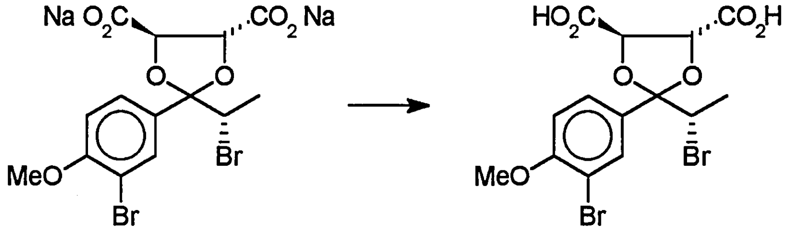


156 **159**

Disodium (4*R*,5*R*)-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **156** (0.100g, 0.26mmol) was dissolved in water (15ml), acidified to pH 2 with conc. HCl and extracted with DCM (2 x 10ml). The combined organic extracts were dried with MgSO$_4$ and the solvent removed under reduced pressure to give the title compound as a colourless liquid (0.066g, 74%). (Found M$^+$, 343.9907. C$_{13}$H$_{13}$O$_6$^{79}Br requires M, 343.9896); ν_{max} (film)/cm^{-1} 3215-2700 O-H$_{(str)}$, 3012-2961 C-H$_{(str)}$ and 1720 C=O$_{(str)}$; δ_H

(250 MHz; $CDCl_3$) 1.60 (3H, d, *J*=7, CHBrC<u>H</u>$_3$), 4.40 (1H, q, *J*=7, C<u>H</u>BrCH$_3$), 4.85 and 5.00 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 7.35 (3H, m, aromatic), 7.55 (2H, m, aromatic) and 11.3 (2H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 20.8 (aliphatic), 53.3 (CHBr), 76.3 and 77.2 (2 x CH-O), 113.5 (O-C-O), 126.3, 126.8, 129.4 and 139.4 (aromatic), 170.7 and 171.0 (2 x C=O).

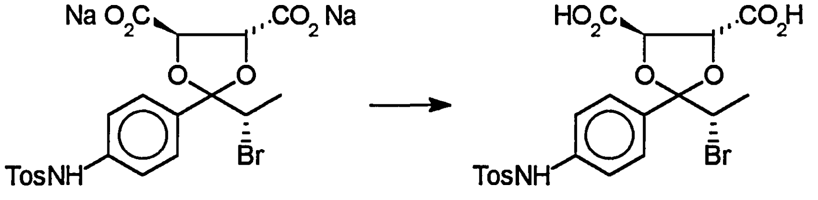
<u>(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylic acid **160**</u>



157 **160**

This compound was prepared from disodium (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **157** (0.130g, 0.26mmol) using the method described above for the preparation of **159**. The title compound was isolated as a colourless viscous liquid (0.100g, 84%). (Found M$^+$, 451.9106. $C_{14}H_{14}O_7{}^{79}Br_2$ requires M, 451.9106); ν_{max} (film)/cm^{-1} 3205-2650 O-H$_{(str)}$, 3010-2955 C-H$_{(str)}$ and 1726 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.60 (3H, t, *J*=7, CHBrC<u>H</u>$_3$), 3.90 (3H, s, OCH$_3$), 4.35 (1H, q, *J*=7, C<u>H</u>BrCH$_3$), 4.80 and 4.95 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.90 (1H, d, *J*=8, aromatic), 7.45 (1H, dd, *J*=8 and 2, aromatic), 7.70 (1H, d, *J*=2, aromatic) and 10.00 (2H, bs, 2 x OH); δ_C (62.88 MHz; $CDCl_3$) 20.9 (aliphatic), 52.8 (CHBr), 56.4 (MeO), 77.3 and 78.2 (CH-O), 113.4 (O-C-O), 113.6, 127.0, 128.8, 129.3 and 160.5 (aromatic), 170.9 and 171.2 (2 x C=O).

