

Description

This invention relates to novel 1,3-dioxan-5-ylalkenoic acids and their derivatives, which antagonise one or more of the actions of thromboxane A₂ (hereafter referred to as "TXA₂"), and are valuable therapeutic agents.

It is known that TXA₂ is a potent aggregator of blood platelets and a powerful vasoconstrictor. TXA₂ is also a potent constrictor of bronchial and tracheal smooth muscle. TXA₂ may therefore be involved in a wide variety of disease conditions, for example ischaemic heart disease such as myocardial infarction and angina, cerebrovascular disease such as transient cerebral ischaemia, migraine and stroke, peripheral vascular disease such as atherosclerosis, microangiopathy, hypertension and blood clotting defects due to lipid imbalance, and pulmonary disease such as pulmonary embolism, bronchial asthma, bronchitis, pneumonia, dyspnoea and emphysema. Accordingly, compounds which antagonise the actions of TXA₂ may be expected to have therapeutic value in the prevention or treatment of any one or more of the above-mentioned diseases or any other disease conditions in which it is desirable to antagonise the actions of TXA₂.

Certain 4-substituted-1,3-dioxan-*trans*-5-ylalkenoic acids typified by the compound of the formula A [set out, together with the other structural formulae referred to herein, on the accompanying formulae sheets] are known (UK Patent application No. 8004647, published as Serial No. 2046733A) as inhibitors of the enzyme responsible for the synthesis of TXA₂. Similarly, certain 6-alkynyl-1,3-dioxan-*cis*-4-ylalkenoic acids typified by the compound of the formula B are known (Fried *et alia* *dv. Prostaglandin and Thromboxane Research*, 1980, 6, 427-436) to inhibit various enzymes in the arachidonic acid cascade. However, neither of these groups of 1,3-dioxanylalkenoic acids has been described as having any antagonist action against the effects of TXA₂.

We have now discovered that the novel, chemically distinct 4-substituted-1,3-dioxan-5-ylalkenoic acids and their derivatives, of formula I below, unexpectedly possess the property of antagonising one or more of the actions of TXA₂ and this is the basis for our invention.

According to the invention there is provided a 4-phenyl-1,3-dioxan-*cis*-5-ylalkenoic acid derivative of the formula I wherein Ra and Rb are independently hydrogen, (2-6C)alkenyl, (1-8C)alkyl optionally bearing up to three halogeno substituents, pentafluorophenyl, aryl or aryl-(1-4C)alkyl, the latter two of which may optionally bear up to three substituents selected from halogeno, (1-6C)alkyl, (1-6C)alkoxy, (1-4C)alkylenedioxy, trifluoromethyl, cyano, nitro, hydroxy, (2-6C)alkanoyloxy, (1-6C)alkylthio, (1-6C)alkanesulphonyl, (1-6C)alkanoylamino, and oxapolymethylene of 2 to 4 carbon atoms, provided that when both Ra and Rb are alkyl or alkenyl, the total number of carbon atoms in Ra and Rb taken together is 8 or less; or Ra and Rb together form polymethylene of 2 to 7 carbon atoms, optionally bearing one or two (1-4C)alkyl substituents; Rc is hydroxy (1-6C)alkoxy or (1-6C)alkanesulphonamido; n is the integer 1 or 2; A is ethylene or vinylene; Y is polymethylene of 2 to 5 carbon atoms optionally bearing (1-4C)alkyl as a substituent; benzene ring B optionally bears one or two substituents selected from halogeno, (1-6C)alkyl, (1-6C)alkoxy, hydroxy, (2-6C)alkanoyloxy, (1-6C)alkanoylamino, trifluoromethyl and nitro; and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry; or for those compounds wherein Rc is hydroxy, a salt thereof with a base affording a physiologically acceptable cation.

It will be appreciated that the compounds of formula I contain at least two asymmetric carbon atoms (i.e. at C₄ and C₅ of the dioxane ring) and may exist and be isolated in racemic and optically active forms. In addition those compounds of formula I wherein A is vinylene exist, and may be isolated, in separate stereoisomeric forms ('E' and 'Z') about that group. It is to be understood that the present invention encompasses any racemic, optically active or stereoisomeric form (or mixtures thereof) which is capable of antagonising one or more of the actions of TXA₂, it being well known in the art how to prepare individual optical isomers (for example by synthesis from optically active starting materials or resolution of a racemic form) and individual 'E' and 'Z' stereoisomers (for example by chromatographic separation of a mixture thereof), and how to determine the TXA₂ antagonist properties using the standard test described hereafter.

In this specification, the terms Ra, Rb and Rc *etc.* are used to depict generic radicals and have no other significance.

A particular value for Ra or Rb when it is (1-8C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl or octyl, and when it is (1-8C)alkyl bearing up to three halogeno atoms is, for example chloromethyl, 2-chloroethyl, trifluoromethyl or 2,2,2-trifluoroethyl.

A particular value for Ra or Rb when it is aryl is, for example, phenyl, 1-naphthyl or 2-naphthyl; when it is aryl-(1-4C)alkyl is, for example, benzyl, 1-phenylethyl or 2-phenylethyl; and when it is (2-6C)alkenyl is, for example, vinyl, allyl or 2-methylallyl.

Particular values for optional substituents, which may be present on benzene ring B or on an aromatic moiety which constitutes or is part of Ra or Rb as defined above, are, for example:—

- for halogeno: fluoro, chloro, bromo or iodo;
- for (1-6C)alkyl: methyl, ethyl, propyl or isopropyl;
- for (1-6C)alkoxy: methoxy, ethoxy or propoxy;
- for (1-4C)alkylenedioxy: methylenedioxy, ethylenedioxy or isopropylidenedioxy;
- for (1-6C)alkylthio: methylthio or ethylthio;

for (1-6C)alkanesulphonyl: methanesulphonyl or ethanesulphonyl;

for (1-6C)alkanoylamino: formamido, acetamido or propionamido;

for (2-6C)alkanoyloxy: acetoxy or propionyloxy; and

for oxapolymethylene of 2 to 4 carbon atoms, a group of the formula $-\text{CH}_2\text{OCH}_2-$ or $-\text{CH}_2\text{CH}_2\text{OCH}_2-$.

In general when one of Ra and Rb is hydrogen it is preferred that the other of Ra and Rb is arranged so as to have *cis*-relative stereochemistry with reference to the substituents at positions 4 and 5 of the dioxane ring.

A particular value for Ra and Rb when together they form polymethylene of 2 to 7 carbon atoms is, for example, ethylene, trimethylene, tetramethylene, pentamethylene or hexamethylene; and a particular value for an optional (1-4C)alkyl substituent thereon is, for example, methyl.

A particular value for Rc when it is (1-6C)alkanesulphonamido is, for example, methanesulphonamido, ethanesulphonamido, propanesulphonamido or 1-methylethanesulphonamido.

A particular value for Rc when it is (1-6C)alkoxy is, for example, methoxy or ethoxy.

A particular value for Y is, for example, ethylene, trimethylene or tetramethylene; and a particular value for an optional substituent thereon is, for example, methyl.

Specific examples of Ra and Rb are, for example, hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, octyl, vinyl, allyl, 2-methylallyl, trifluoromethyl, chloromethyl, 2-chloroethyl, phenyl optionally bearing a fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, methylthio, methanesulphonyl, nitro, hydroxy, cyano, acetamido, methylenedioxy or a methyleneoxymethylene ($-\text{CH}_2\text{OCH}_2-$) substituent, dichlorophenyl, dimethylphenyl, pentafluorophenyl, 1-naphthyl, 2-naphthyl or benzyl; or are, for example, when they together form trimethylene, pentamethylene or hexamethylene, optionally bearing a methyl substituent.

Specific values for benzene ring B are, for example, when it is phenyl, 2-methylphenyl, 2-ethylphenyl, 2-isopropylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-fluorophenyl, 4-methylphenyl or 2,6-difluorophenyl.

A preferred value for Rc is, for example, hydroxy, methoxy, ethoxy, methanesulphonamido or ethanesulphonamido; of which hydroxy is especially preferred.

A preferred value for A is vinylene, and for Y is, for example, trimethylene. A preferred value for n is the integer 1.

In general when A is vinylene it is preferred that the adjacent carbon atoms have *cis*-relative stereochemistry i.e. the 'Z' configuration.

A preferred value for benzene ring B is, for example, when it is unsubstituted; *ortho*-substituted by fluoro, chloro, methyl, hydroxy, methoxy, ethyl or isopropyl; or *meta*-substituted by fluoro or chloro.

A preferred group of acid derivatives of the invention comprises those compounds of formula Ia wherein Ra and Rb are:—

(i) independently hydrogen or (1-4C)alkyl, optionally bearing 1 to 3 halogeno substituents;

(ii) one of the two is hydrogen or (1-4C)alkyl, and the other is phenyl, naphthyl or phenyl-(1-4C)alkyl, optionally bearing 1 or 2 substituents selected from halogeno, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylenedioxy, trifluoromethyl, cyano, nitro, hydroxy, (2-4C)alkanoyloxy, (1-4C)alkylthio, (1-4C)alkanesulphonyl, (1-4C)alkanoylamino and oxapolymethylene of 2 to 4 carbon atoms, or pentafluorophenyl;

(iii) one of the two is hydrogen and the other is (5-8C)alkyl or (2-6C)alkenyl; or

(iv) both together form polymethylene of 2 to 7 carbon atoms optionally bearing a (1-4C)alkyl substituent;

Rc is hydroxy; (1-4C)alkoxy or (1-4C)alkanesulphonamido; and benzene ring B optionally bears a single substituent located at the 2-position selected from halogeno, (1-4C)alkyl, (1-4C)alkoxy, hydroxy, (2-4C)alkanoyloxy, (1-4C)alkanoylamino and trifluoromethyl, or bears a 3-halogeno substituent; and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry; or for those compounds wherein Rc is hydroxy, a salt thereof with a base affording a physiologically acceptable cation.

Particular values for the various substituents in the above preferred group are, for example:—

for (1-4C)alkyl: methyl, ethyl, propyl, isopropyl or butyl;

for (5-8C)alkyl: pentyl, hexyl, heptyl or octyl;

for (1-4C)alkoxy: methoxy or ethoxy;

for (1-4C)alkyl bearing 1 to 3 halogeno substituents: chloromethyl, 2-chloroethyl, 2,2,2-trifluoroethyl or trifluoromethyl;

for phenyl-(1-4C)alkyl: benzyl, 2-phenylethyl or 1-phenylethyl;

for halogeno: fluoro, chloro or bromo;

for (1-4C)alkylenedioxy: methylenedioxy, ethylenedioxy or isopropylidenedioxy;

for (2-4C)alkanoyloxy: acetoxy or propionyloxy;

for (1-4C)alkylthio: methylthio or ethylthio;

for (1-4C)alkanesulphonyl: methanesulphonyl or ethanesulphonyl;

for (1-4C)alkanoylamino: acetamido or propionamido; and

for oxapolymethylene of 2 to 4 carbon atoms: methyleneoxymethylene ($-\text{CH}_2\text{OCH}_2-$) or ethyleneoxy ($-\text{CH}_2\text{CH}_2\text{O}-$).

Specific combinations of Ra and Rb which are preferred are, by way of example:—

(i) Ra and Rb are both hydrogen, methyl, ethyl, propyl, butyl or trifluoromethyl;

(ii) one of Ra is hydrogen and the other is trifluoromethyl, chloromethyl, benzyl, isopropyl, hexyl, octyl, phenyl (optionally bearing 1 or 2 fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, hydroxy, cyano, methylthio or acetamido), phenyl bearing methylenedioxy or methyleneoxymethylene ($-\text{CH}_2\text{OCH}_2-$), pentafluorophenyl, 1-naphthyl or 2-naphthyl; and

(iii) Ra and Rb together form trimethylene, tetramethylene, pentamethylene, hexamethylene or a group of the formula: $-\text{CH}_2\text{CH}_2\cdot\text{CHCH}_3\cdot\text{CH}_2\text{CH}_2-$.

Specific preferred values for Ra or Rb when it is a mono or disubstituted phenyl are, for example, 2-fluoro-, 3-fluoro-, 4-fluoro-, 2-chloro-, 3-chloro-, 4-chloro-, 2-bromo-, 3-bromo-, 4-bromo-, 2-methyl-, 3-methyl-, 4-methyl-, 2-methoxy-, 3-methoxy-, 4-methoxy-, 2-trifluoromethyl-, 3-trifluoromethyl-, 4-trifluoromethyl-, 3-hydroxy-, 4-cyano-, 4-methylthio-, 4-acetamido-, 3,4-dichloro-, 2,4-dimethyl-, 3,4-methylenedioxy- and 3,4-(methyleneoxymethylene)-phenyl.

Specific preferred values for benzene ring B are, for example, when it is phenyl, or 2-fluoro-, 2-chloro-, 2-bromo-, 2-methyl-, 2-ethyl-, 2-isopropyl-, 2-methoxy-, 2-hydroxy-, 3-fluoro- or 3-chloro-phenyl.

A further preferred group of acids of the invention comprises compounds of the formula Ib wherein:—

(i) Ra and Rb are both hydrogen, methyl, ethyl, propyl, butyl, or trifluoromethyl;

(ii) or together form trimethylene, tetramethylene, pentamethylene, hexamethylene or a group of the formula: $-\text{CH}_2\text{CH}_2\cdot\text{CHCH}_3\cdot\text{CH}_2\text{CH}_2-$; or

(iii) Ra is (3—8C)alkyl, trifluoromethyl, chloromethyl, 2-chloroethyl, pentafluorophenyl, or phenyl, benzyl or naphthyl, the last three of which may optionally bear 1 or 2 halogeno, (1—4C)alkyl, (1—4C)alkoxy, trifluoromethyl, hydroxy, cyano, (1—4C)alkylthio or (1—4C)alkanoylamino substituents, or a methylenedioxy or methyleneoxymethylene substituent, and Rb is hydrogen;

benzene ring B is unsubstituted or is 2-halogeno-, 2-(1—4C)alkyl-, 2-(1—4C)alkoxy-, 2-hydroxy- or 3-halogeno-phenyl;

Ra and the substituents at the 4 and 5-positions of the dioxane ring have *cis*-relative stereochemistry; and the carbon atoms adjacent to the vinylene group have the indicated *cis*-relative stereochemistry; or a salt thereof with a base affording a physiologically acceptable cation; or a methyl or ethyl ester thereof; or a methanesulphonamido, ethanesulphonamido or 1-methylethanesulphonamido derivative thereof.

A preferred value for Ra when it is (3—8C)alkyl is, for example, isopropyl, butyl, hexyl or octyl.

Preferred values for substituents on Ra when it is phenyl, benzyl or naphthyl are, for example:—

for halogeno: fluoro, chloro or bromo;

for (1—4C)alkyl: methyl;

for (1—4C)alkoxy: methoxy;

for (1—4C)alkylthio: methylthio; and

for (1—4C)alkanoylamino: acetamido.

Preferred values for substituents on benzene ring B are, for example:—

for 2-halogeno: 2-fluoro, 2-chloro or 2-bromo;

for 3-halogeno: 3-fluoro or 3-chloro;

for 2-(1—4C)alkyl: 2-methyl, 2-ethyl or 2-isopropyl; and

for 2-(1—4C)alkoxy: 2-methoxy.

Particular salts of compounds of formula I wherein Rc is hydroxy are, for example, alkali metal and alkaline earth metal salts such as lithium, sodium, potassium, magnesium and calcium salts, aluminium and ammonium salts, and salts with organic amines or quaternary bases forming physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, ethylenediamine, piperidine, morpholine, pyrrolidine, piperazine, ethanolamine, triethanolamine, N-methylglucamine, tetramethylammonium hydroxide and benzyltrimethylammonium hydroxide.

Specific compounds of the invention are described in the accompanying Examples and of these a compound of particular interest is 5(Z)-7-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid or a pharmaceutically acceptable salt thereof.