(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylic acid **161**

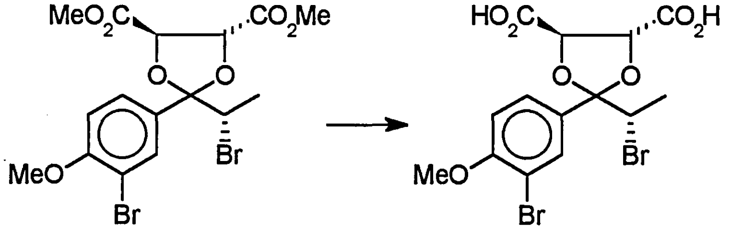


158 **161**

This compound was prepared from disodium (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **158** (0.145g, 0.26mmol) using the method described above for the preparation of **159**. The title compound was isolated as an off-white hygroscopic crystalline solid (0.111g, 83%) m.p. 189-192°C. (Found M$^+$, 513.0082. $C_{20}H_{20}NO_8S^{79}Br$ requires M, 513.0093); ν_{max} (film)/cm^{-1} 3295 N-H$_{(str)}$, 3200-2680 O-H$_{(str)}$, 3010-2953 C-H$_{(str)}$ and 1723 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, t, *J*=7, $CHBrC\underline{H}_3$), 2.35 (3H, s, $ArCH_3$), 4.30 (1H, q, *J*=7, $C\underline{H}BrCH_3$), 4.90 (2H, s, 2 x CH-O), 7.10 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.40 (2H, d, *J*=9, aromatic), 7.70 (2H, d, *J*=8, aromatic), 7.85 (1H, s, N-H) and 8.10 (2H, bs, 2 x OH); δ_C (62.88 MHz; $CDCl_3$) 20.9 and 21.8 (aliphatic), 52.9 (CHBr), 113.5 (O-C-O), 120.3, 127.6, 128.6, 130.1, 133.3, 136.2, 138.1 and 144.5 (aromatic), 169.0 and 171.8 (2 x C=O).

Bromoacetal diester to bromoacetal diacid

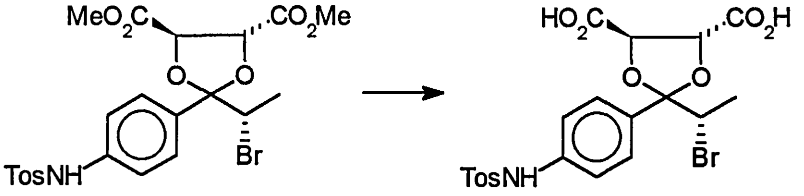
(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylic acid **160**



112 **160**

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate **112** (0.89g, 1.85mmol) was dissolved in dry methanol (10ml) prior to the addition of NaOH (0.15g, 3.75mmol) and water (0.04g, 2.22mmol). The reaction was stirred overnight at room temperature after which analysis by TLC (ethyl acetate) and ^{1}H NMR indicated complete conversion of the starting material. The reaction was adjusted to pH 2 with 2N HCl and extracted with DCM (2 x 25ml). The combined organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound as a brown viscous liquid (0.65g, 78%). (Found M$^+$, 451.9101. $C_{14}H_{14}O_7{}^{79}Br_2$ requires M, 451.9106); ν_{max} (film)/cm^{-1} 3205-2650 O-H$_{(str)}$, 3010-2955 C-H$_{(str)}$ and 1726 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.60 (3H, t, *J*=7, CHBrC<u>H</u>$_3$), 3.90 (3H, s, OCH_3), 4.35 (1H, q, *J*=7, C<u>H</u>BrCH$_3$), 4.80 and 4.95 (2 x 1H, 2 x d, *J*=6, 2 x CH-O), 6.90 (1H, d, *J*=8, aromatic), 7.45 (1H, dd, *J*=8 and 2, aromatic), 7.70 (1H, d, *J*=2, aromatic) and 10.00 (2H, bs, 2 x O<u>H</u>); δ_C (62.88 MHz; $CDCl_3$) 20.9 (aliphatic), 52.8 (CHBr), 56.4 (MeO), 77.3 and 78.2 (CH-O), 113.4 (O-C-O), 113.6, 127.0, 128.8, 129.3 and 160.5 (aromatic), 170.9 and 171.2 (2 x C=O).