The compounds of formula I may be manufactured by conventional procedures of organic chemistry well known in the art for the production of analogous compounds. Such processes are provided as a further feature of the invention and are illustrated by the following preferred procedures in which Ra, Rb, Rc, benzene ring B, n, A and Y have any of the meanings defined hereinbefore:—

a) For a compound wherein Rc is hydroxy and A is vinylene, reacting an aldehyde of the formula II with a Wittig reagent of the formula:—



III

wherein Rd is (1—6C)alkyl (especially methyl or ethyl) or aryl (especially phenyl), and M^+ is, for example, an alkali metal cation such as the lithium, sodium or potassium cation.

The process in general produces compounds of formula I in which the carbon atoms adjacent to the vinylene have predominantly *cis*-relative stereochemistry i.e. the "Z" isomer. However the compounds of formula I having *trans*-relative stereochemistry (i.e. the "E" isomer) are also formed in the process and may be obtained by conventional separation of the mixture of "Z"- and "E"-isomers first obtained.

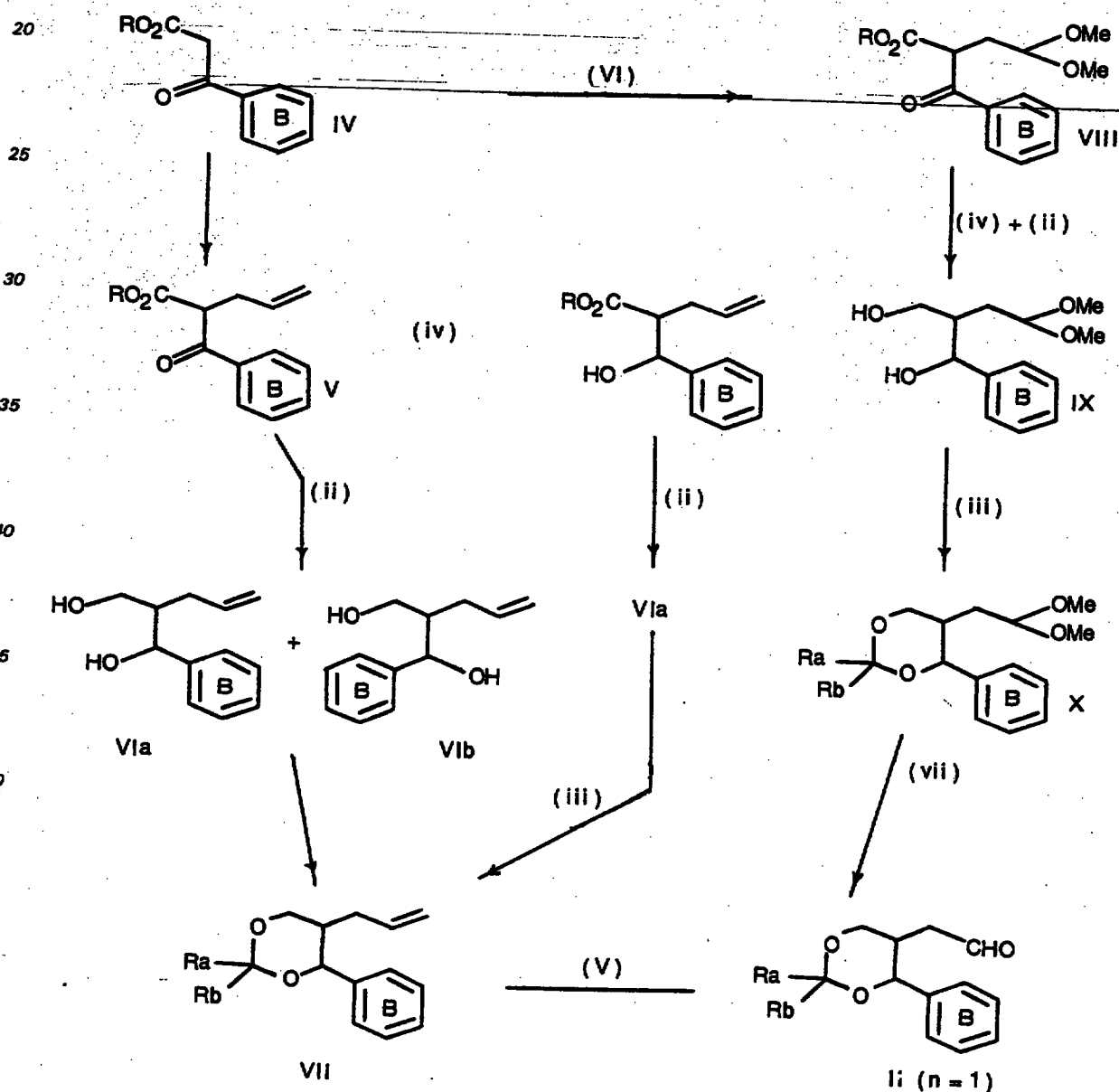
The process is conveniently performed in a suitable solvent or diluent, for example an aromatic solvent such as benzene, toluene or chlorobenzene, an ether such as 1,2-dimethoxyethane, dibutyl ether, tetrahydrofuran, dimethyl sulphoxide or tetramethylene sulphone, or in a mixture of one or more such solvents or diluents. The process is generally performed at a temperature in the range, for example, -80°C . to 40°C . but is conveniently performed at or near room temperature, that is in the range 15 to 35°C .

If desired the proportion of the product of the process with *trans*-relative stereochemistry about the double bond may frequently be increased by choice of a suitable solvent, for example tetramethylene sulphone, and/or addition of an alkali halide, for example lithium bromide, to the reaction mixture.

The starting Wittig reagents of formula III are in general well known in the art or may be obtained by analogous procedures. They are generally formed by treatment of the corresponding phosphonium halides with a strong base such as sodium hydride, lithium diisopropylamide, potassium *t*-butoxide or butyl lithium in a suitable solvent such as that used for the process itself, and are generally formed *in situ* immediately prior to carrying out process (a).

The starting materials of formula II may be obtained by the sequences shown in Schemes 1 or 2, (attached hereafter), many of which are illustrated in the accompanying Examples.

SCHEME I

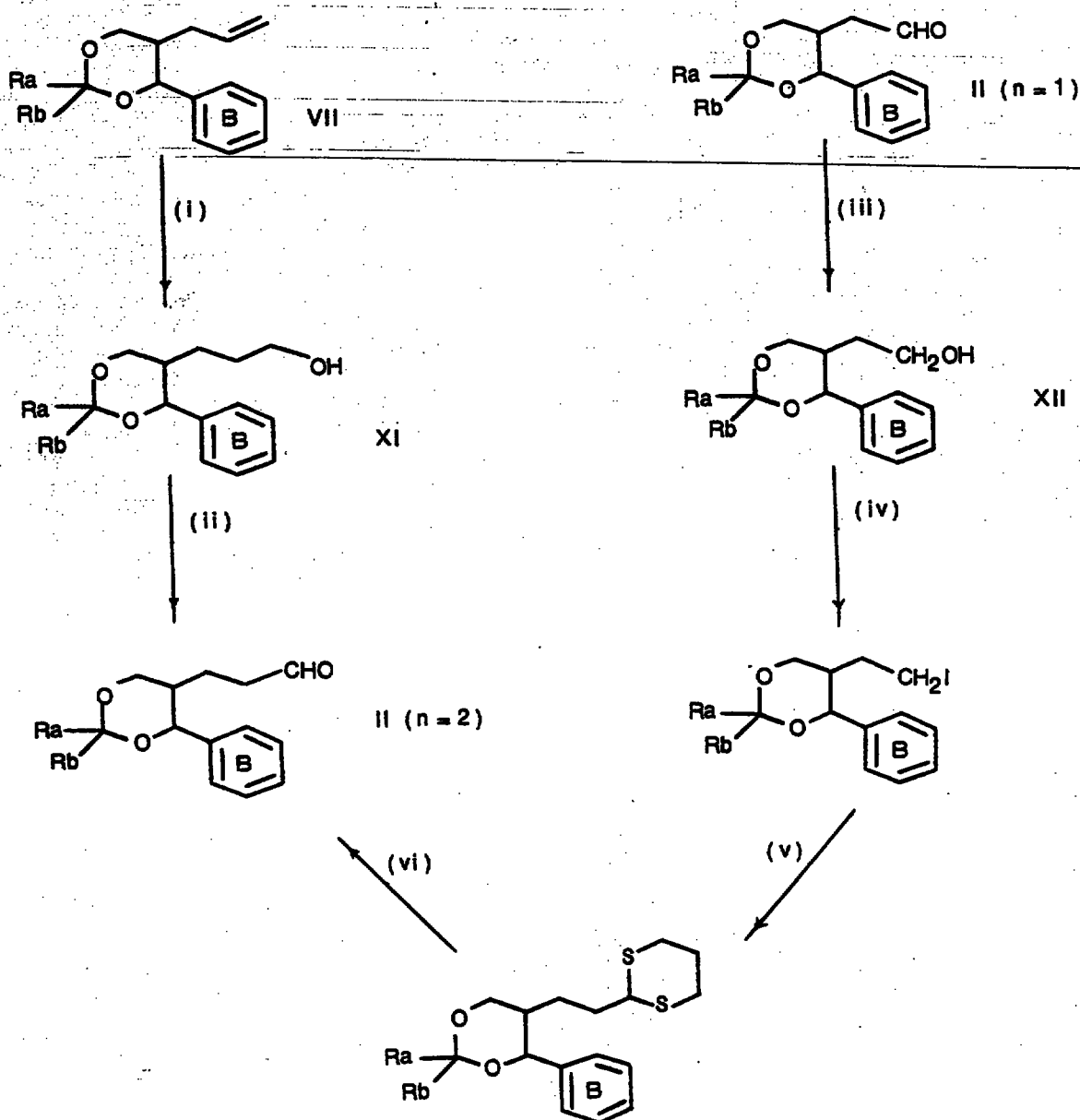


- (iii) p-TsOH, RaRb.Co or RaRb.C(OMe)₂
 (iv) Zn(BH₄)₂, Et₂O
 (v) O₃, CH₂Cl₂, then Ph₃P; or
 OsO₄, NaIO₄, t-BuOH, H₂O
 (vi) NaH, DMSO, BrCH₂CH(OMe)₂
 (vii) H⁺, H₂O

Notes:

R=(1-4C)alkyl, for example Me or Et.

SCHEME II



Reagents:

- (i) B₂H₆; then H₂O₂
 (ii) Pyridinium chlorochromate, CH₂Cl₂; or
 DCCI, DMSO, pyridine, TFA

(iii) NaBH_4 , EtOH

(iv) $p\text{-TsCl}$, pyridine; then NaI , acetone, ΔH

(v) 1,3-dithiane, lithium diisopropylamide, THF, -78°C .

(vi) Ceric ammonium nitrate, 0°C .

5

These sequences involve selective conversions of functional groups which are well known in the synthesis of structurally analogous compounds, such as the prostaglandins and their analogues and, in general, similar reaction conditions to those well known in the art are used. For example, when alkylthio substituents are to be present then an appropriate sequence is used which avoids a non-specific oxidation step (e.g. step (v) of Scheme 1 and step (vi) of Scheme 2. Similarly, when a hydroxy substituent is to be present on benzene ring B then a starting material of formula IV may be used in which the hydroxy substituent has been protected for example as its trimethylsilyl ether. The protecting group is then removed, for example by reaction with tetrabutylammonium fluoride, in a conventional manner as a final step prior to carrying out process (a). Similarly, when an acyloxy substituent is to be present on benzene ring B, this may be produced by acylation of the corresponding hydroxy derivative of formula II using a conventional procedure as a final step.

15

It will be seen that a mixture of stereoisomers at positions 4,5 of the dioxane rings is generally obtained from Scheme 1 and that it is necessary to separate out the required *cis*-stereoisomer, conveniently after cyclisation of the 5-allyl-1,3-dioxanes VII, using a conventional procedure such as chromatography.

20

The 5-allyl-1,3-dioxanes VII may also be obtained by an acetal exchange reaction analogous to that described in process (b), for example by reacting [4,5-*cis*]-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane with an excess of the appropriate ketone or aldehyde of the formula RaRb.CO (or its dimethyl acetal or ketal) in the presence of *p*-toluenesulphonic acid. This procedure and related alternatives are described in the accompanying Examples.

25

The keto esters IV may be obtained by conventional organic syntheses as illustrated in the accompanying Examples.

(b) Reacting an *erythro*-diol derivative of the formula XIII wherein one of Qa and Qb is hydrogen and the other is hydrogen, alkanesulphonyl, arenesulphonyl or a group of the formula $-\text{CRR}^1.\text{OH}$ wherein R and R^1 are the same or different alkyl, with a carbonyl compound of the formula RaRb.CO , or an acetal, hemiacetal or hydrate thereof.

30

A suitable value for Qa or Qb when it is alkanesulphonyl is, for example, methanesulphonyl or ethanesulphonyl and when it is arenesulphonyl is, for example, benzenesulphonyl or *p*-toluenesulphonyl. A suitable value for R or R^1 is, for example, methyl or ethyl.

The carbonyl compound of the formula RaRb.CO (or its hydrate, or its acetal or hemiacetal with a (1-4C)alkanol) is preferably used in excess.

35

Depending on the nature of Qa and Qb different reaction conditions are necessary. Thus, when Qa and Qb are both hydrogen or when one is a group of the formula $-\text{CRR}^1.\text{OH}$ and the other is hydrogen, the reaction is carried out in the presence of an acid catalyst, for example, hydrogen chloride, hydrogen bromide, sulphuric acid, phosphoric acid, *p*-toluenesulphonic acid or the anionic form of a sulphonated polystyrene catalyst, conveniently in a suitable solvent or diluent, for example an ether such as diethyl ether, dibutyl ether, 1,2-dimethoxyethane or tetrahydrofuran, and at a temperature in the range, for example, 10 to 120°C . The acid catalyst may also be provided by the inherent acidity of the starting material of formula XIII wherein Rc is hydroxy, as illustrated in Example 8 hereafter.

40

Similarly, when one of Qa and Qb is alkanesulphonyl or arenesulphonyl and the other is hydrogen, the reaction is carried out first in the presence of an acid catalyst, for example under the conditions described above to produce an intermediate of the formula XIII, wherein one of Qa and Qb is alkanesulphonyl or arenesulphonyl, and the other is a group of the formula $-\text{CRaRb.OH}$. The latter intermediate may then be cyclised *in situ* to the required compound of formula I by addition of a strong base, for example, sodium hydride or butyl lithium, in a suitable solvent or diluent, for example in the ether solvent used for the acid catalysed step above, and at a temperature in the range, for example, $30-100^\circ\text{C}$.

45

It will be appreciated that the above mentioned intermediate may also be isolated, characterised and separately cyclised under the influence of strong base to give a compound of formula I. Such a procedure is encompassed by the invention.

50

Those starting materials of formula XIII wherein Qa and Qb are both hydrogen (that is an *erythro*-diol of formula XIII) may be obtained by mild hydrolysis or alcoholysis of the dioxane ring of a compound of formula I, for example, in which Ra and Rb are both methyl or ethyl radicals, obtained by another process described herein. This reaction will normally be carried out at a temperature in the range, for example, $25-100^\circ\text{C}$. and preferably in the range $30-60^\circ\text{C}$., using an aqueous mineral acid such as hydrochloric acid in an alcoholic solvent such as ethanol or 2-propanol. Those starting materials of formula XIII wherein one of Qa and Qb is a group of the formula $-\text{CRR}^1.\text{OH}$ and the other is hydrogen, are generally obtained as intermediates in the above mentioned formation of the *erythro*-diol of formula XIII ($\text{Qa}=\text{Qb}=\text{H}$) and are not normally isolated or characterised. Accordingly, the invention also provides a process which comprises reacting a compound of formula I for example wherein Ra and Rb are methyl or ethyl, with an excess of a compound of the formula RaRb.CO in the presence of an acid-catalyst (such as those mentioned above), conveniently in a suitable solvent or diluent (such as an ether mentioned above) and at a temperature in the

55

60

65



range for example 10 to 120°C.

Those starting materials of formula XIII wherein one Qa and Qb is alkanesulphonyl or arenesulphonyl and the other is hydrogen, may be obtained from the corresponding *erythro*-diol of formula XIII (Qa=Qb=H) by reaction with one molecular equivalent of the appropriate alkanesulphonyl or arenesulphonyl halide, for example methanesulphonyl chloride or *p*-toluenesulphonyl chloride, in a suitable solvent or diluent (such as an ether or dichloromethane) and in the presence of a base such as pyridine or triethylamine.