(4*R*,5*R*)-2-[(1*S*)-1-Bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylic acid **161**

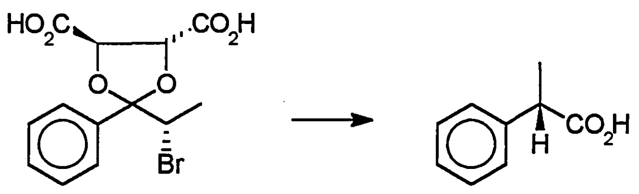


117 **161**

This compound was prepared from dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylate **117** (1.00g, 1.85mmol) using the method described above for the preparation of **160**. The title compound was isolated as an off-white hygroscopic crystalline solid (0.41g, 44%) m.p. 189-192°C. (Found M$^+$, 513.0088. $C_{20}H_{20}NO_8S^{79}Br$ requires M, 513.0093); ν_{max} (film)/cm^{-1} 3295 N-H$_{(str)}$, 3200-2680 O-H$_{(str)}$, 3010-2953 C-H$_{(str)}$ and 1723 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, t, *J*=7, CHBrC<u>H</u>$_3$), 2.35 (3H, s, $ArCH_3$), 4.30 (1H, q, *J*=7, C<u>H</u>BrCH$_3$), 4.90 (2H, s, 2 x CH-O), 7.10 (2H, d, *J*=9, aromatic), 7.25 (2H, d, *J*=8, aromatic), 7.40 (2H, d, *J*=9, aromatic), 7.70 (2H, d, *J*=8, aromatic), 7.85 (1H, s, N-H) and 8.10 (2H, bs, 2 x OH); δ_C (62.88 MHz; $CDCl_3$) 20.9 and 21.8 (aliphatic), 52.9 (CHBr), 113.5 (O-C-O), 120.3, 127.6, 128.6, 130.1, 133.3, 136.2, 138.1 and 144.5 (aromatic), 169.0 and 171.8 (2 x C=O).

Rearrangement of bromoacetal diacids

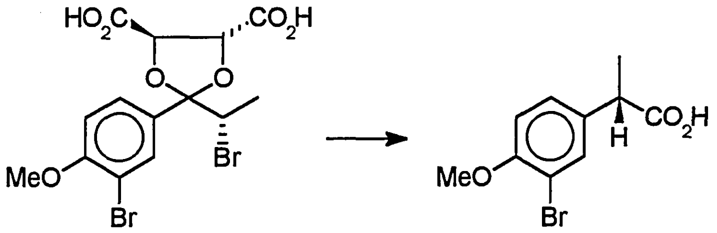
(*S*)-2-Phenylpropanoic acid **151(*S*)**



159 **151(*S*)**

(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylic acid **159** (1.00g, 2.89mmol) was dissolved in water (40ml) to which NaOH (0.29g, 7.25mmol) and KH_2PO_4 (5.78g, 42.5mmol) were added. The solution was heated at reflux until TLC (2:1 petrol / ethyl acetate) indicated that no starting material remained. The reaction was allowed to cool to room temperature before acidification to pH 2 with conc. HCl and extraction with DCM (2 x 25ml). The combined organic extracts were dried with $MgSO_4$ and the solvent removed under reduced pressure to give the title compound as an almost colourless viscous liquid (0.19g, 44%). (Found M^+, 150.0686. $C_9H_{10}O_2$ requires M, 150.0681); ν_{max} (film)/cm^{-1} 3200-2630 O-$H_{(str)}$, 3001, 2980 and 2933 C-$H_{(str)}$ and 1718 C=$O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.55 (3H, d, *J*=7, CH_3), 3.80 (1H, q, *J*=7, CH), 7.35 (5H, m, aromatic), 9.20 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 20.0 and 41.8 (aliphatic), 125.0, 126.9, 128.1 and 145.2 (aromatic) and 172.0 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester which was purified by flash chromatography (9:1 petrol / ethyl acetate) and analysed by ^{1}H NMR in the presence of Eu(hfc)$_3$ which determined the enantiomeric excess to be 78%.

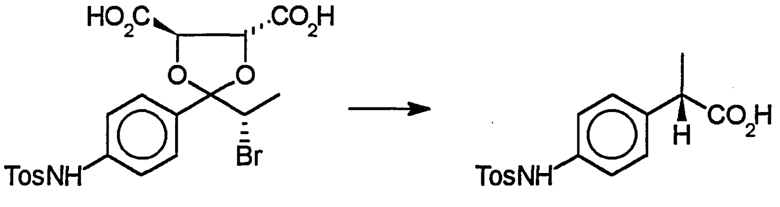
(*S*)-2-(3-Bromo-4-methoxyphenyl)propanoic acid **152(*S*)**