The *erythro*-diols of formula XIII (Qa=Qb=H A=vinylene, Rc=OH) may alternatively be obtained by carrying out the Wittig reaction in process (a) hereinbefore using a trimethylsilylated aldehyde of the formula XIV (itself prepared, for example, by replacing step (iii) in Scheme 1 by a conventional silylation procedure) and then removing the trimethylsilyl protecting groups in a conventional manner, for example with tetrabutylammonium fluoride, from the Wittig reaction product of the formula XV. When a starting material of formula XIII wherein Rc is other than hydroxy is required, the carboxylic acid group of the Wittig reaction product XV may be derivatised by the procedures described hereinafter, prior to the removal of the trimethylsilyl protecting groups.

The starting materials of formula XIII wherein A is ethylene may be obtained by conventional hydrogenation of the corresponding compounds wherein A is vinylene.

Process (b) is not normally suitable for the production of compounds of formula I wherein both Ra and Rb are trifluoromethyl.

Under some circumstances when Rc is hydroxy in the starting materials of formula XIII, some degree of concomitant esterification may occur during process (b) (see Example 83 hereafter), such that hydrolysis [according to process (d) hereafter] of the reaction product may be necessary in order to obtain the required compound of formula I wherein Rc is hydroxy.

The necessary starting ketones of formula RaRb.CO and their derivatives are generally already known or may readily be obtained by standard techniques of organic chemistry.

(c) For a compound of formula I wherein Rc is hydroxy, oxidising an alcohol of the formula XVI.

A range of oxidising agents is suitable for use in this process, for example, chromium trioxide in aqueous sulphuric acid and acetone; platinum and oxygen in aqueous acetone or tetrahydrofuran; or alkaline persulphate in the presence of ruthenium trichloride. A suitable solvent or diluent which is compatible with the oxidising agent may conveniently be employed.

The process may be carried out at a temperature in the range, for example 10 to 50°C., but is preferably performed at or near room temperature in order to minimise the risk of oxidation of other sensitive substituents in the molecule. Equally, where such substituents are present, the process may be conveniently performed in two steps using two oxidising agents, that is by intermediate formation of the corresponding aldehyde of the formula XVII using an oxidising agent such as pyridinium chlorochromate (preferably in a solvent such as dichloromethane), or the Pfitzner-Moffatt reagent (dicyclohexylcarbodiimide and dimethyl sulphoxide in the presence of an acid catalyst for example pyridine trifluoroacetate), in both cases at or near room temperature. The aldehyde of formula XVII may then be separately oxidised to the required carboxylic acid of formula I (Rc=OH) by reaction with a mild oxidising agent such as silver oxide in the presence of an alkali metal hydride such as sodium hydroxide, conveniently in a solvent or diluent, for example a (1-4C)alkanol such as ethanol, and at or near room temperature. This latter process is also provided as a feature of the invention.

The starting materials of formula XVI wherein A is a vinylene radical may be obtained by analogy with process (a) but using a Wittig reagent of the formula:—



(wherein Rd has the meaning defined previously) and an aldehyde of formula II and then removing the trimethylsilyl protecting group in a conventional manner from the product to give the required alcohol of formula XVI. Similarly those starting materials of formula XVI wherein A is ethylene may be obtained by conventional hydrogenation of the corresponding compounds of formula XVI wherein A is vinylene.

(d) For a compound of formula I wherein Rc is hydroxy, hydrolysing a compound of the formula XVIII wherein W is alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, cyano or carbamoyl.

A particular value for W when it is alkoxycarbonyl is methoxycarbonyl or ethoxycarbonyl.

The hydrolysis is conveniently carried out under the influence of base, for example an alkali metal hydroxide (such as sodium or potassium hydroxide) in a suitable aqueous solvent, for example a (1-4C)alkanol (such as methanol or ethanol) or a glycol (such as ethylene glycol) at a temperature in the range, for example 15 to 150°C. In general, higher reaction temperatures are required when W is cyano or carbamoyl, for example in the range 80-150°C.

The starting materials of formula XVIII wherein W is cyano may be obtained by reaction of an alcohol of the formula XIX with methanesulphonyl chloride in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine to give the mesylate of the formula XX, which is then reacted with potassium cyanide in dimethyl sulphoxide at 50-100°C. The starting alcohols of formula XIX may themselves be obtained by analogy with those of formula XVI in process (c) hereinbefore by using a Wittig reagent of the formula:



wherein Rd has the meaning defined previously. When A is ethylene the alcohol of formula XIX may be hydrogenated prior to reaction with methanesulphonyl chloride.

The necessary starting materials of formula XVIII may be obtained by analogy with other processes described herein.

(e) For a compound of formula I wherein Ra, Rb or benzene ring B bears a hydroxy substituent, deprotecting a corresponding derivative of said compound wherein the hydroxy substituent is protected by a trimethylsilyl, (1-6C)alkyl (such as methyl or ethyl) or acyl (such as acetyl or benzoyl) protecting group.

The deprotection conditions required necessarily depend on the protecting groups concerned. Thus, for example, when it is methyl or ethyl (i.e. the starting material is the corresponding methoxy or ethoxy compound of formula I) the deprotection may be carried out, for example, by heating with sodium thioethoxide in a suitable solvent (such as N,N-dimethylformamide) at an elevated temperature, for example 90-160°C. Similarly, when the protecting group is acyl, it may be removed, for example by hydrolysis in the presence of a base (such as sodium or potassium hydroxide) in a suitable aqueous solvent [such as a (1-4C)alkanol or a glycol] at a temperature in the range, for example 10-60°C. Similarly in the case of a trimethylsilyl protecting group, it may be removed for example, by reaction with aqueous tetrabutylammonium fluoride or sodium fluoride in conventional manner.

The necessary protected derivatives of the formula I compounds may be made by analogy with the other processes described herein.

(f) For a compound of formula I wherein Ra and Rb are both hydrogen, reacting an *erythro*-diol of the formula XIII wherein Qa and Qb are both hydrogen, with methylene bromide in the presence of base.

A particularly suitable base is for example, sodium or potassium hydroxide, or sodium hydride.

The process is preferably carried out in a suitable solvent or diluent, for example dimethyl sulphoxide, and at a temperature in the range, for example 10 to 40°C., conveniently at or near room temperature.

When a compound of formula I wherein Rc is (1-6C)alkoxy is required, the corresponding acid of formula I wherein Rc is hydroxy, or a reactive derivative thereof, is esterified using a conventional procedure.

Thus, for example, an acid of formula I wherein Rc is hydroxy, or a reactive derivative thereof, may be esterified by reaction with the appropriate (1-6C)alkanol.

It will be appreciated that when a free acid of formula I is used in the process, water is produced during the reaction. Consequently, in such cases it is particularly convenient to perform the process in the presence of a suitable dehydrating agent, for example dicyclohexylcarbodiimide, in the presence of a suitable solvent or diluent for example tetrahydrofuran, acetone, methylene chloride or 1,2-dimethoxyethane, at a temperature in the range, for example, 10 to 50°C., but preferably at or near room temperature.

A suitable reactive derivative of an acid of formula I is, for example, an acid chloride, bromide, anhydride, mixed anhydride with formic acid, or an azide, which may be produced from the free acid in conventional manner. When such a derivative is used in the process, no additional dehydrating agent is necessary, and the (1-6C)alkanol is conveniently used in large excess, optionally diluted with a suitable diluent or solvent such as an ether, for example tetrahydrofuran or 1,2-dimethoxyethane.

In general, when a reactive derivative of an acid of formula I is used no external heating of the reaction is necessary.

When a compound of formula I wherein Rc is (1-6C)alkanesulphonamido is required, the corresponding acid of formula I wherein Rc is hydroxy, or a reactive derivative thereof, is reacted with the appropriate (1-6C)alkanesulphonamide.