160 **152(*S*)**

This compound was prepared from (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylic acid **160** (1.31g, 2.89mmol) using the method described above for the preparation of **151(*S*)** from **159**. The title compound was isolated as an almost colourless viscous liquid (0.24g, 32%). (Found M$^+$, 257.9899. $C_{10}H_{11}O_3{}^{79}Br$ requires M, 257.9892); ν_{max} (film)/cm^{-1} 3150-2600 O-H$_{(str)}$, 3006, 2969 and 2926 C-H$_{(str)}$ and 1710 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.50 (3H, d, *J*=7, CHC$\underline{H}_3$), 3.65 (1H, q, *J*=7, C$\underline{H}$CH$_3$), 3.90 (3H, s, OCH$_3$), 6.85 (1H, d, *J*=8, aromatic), 7.20 (1H, dd, *J*=8 and 2, aromatic), 7.50 (1H, d, *J*=2, aromatic) 10.15 (1H, bs, OH); δ_C (62.88 MHz; $CDCl_3$) 20.0 and 41.6 (aliphatic), 56.4 (MeO), 112.5, 113.9, 125.4, 128.9, 132.7 and 158.5 (aromatic) and 172.0 (C=O). Treatment of a small aliquot of the title compound with diazomethane gave the corresponding methyl ester which was purified by flash chromatography (9:1 petrol / ethyl acetate) and analysed by ^{1}H NMR in the presence of Eu(hfc)$_3$ which determined the enantiomeric excess to be 71%.

(*S*)-2-(4-*p*-Toluenesulphonamidophenyl)propanoic acid **162(*S*)**

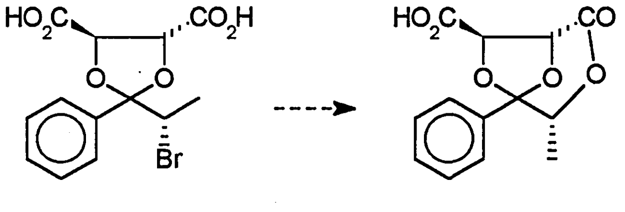


161 **162(*S*)**

This compound was prepared from (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-*p*-toluenesulphonamidophenyl)-1,3-dioxolane-4,5-dicarboxylic acid **161** (1.48g, 2.89mmol) using the method described above for the preparation of **151(*S*)** from **159**. The title compound was isolated as an off-white crystalline solid (0.33g, 36%) m.p. 80-81°C. (Found M$^+$, 319.0882. $C_{16}H_{17}NO_4S$ requires M, 319.0878); ν_{max} (film)/cm^{-1} 3295 N-H$_{(str)}$, 3230-2610 O-H$_{(str)}$, 3006, 2972 and 2951 C-H$_{(str)}$ and 1712 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.40 (3H, d, *J*=7, CHC<u>H</u>$_3$), 2.20 (3H, s, ArCH$_3$), 3.65 (1H, q, *J*=7, C<u>H</u>CH$_3$), 7.00 (2H, d, *J*=8, aromatic), 7.05 (2H, d, *J*=8, aromatic), 7.10 (2H, d, *J*=8, aromatic), 7.65 (2H, d, *J*=8, aromatic), 8.15 (1H, s, N-H), 11.20 (1H, bs, OH); δ_C (62.88 MHz; CDCl$_3$) 18.4, 21.9 and 44.9 (aliphatic), 121.7, 127.6, 128.8, 130.1, 136.2, 136.4, 136.8 and 144.3 (aromatic) and 180.3 (C=O).

Treatment of a small aliquot of the title compound with diazomethane was not attempted because we had shown that the title compound **162** undergoes methylene insertion at the sulphonamide as well as at the carboxylic acid functional group.

<u>Attempted preparation of a lactone derived from propiophenone bromoacetal diacid **163**</u>

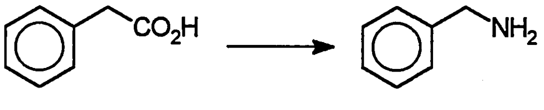


159 **163**

(4*R*,5*R*)-2-[(*S*)-1-Bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylic acid **159** (0.090g, 0.261mmol) and sodium hydride (0.01g, 0.42mmol) in DMF (2ml) were heated at 105°C for 36 hours. Analysis by TLC (ethyl acetate) showed numerous spots but we were unable to remove sufficient DMF to allow characterisation of any of the products.

<u>Curtius rearrangement of phenylacetic acid</u>

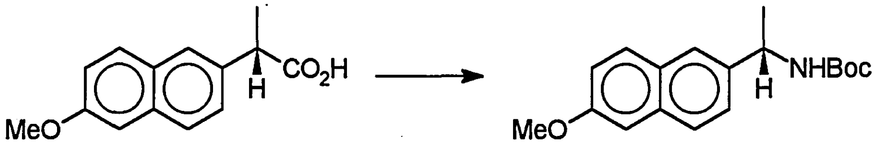
<u>Preparation of benzylamine **165**</u>



164 **165**

Phenylacetic acid **164** (3.4g, 25mmol) was dissolved in conc. sulphuric acid (10ml) and oleum (3ml) prior to the addition of chloroform (10ml). The reaction was heated to 45°C before sodium azide (1.75g, 27mmol) was added slowly, the reaction was then heated at reflux for 2 hours. Analysis by TLC (2:1 petrol / ethyl acetate) indicated the complete conversion of starting material. The reaction mixture was allowed to cool before being poured into saturated aqueous Na_2CO_3 solution (100ml) and extracted with DCM (2 x 25ml). The combined organic extracts were washed with water (50ml), dried with $MgSO_4$ and the solvent removed under reduced pressure to give the crude product as a pale yellow oil (1.61g, 60%). The ^{13}C and ^1H NMR spectra were identical to those of benzylamine.

(*S*)-*N*-*t*-Butoxycarbonyl-1-(6-methoxy-2-naphthyl)ethylamine **166(*S*)**

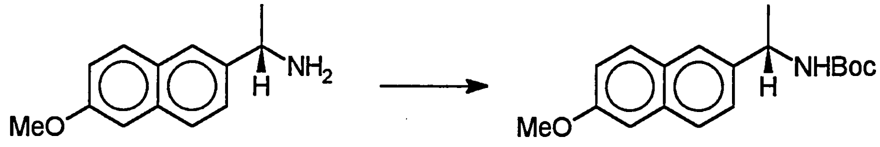


11(*S*) **166(*S*)**

(*S*)-2-(6-Methoxy-2-naphthyl)propanoic acid **11(*S*)** (1.00g, 4.35mmol) was dissolved in dry *t*-butanol (25ml), prior to the addition of triethylamine (0.88g, 8.70mmol) and diphenylphosphoryl azide (2.39g, 8.70mmol). The reaction mixture was heated at reflux overnight after which analysis by TLC (4:1 petrol / ethyl acetate) indicated complete conversion of starting material. The reaction was allowed to cool before being poured into stirred saturated aqueous Na_2CO_3 solution (25ml) and filtering off the white solid. The solid was washed with saturated Na_2CO_3 solution (25ml) and water (25ml). The solid was then dissolved in ethyl acetate, dried with $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product. Purification by flash chromatography (4:1 petrol / ethyl acetate) to yield the title compound as a white crystalline solid (0.87g, 56%) m.p. 143-145°C. (Found M^+, 301.1693. $C_{18}H_{23}NO_3$ requires M, 301.1678); ν_{max} (KBr disk)/cm^{-1} 3230 $N\text{-}H_{(str)}$, 3010, 2995 and 2968 $C\text{-}H_{(str)}$ and 1705 $C{=}O_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, d, *J*=7, $CH\underline{H_3}$), 1.50 (9H, s, $C(CH_3)_3$), 3.85 (3H, s, OCH_3), 4.40 (1H, q, *J*=7, $C\underline{H}CH_3$), 6.40 (1H, s, N-H), 6.80 (1H, d, *J*=8, aromatic), 7.25 (1H, m, aromatic), 7.35 (1H, d, *J*=8, aromatic), 7.50 (1H, d, *J*=8, aromatic), 7.65 (1H, m, aromatic), 7.95 (1H, d, *J*=8, aromatic). δ_C (62.88 MHz; $CDCl_3$) 22.9, 28.8 and 50.6 and(aliphatic), 55.4 (MeO), 79.0 ($\underline{C}$-Me_3), 106.0, 117.7, 124.0, 126.3, 127.5, 129.1, 130.4, 136.3 and 139.6 (aromatic), 155.6 (N-C=O) and 158.4 (aromatic).