Thus, for example a free acid of formula I wherein Rc is hydroxy may be reacted with a suitable dehydrating agent, for example dicyclohexylcarbodiimide, optionally together with an organic base, for example 4-dimethylaminopyridine, in the presence of a suitable solvent or diluent, for example methylene chloride at a temperature in the range, 10 to 50°C., but preferably at or near room temperature. Alternatively, a reactive derivative of an acid of formula I, wherein Rc is hydroxy, for example an acid halide (such as the acid chloride) may be reacted with an alkali metal salt (such as the sodium salt) of the appropriate (1-6C)alkanesulphonamide, conveniently at or near room temperature and in a suitable solvent or diluent, for example an ether, N,N-dimethylformamide or methylene chloride.

When a compound of formula I wherein A is ethylene is required, the corresponding compound of formula I wherein A is vinylene is hydrogenated, in the presence of a catalyst.

The hydrogenation may be carried out in a suitable solvent or diluent, for example a (1-4C)alkanol (such as ethanol or 2-propanol), optionally in the presence of water, and at a temperature in the range, for example, 15 to 35°C., using hydrogen at a pressure of, for example, 1 to 2 atmospheres.

A suitable catalyst is, for example, a noble metal catalyst such as palladium metal conveniently on an inert support such as carbon, barium sulphate or barium carbonate.

When a salt of a compound of formula I wherein Rc is hydroxy is required, it is obtained by reaction with the appropriate base affording a physiologically acceptable cation, or by any other conventional procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid

processes is carried out using an optically active starting material. Alternatively, when R_c is hydroxy, a racemic form of the said compound may be reacted with an optically active form of a suitable organic base, for example ephedrine, N,N,N-trimethyl (1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure for example using an aqueous-mineral acid such as dilute hydrochloric acid.

When an optically active form of a compound of formula I wherein R_c is other than hydroxy is required, it may be obtained using the aforementioned esterification or amidification procedures using the appropriate optically active form of said acid.

The intermediates of formula II and VII as defined hereinbefore are novel and are provided as further separate features of the invention.

As stated earlier, the compounds of formula I are antagonists of one or more of the actions of TXA₂, for example certain of its actions on blood platelets, the vasculature and/or the lung. The antagonism may be demonstrated in one or other of the following tests:—

(a) The standard rabbit aortal strip model devised by Piper and Vane (*Nature*, 1969, 223, 29—35) using as agonist a freshly prepared sample of TXA₂, generated by addition of arachidonic acid (25 µg.) to citrated, platelet rich rabbit plasma (250 µl.) and allowing the mixture to aggregate fully over 90 seconds before use;

(b) a standard blood platelet-aggregation test based on that described by Born (*Nature*, 1962, 194, 927—929) and involving measuring the inhibition by a test compound of aggregation of citrated, platelet rich human plasma induced by a sub-maximal concentration (in the range 25—100 µg/ml.) of arachidonic acid; and

(c) a standard bronchoconstriction test involving measuring the inhibition by a test compound of the bronchoconstriction induced in the Konzett-Rossler guinea-pig model (as modified by Collier and James, *Brit. J. Pharmacol.*, 1967, 30, 283—307) by intravenous administration of the TXA₂ mimetic agent, U46619 at 1—1.5 µg/kg.

By way of illustration only, the compound of the formula I, 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptanoic acid possessed the following properties in the above tests:—

(a) pA₂ 6.28;

(b) IC₅₀ ca 6.7 × 10⁻⁶M; and

(c) 90% reduction of bronchoconstriction at 5 mg/kg. i.v. In general, other compounds of formula I show similar or better levels of activity in test (a) [pA₂ 5.0], and in at least one of tests (b) and (c) without any signs of overt toxicity at the active dose in test (c).

Similarly, the following representative group of acids of formula Ib show significant activity in test (a) [pA₂ ≥ 5.9] and oral activity at 50 mg/kg. (or much less) in test (c) without any signs of overt toxicity:—

Compound	Ra	Rb	Benzene Ring B
1	Ethyl	Ethyl	Phenyl
2	Pentamethylene		Phenyl
3	Methyl	Methyl	3-Fluorophenyl
4	Methyl	Methyl	3-Chlorophenyl
5	Methyl	Methyl	2-Methoxyphenyl
6	Methyl	Methyl	Phenyl*
7	Ethyl	Ethyl	2-Fluorophenyl
8	Hexamethylene		Phenyl
9	(3-Methyl)pentamethylene		Phenyl
10	Trifluoromethyl	H	Phenyl
11	2-Chlorophenyl	H	Phenyl
12	3-Chlorophenyl	H	Phenyl
13	4-Chlorophenyl	H	Phenyl
14	3-Fluorophenyl	H	Phenyl
15	4-Fluorophenyl	H	Phenyl
16	2-Methylphenyl	H	Phenyl
17	2-Ethylphenyl	H	Phenyl
18	4-Methoxyphenyl	H	Phenyl
19	3-Methylthiophenyl	H	Phenyl
20	Isopropyl	H	Phenyl
21	3,4-Methylenedioxyphenyl	H	Phenyl
22	3,4-(Methyleneoxy-methylene)phenyl	H	Phenyl
23	Methyl	H	Phenyl
24	Methyl	Methyl	2-Methylphenyl
25	Methyl	Methyl	2-Hydroxyphenyl

* methanesulphonamido derivative

The antagonism of the effects of TXA_2 on the vasculature may be demonstrated in the following manner:—

Male rats (Alderley Park strain) are anaesthetised with sodium pentobarbital and blood pressure is monitored at the carotid artery. The TXA_2 mimetic agent known as U46619 (e.g. R. L. Jones, *et alia*, in "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids" eds. S. M. Roberts and F. Scheinmann, at p. 211; Pergamon Press, 1979) is administered intravenously via the jugular vein and an ED_{50} (dose necessary to produce 50% of the maximum hypertensive effect) is established ($n=3$). The ED_{50}

for U46619 is approximately 5 µg/kg. A test compound is then administered either intravenously via the jugular vein or orally via a cannula directly into the stomach and the animal challenged with an ED₅₀ dose of U46619, five minutes after dosing with test compound and then successively every ten minutes until the hypertensive effect of U46619 is no longer blocked.

By way of illustration only, in this test the laevorotatory form of 5(Z)-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid showed significant reduction (>30%) of the hypertensive effects of the TXA₂ mimetic U46619 for a period of 120 minutes after oral administration at 50 mg/kg. However, in general preferred compounds of formula I show significant reduction of the hypertensive effect of U46619, for example for at least 60 minutes after intravenous administration at 10 mg/kg. or less, without any signs of overt toxicity at the active dose. Other illustrative compounds of the invention which may be mentioned as showing significant reduction of the hypertensive effects of U46619 for at least 60 minutes after oral administration in the above test are, for example, compounds 1, 2, 3, 5, 11, 13, 20, 21, 23 and 24 in the above list.

As stated previously, the compounds of formula I may be used in the therapy or prevention of diseases or adverse conditions in warm-blooded animals in which it is desirable to antagonise one or more of the actions of TXA₂. In general, a compound of formula I will be administered for this purpose by an oral, rectal, intravenous, subcutaneous, intramuscular or inhalation route, so that a dose in the range, for example 0.5–20 mg/kg. body weight, will be given up to four times per day, varying with the route of administration, the severity of the condition and the size and age of the patient under treatment.

The compounds of formula I will generally be used in the form of a pharmaceutical composition comprising a compound of formula I or, where appropriate, a salt thereof as defined hereinbefore, together with a pharmaceutically acceptable diluent or carrier. Such compositions are provided as a further feature of the invention and may be in a variety of dosage forms. For example, they may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of suppositories for rectal administration; in the form of sterile solutions or suspensions for administration by intravenous or intramuscular injection; in the form of aerosols or nebuliser solutions or suspensions for administration by inhalation; and in the form of powders together with pharmaceutically acceptable inert solid diluents such as lactose for administration by insufflation.

The pharmaceutical compositions may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with an enteric coating, for example comprising cellulose acetate phthalate, to minimise contact of the active ingredient of formula I with stomach acids.