A mixed fraction (200mg) containing the title compound and (1*S*)-1-(6-methoxy-2-naphthyl)ethylamine **167**(S) was also isolated.

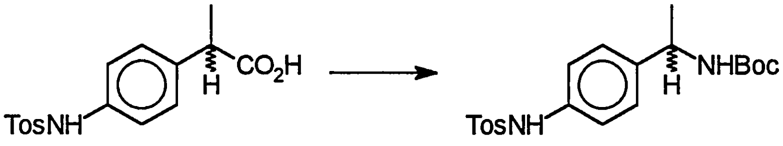
(*S*)-*N*-*t*-Butoxycarboyl-1-(6-methoxy-2-naphthyl)ethylamine **166**(*S*)



167(*S*) **166**(*S*)

A mixture of the amine **167**(S) and Boc protected amine **166**(*S*) (0.05g) was dissolved in dioxane (1ml) prior to the addition of 0.5N sodium hydroxide (1ml), di-t-butyl pyrocarbonate (0.06g, 0.27mmol) and the reaction stirred overnight. The dioxane was then removed under reduced pressure to give a gelatinous solid. The gelatinous solid was dissolved in ethyl acetate (10ml), acidified with dilute potassium hydrogen carbonate solution until pH 3, the phases separated and the aqueous phase re-extracted with ethyl acetate (10ml). The combined organic extracts were then washed (10ml) with water, dried with $MgSO_4$ and the solvent removed under reduced pressure to give the crude product. Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a white crystalline solid (0.025g, N /A %) m.p. 143-145°C. (Found M^+, 301.1689. $C_{18}H_{23}NO_3$ requires M, 301.1678); ν_{max} (KBr disk)/cm^{-1} 3226 N-H$_{(str)}$, 3006, 2989 and 2965 C-H$_{(str)}$ and 1708 C=O$_{(str)}$; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, d, *J*=7, CHCH$_3$), 1.50 (9H, s, C(CH$_3$)$_3$), 3.85 (3H, s, OCH$_3$), 4.40 (1H, q, *J*=7, CHCH$_3$), 6.55 (1H, s, N-H), 6.80 (1H, d, *J*=8, aromatic), 7.25 (1H, m, aromatic), 7.35 (1H, d, *J*=8, aromatic), 7.50 (1H, d, *J*=8, aromatic), 7.65 (1H, m, aromatic), 7.95 (1H, d, *J*=8, aromatic). δ_C (62.88 MHz; $CDCl_3$) 22.8, 29.1 and 50.8 and(aliphatic), 55.4 (MeO), 79.0 (C-Me$_3$), 105.8, 117.8, 124.0, 126.3, 127.6, 129.2, 130.5, 136.8 and 139.6 (aromatic), 155.8 (N-C=O) and 158.6 (aromatic).

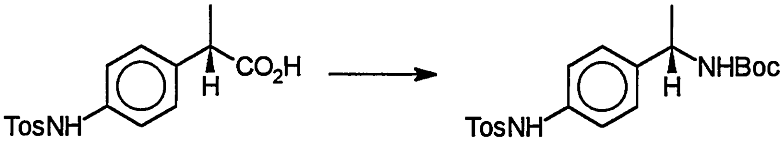
Preparation of *tert*-butyl N-[1-(4-*p*-toluenesulphonamidophenyl)ethyl]carbamate **168**



152 **168**

This compound was prepared from 2-(4-*p*-toluenesulphonamidophenyl)propanoic acid **152** (0.30g, 0.94mmol), dry t-butanol (5ml), triethylamine (0.250g, 2.50mmol) and diphenylphosphoryl azide (0.52g, 1.9mmol) using the method described above for the preparation of **166**(*S*) from **11**(*S*). Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a viscous liquid (0.132g, 36%). (Found M$^+$, 390.1617. $C_{20}H_{26}N_2O_4S$ requires M, 390.1613); ν_{max} (film)/cm^{-1} 3285-3210 N-H$_{(str)}$, 3009, 2986 and 2958 C-H$_{(str)}$ and 1714 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.40 (3H, d, *J*=7, CHC<u>H</u>$_3$), 1.55 (9H, s, C(CH$_3$)$_3$), 2.40 (3H, s, ArCH$_3$), 4.30 (1H, q, *J*=6, C<u>H</u>CH$_3$), 6.45 (1H, s, NHBoc), 7.10-7.40 (6H, m, aromatic), 7.65 (2H, d, *J*=8, aromatic), 9.35 (1H, s, SO$_2$NH); δ_C (62.88 MHz; CDCl$_3$) 21.6, 22.2, 28.2, 55.4 and 79.0 (aliphatic), 120.4, 126.3, 129.0, 129.9, 133.5, 135.0, 137.8 and 145.1 (aromatic) and 155.6 (C=O).

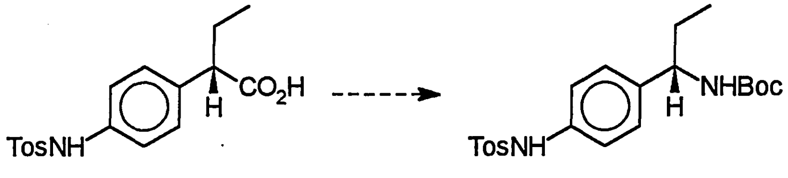
Preparation of *tert*-butyl N-[(1*S*)-1-(4-*p*-toluenesulphonamidophenyl)ethyl] carbamate **168(*S*)**



152(*S*) **168**(*S*)

This compound was prepared from (*S*)-2-(4-*p*-toluenesulphonamidophenyl)propanoic acid **152**(*S*) (0.30g, 0.94mmol), dry t-butanol (5ml), triethylamine (0.250g, 2.50mmol) and diphenylphosphoryl azide (0.52g, 1.9mmol) using the method described above for the preparation of **166**(*S*) from **11**(*S*). Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a viscous liquid (0.103g, 28%). (Found M$^+$, 390.1639. $C_{20}H_{26}N_2O_4S$ requires M, 390.1613); ν_{max} (film)/cm^{-1} 3290-3215 N-H$_{(str)}$, 3006, 2986 and 2959 C-H$_{(str)}$ and 1712 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.40 (3H, d, *J*=7, CHCH_3), 1.55 (9H, s, $C(CH_3)_3$), 2.40 (3H, s, $ArCH_3$), 4.30 (1H, q, *J*=6, $CHCH_3$), 6.45 (1H, s, NHBoc), 7.10-7.40 (6H, m, aromatic), 7.65 (2H, d, *J*=8, aromatic), 9.35 (1H, s, SO_2NH); δ_C (62.88 MHz; $CDCl_3$) 21.8, 22.3, 28.24, 55.6 and 79.1 (aliphatic), 120.6, 126.7, 129.0, 129.5, 133.8, 135.1, 137.5 and 145.6 (aromatic) and 156.6 (C=O).

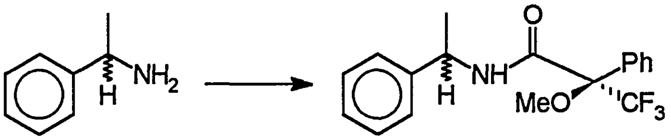
Attempted preparation of *tert*-butyl N-[(1*S*)-1-(4-*p*-toluenesulphonamidophenyl) propyl]carbamate 169(*S*)



153(*S*) **169(*S*)**

This compound was prepared from (*S*)-2-(4-*p*-toluenesulphonamidophenyl)butanoic acid **153(*S*)** (0.030g, 0.094mmol), dry t-butanol (1ml), triethylamine (0.025g, 0.25mmol) and diphenylphosphoryl azide (0.052g, 1.9mmol) using the method described above for the preparation of **166(*S*)**. Purification by flash chromatography (4:1 petrol / ethyl acetate) failed to isolate the title compound.

Preparation of N-(1-phenylethyl)-(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide 172