The pharmaceutical compositions of the invention may also contain one or more agents known to be of value in diseases or conditions intended to be treated; for example, a known platelet aggregation inhibitor, hypolipidemic agent, anti-hypertensive agent, beta-adrenergic blocker or a vasodilator may usefully also be present in a pharmaceutical composition of the invention for use in treating a heart or vascular disease or condition. Similarly, by way of example, an anti-histamine, steroid (such as beclomethasone dipropionate), sodium cromoglycate, phosphodiesterase inhibitor or a beta-adrenergic stimulant may usefully also be present in a pharmaceutical composition of the invention for use in treating a pulmonary disease or condition.

In addition to their use in therapeutic medicine the compounds of formula I are also useful as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of TXA₂ in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents. The compounds of formula I may also be used because of their TXA₂ antagonist properties in helping to maintain the viability of blood and blood vessels in warm-blooded animals (or parts thereof) undergoing artificial extracorporeal circulation, for example during limb or organ transplants. When used for this purpose a compound of formula I or a physiologically acceptable salt thereof will generally be administered so that a steady state concentration in the range, for example, 0.5 to 50 mg. per litre is achieved in the blood.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:—

(i) evaporations were carried out by rotary evaporation *in vacuo*;

(ii) operations were carried out at room temperature, that is in the range 18–26°C;

(iii) column chromatography was performed on Merck Kieselgel 60 (Art. 7734) using approximately 50–70 g. of SiO₂ per g. of sample, and monitoring the process by thin layer chromatography on Merck 0.25 mm. Kieselgel 60F 254 plates (Art. 5715), flash chromatography was performed on Merck Kieselgel (Art. 9385); these materials were obtained from E. Merck, Darmstadt, W. Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) NMR spectra were normally determined at 90 MHz in CDCl₃ using tetramethylsilane (TMS) as an internal standard, and expressed as chemical shifts (delta values) relative to TMS using the following abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet.

When a single chemical shift value is given for a multiplet (m) this corresponds to the centre point of the signals making up the multiplet;

(vi) all end-products were isolated as racemates, and

(vii) those compounds of formula I wherein A is vinylene may contain 3—5% by weight of the E-stereoisomeric form.

Example 1

(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (2.0 g.) was added under argon with stirring and ice-cooling to a solution of the ylid prepared from (4-carboxybutyl)triphenylphosphonium bromide (11.25 g.) and dimethyl sodium (5.4 g.) in dry dimethyl sulphoxide (150 ml.) and the mixture was stirred overnight. Cautious addition of water (200 ml.) followed by extraction with ether (3 × 150 ml.) removed the bulk of neutral material; acidification of the aqueous layer to pH 5—6 with aqueous oxalic acid followed by extraction with ether, drying (Na_2SO_4) and evaporation, gave the crude product as a yellow oil. Column chromatography, eluting with toluene/ethyl acetate/acetic acid (80:20:2 v/v) gave 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as an oil (1.8 g.) which solidified on standing to give material of m.p. 76—78°C; NMR: 1.55 (6H, s), 1.3—2.6 (9H, m), 3.7—4.3 (2H, m), 5.1—5.5 (3H, m), 7.3 (5H, br s) and 9.59 (1H, s) ppm.

The starting material was obtained as follows:—

A solution of ethyl 2-allyl-3-oxo-3-phenyl propionate* (10 g.) in dry tetrahydrofuran (20 ml.) was added over 5 minutes to a suspension of lithium aluminium hydride (2 g.) in tetrahydrofuran (130 ml.) with stirring at -78°C. under argon. The mixture was allowed to warm to room temperature, stirred for 6 hours and was then treated with ethyl acetate (25 ml.) and saturated aqueous ammonium chloride solution (100 ml.). Filtration, extraction of the aqueous phase with ether (3 × 150 ml.), drying the ether layer (Na_2SO_4) and evaporation gave a pale brown oil (10 g.). Column chromatography, eluting with chloroform/ethyl acetate (9:1 v/v) gave 2-allyl-1-phenyl-1,3-propanediol as a colourless oil (5.4 g.); NMR: 1.6—2.2 (3H, m), 3.0 (1H, s), and 7.3 (5H, br s).

A solution of 2-allyl-1-phenyl-1,3-propanediol (5.4 g.) in 2,2-dimethoxypropane (250 ml.) was treated with *p*-toluenesulphonic acid (25 mg.) and allowed to stand overnight at room temperature. Addition of triethylamine (5 drops) followed by evaporation gave a brown oil which on flash column chromatography, (silica 30:1 per g. sample weight), eluting with toluene/hexane (1:1 v/v) gave (4,5-*cis*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane as a colourless oil (2.1 g.) which solidified on standing to give material of m.p. 41—43°C.; NMR: 1.55 (6H, s), 1.2—1.6 (3H, m), 3.8—4.2 (2H, m), 4.8—5.9 (3H, m), 5.2 (1H, d, $J=2.7$ Hz) and 7.3 (5H, br s) ppm. and (4,5-*trans*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane as a colourless oil (1.8 g.) which solidified on standing to give material of m.p. 31—34°C.; NMR: 1.4 (3H, s), 1.5 (3H, s), 1.3—2.2 (3H, m), 3.5—4.0 (2H, m), 4.5 (1H, d, $J=10$ Hz), 4.7—5.8 (3H, m) and 7.3 (5H, br s) ppm. Ozone was passed through a solution of (4,5-*cis*-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (2.1 g.) in methylene chloride (200 ml.) at -78°C. until a permanent blue colour developed. The solution was flushed with argon until colourless. A solution of triphenylphosphine (2.1 g.) in dichloromethane (40 ml.) was added and the mixture was allowed to warm to room temperature. Evaporation followed by column chromatography, eluting with chloroform/ethyl acetate (19:1 v/v) gave (2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a white solid (2.0 g.), m.p. 67—69°C; NMR: 1.55 (6H, s), 2.0—3.1 (3H, m), 3.7—4.4 (2H, m), 5.2 (1H, d, $J=2.0$ Hz) and 7.3 (5H, br s) ppm.

[*Obtained as an oil by an analogous procedure to that of C. S. Marvel and F. D. Hager, *Organic Syntheses*, Coll., Vol. I, p. 248].

Example 2

Diazomethane was distilled into a solution of 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (320 mg.) in dry ether (10 ml.) with ice-cooling until a yellow-green colour persisted in the mixture. A solution of acetic acid in ether (10% v/v) was added until effervescence ceased. The mixture was concentrated, diluted with tetrachloromethane (20 ml.), decolourised with activated charcoal at room temperature and evaporated to give methyl 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoate as a colourless oil (300 mg.); NMR: 1.5 (6H, s), 1.4—2.4 (9H, m), 3.65 (3H, s), 3.7—4.3 (2H, m), 5.2 (3H, m) and 7.3 (5H, s) ppm; m/e 332 (M^+).

Example 3

In a similar manner to Example 1, except that (4-carboxypentyl)triphenylphosphonium bromide was used instead of (4-carboxybutyl)triphenylphosphonium bromide, there was obtained 6(Z)-8-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)octenoic acid as a colourless oil (2.2 g.); NMR: 1.5 (6H, s), 1.2—3.5 (11H, m), 3.7—4.3 (2H, m) and 7.3 (5H, m) ppm; m/e 404 [$\text{M}^+ + (\text{CH}_3)_3\text{Si}$].

Example 4

In a similar manner to Example 1, but starting from (2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde, there was obtained 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as a colourless oil in 45% yield; NMR: 0.7—1.2 (6H, m), 1.3—2.6 (13H, m), 3.7—4.3 (2H, m), 5.1—5.5 (3H, m) and 7.3 (5H, br s) ppm; m/e : 347 ($\text{M}^+ + \text{H}$) and 317 ($\text{M}^+ - \text{C}_2\text{H}_6$).

The starting material was obtained as follows:—

A solution of (4,5-*cis*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (20 g.) in tetrahydrofuran (400 ml.) was treated with a solution of hydrochloric acid (2M, 10 ml.) in water (100 ml.) and the resulting solution was



heated under reflux for 3 hours. The mixture was evaporated. The brown oil obtained was dissolved in ethyl acetate (200 ml.). The solution was washed with water (3 × 100 ml.), dried (Na₂SO₄) and evaporated to give crude *erythro*-2-allyl-1-phenyl-1,3-propanediol (17 g.) as a colourless oil which was used without further purification.