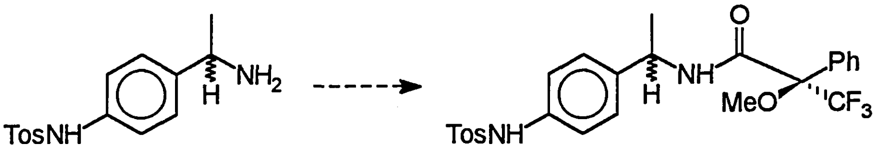
171 **172**

Racemic α-methyl benzylamine **171** (0.28g, 2.31mmol) was dissolved in DCM (10ml) to which was added (*R*)-Mosher's acid (0.68g, 2.91mmol), DMAP (~5 mg) and DCC (0.60g, 2.91mmol). The reaction was monitored by ^1H NMR spectroscopy and TLC (4:1 petrol / ethyl acetate) until no starting material was observed. The reaction mixture was then washed with 2N HCl, then 2N NaOH, dried with $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product as a colourless liquid. Purification by flash chromatography (4:1 petrol / ethyl acetate) gave the title compound as a viscous oil (0.132g, 17%). (Found M^+, 337.1281. $C_{18}H_{18}F_3NO_2$ requires M, 337.1290); ν_{max}

(film)/cm^{-1} 3294 N-H$_{(str)}$, 3056, 2989 and 2925 C-H$_{(str)}$, 1680 C=O$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.50 (1.5H, d, *J*=8, 0.5 x CHC$\underline{H}_3$), 1.55 (1.5H, d, *J*=8, 0.5 x CHC$\underline{H}_3$), 3.40 (1.5H, d, *J*=2, 0.5 x OCH$_3$), 3.45 (1.5H, d, *J*=2, 0.5 x OCH$_3$), 5.20 (1H, m, C$\underline{H}$CH$_3$), 7.05 (1H, bd, *J*=7, NH), 7.30-7.80 (10H, m, aromatic); δ_C (62.88 MHz; CDCl$_3$) 21.8 and 49.2 (aliphatic), 55.3(MeO), 82.6 (q$^{\#}$, $\underline{C}$-CF$_3$), 126.5, 128.0, 129.0, 129.8, 132.8 and 142.7 (aromatic) and 165.7 (C=O).

$^{\#}$ appearance similar to a quartet.

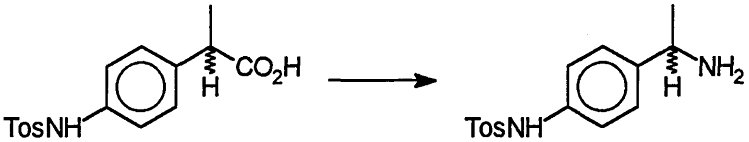
Attempted preparation of the Mosher's amide of racemic 1-(4-*p*-toluenesulphonamidophenyl) ethylamine **173**



170 **173**

1-(4-*p*-Toluenesulphonamidophenyl)ethylamine **170** (0.0126g, 0.0434mmol) was dissolved in chloroform (1ml) to which (*R*)-Mosher's acid (0.0127g, 0.0543mmol), DMAP, (~1mg) and DCC (0.0112g, 0.0543mmol) were added. The reaction was monitored by ^{1}H NMR spectroscopy and TLC (4:1 petrol / ethyl acetate) for 21 days, no product was observed.

Preparation of 1-(4-*p*-toluenesulphonamidophenyl)ethylamine **170**



152 **170**

This compound was prepared from 2-(4-*p*-toluenesulphonamidophenyl)propanoic acid **152** (0.99g, 3.10mmol), t-butanol (5ml), triethylamine (0.75g, 7.4mmol) and diphenylphosphoryl azide (1.58g, 5.76mmol) using the method described above for the preparation of **166**(*S*) except that the t-butanol was not dried. Purification by flash chromatography (4:1 petrol / ethyl acetate) afforded the title compound as a viscous liquid (0.08g, 9%). (Found M$^+$, 290.1077. C$_{15}$H$_{18}$N$_2$O$_2$S requires M, 290.1089); ν_{max}

(film)/cm^{-1} 3254 N-H$_{(str)}$, 3086, 2979 and 2930 C-H$_{(str)}$; δ_H (250 MHz; CDCl$_3$) 1.45 (3H, d, *J*=7,), 2.35 (3H, s, ArCH$_3$), 4.60 (1H, q, *J*=7, C$\underline{H}$CH$_3$), 5.00 (2H, s, CHN$\underline{H_2}$), 7.10-7.35 (6H, m, aromatic), 7.40 (1H, s, SO$_2$NH), 7.70 (2H, d, *J*=7, aromatic); δ_C (62.88 MHz; CDCl$_3$) 21.7, 21.9 and 60.8 (aliphatic), 121.8, 127.6, 127.8, 130.1, 136.4, 136.9, 137.9 and 144.4 (aromatic).

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