A solution of crude *erythro*-2-allyl-1-phenyl-1,3-propanediol (17 g.) in toluene (200 ml.) containing 3-pentanone (10 g.) and *p*-toluenesulphonic acid (50 mg.) was heated under reflux for 4 hours using a Dean and Stark apparatus for removal of water. The reaction mixture was diluted with toluene (100 ml.), washed with aqueous sodium hydroxide (2M, 50 ml.) and then water (100 ml.), dried (Na₂SO₄) and evaporated to give a brown oil which on column chromatography, eluting with toluene, gave (4,5-*cis*)-5-allyl-2,2-diethyl-4-phenyl-1,3-dioxane (5.8 g.) as a colourless oil; NMR: 0.7—1.2 (6H, m), 1.4—2.6 (7H, m), 3.7—4.3 (2H, m), 4.7—5.9 (3H, m), 5.2 (1H, d, J=3Hz) and 7.3 (5H, m) ppm.

Ozone was passed through a solution of (4,5-*cis*)-5-allyl-2,2-diethyl-4-phenyl-1,3-dioxane (5.8 g.) in dichloromethane (600 ml.) at -78°C. until a permanent blue colour developed. The solution was flushed with argon until colourless. A solution of triphenylphosphine (7.5 g.) in dichloromethane (150 ml.) was then added and the mixture was stirred overnight at -20°C. and for 3 hours at room temperature. The mixture was evaporated and the residue was purified by column chromatography, eluting with chloroform/ethyl acetate (19:1, v/v) to give (2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a colourless oil (4.3 g.); NMR: 0.7—1.2 (6H, m), 1.6—3.0 (7H, m), 3.6—4.4 (2H, m), 5.2 (1H, d, J=2.4 Hz), 7.3 (5H, br s) and 9.5 (1H, s) ppm.

Example 5

In a similar manner to Example 1, but starting from [2,2-dimethyl-4-(2-methylphenyl)-1,3-dioxan-*cis*-5-yl]acetaldehyde, there was obtained 5(Z)-7-[2,2-dimethyl-4-(2-methylphenyl)-1,3-dioxan-*cis*-5-yl]-heptenoic acid as a white solid (0.69 g.); m.p. 72—75°C.; NMR: 1.55 (6H, s), 2.3 (3H, s), 1.3—2.7 (9H, m), 3.7—4.3 (2H, m), 5.0—5.6 (3H, m) and 7.1—7.6 (4H, m) ppm; m/e: 333 [M⁺+H].

The starting material was obtained as an oil using an analogous procedure to that described in Example 1; NMR: 1.5 (3H, s), 1.6 (3H, s), 1.8—2.9 (3H, m), 2.4 (3H, s), 3.6—4.2 (2H, m), 4.9 (1H, d, J=9Hz), 7.1—7.6 (4H, m) and 9.45 (1H, s) ppm; starting from ethyl 2-allyl-3-(2-methylphenyl)-3-oxopropionate, itself obtained as an oil using a similar procedure to that of C. S. Marvel and F. D. Hager, *Organic Synthesis Coll.* Vol. I, p 248.

The following intermediates analogous to those in Example 1 were isolated:—

(a) 2-allyl-1-(2-methylphenyl)-1,3-propanediol as a colourless oil; NMR: 1.6—2.6 (3H, m), 2.3 (3H, s), 3.7 (2H, d), 4.8—6.0 (4H, m) and 7.0—7.7 (4H, m) ppm;

(b) (4,5-*cis*)-5-allyl-2,2-dimethyl-4-(2-methylphenyl)-1,3-dioxane as an oil; NMR: 1.3—2.6 (3H, m), 1.55 (6H, s), 2.3 (3H, s), 3.7—4.3 (2H, m), 4.8—5.8 (3H, m), 5.3 (1H, d, J=2.7 Hz) and 7.0—7.7 (4H, m) ppm.

Example 6

In a similar manner to Example 1, but starting from (4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde, there was obtained: 5(Z)-7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as a colourless oil in 61% yield, which solidified to give material of m.p. 42—46°C.; NMR: 1.5—2.6 (9H, m), 3.7—4.3 (2H, m), 4.8—5.6 (5H, m) and 7.3 (5H, br s) ppm; m/e 290 [M⁺].

The starting material was obtained as follows:—

A solution of crude *erythro*-2-allyl-3-phenyl-1,3-propanediol (50 g.) in toluene (100 ml.) containing dimethoxymethane (5 ml.) and *p*-toluenesulphonic acid (25 mg.) was heated under reflux for 2 hours. Further dimethoxymethane (2 ml.) was added and heating was continued for 1 hour. The reaction mixture was cooled and washed with water (2 × 50 ml.). The organic phase was dried (Na₂SO₄) and evaporated. The brown oil obtained was purified by column chromatography, eluting with toluene to give (4,5-*cis*)-5-allyl-4-phenyl-1,3-dioxane (A) (520 mg.) as a colourless oil; NMR 1.5—2.6 (3H, m), 2.7—4.3 (2H, m), 4.8—5.9 (5H, m), 5.3 (1H, d, J=6Hz) and 7.3 (5H, br s) ppm.

A solution of A (500 mg.) in *t*-butyl alcohol (5 ml.) was added to a solution containing sodium periodate (1.2 g.), water (5 ml.), *t*-butyl alcohol (35 ml.) and osmium tetroxide (5 ml.). The mixture was stirred for 3 hours. Water (100 ml.) was added to dissolve the precipitate and the aqueous solution was extracted with toluene (3 × 50 ml.). The extracts were dried (Na₂SO₄), evaporated and gave, after column chromatography, eluting with chloroform/ethyl acetate (19:1 v/v), (4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a colourless oil (200 mg.); NMR: 2.1—3.2 (3H, m), 4.1 (2H, m), 4.9—5.4 (3H, m), 7.3 (5H, br s) and 9.6 (1H, br s) ppm.

Example 7

A solution of 3-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)propionaldehyde (500 mg.) in dry dimethyl sulphoxide (5 ml.) was added under argon with ice-cooling to a stirred solution of the ylid prepared from (4-carboxypropyl)triphenylphosphonium bromide (2.4 g.) and dimethyl sodium (1.2 g.) in dry dimethyl sulphoxide (20 ml.). The mixture was stirred for 18 hours. Water (50 ml.) was added and the aqueous mixture was extracted with ether (3 × 50 ml.) to remove the bulk of the neutral material. The aqueous layer was acidified to pH 5—6 (2M hydrochloric acid) and extracted with ether (4 × 50 ml.). The combined extracts were dried (Na₂SO₄) and evaporated. The residual yellow oil was purified by column chromatography.

58

graphy eluting with toluene/ethyl acetate/acetic acid (80/20/2 v/v) to give 4(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)-heptenoic acid as an oil (300 mg.); NMR: 1.5 (6H, s), 1.3—2.6 (9H, m), 3.7—4.3 (2H, m), 4.9—5.4 (3H, m) and 7.3 (5H, br s) ppm; m/e: 191, 107 and 91.

The starting material was obtained as follows:—

A solution of borane in tetrahydrofuran (1M, 11 ml.) was added over 10 minutes to an ice-cooled, stirred solution of (4,5-*cis*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (2.32 g.) in dry tetrahydrofuran (50 ml.) under argon. Stirring was continued for 30 minutes and the mixture was treated sequentially with aqueous sodium hydroxide (1M, 20 ml.) and hydrogen peroxide (30% w/v; 5 ml.). After a further 30 minutes, saturated brine (100 ml.) was added and the mixture was extracted with ethyl acetate (3 × 70 ml.). The extracts were dried (Na₂SO₄) and evaporated to give 3-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)-1-propanol (B) (2.6 g.) as a colourless oil which was used without further purification. A suspension of pyridinium chlorochromate (1.62 g.) in dichloromethane (25 ml.) was treated with a solution of B (1.25 g.) in dichloromethane (10 ml.). The mixture was stirred for 40 minutes. Ether (100 ml.) was then added and the solution was poured through a short column containing activated magnesium silicate (25 g., 60—100 Mesh). The column was thoroughly eluted with ether and the eluate was evaporated. The residual oil was purified by column chromatography, eluting with chloroform/ethyl acetate (9:1 v/v), to give 3-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)propionaldehyde as a colourless oil (550 mg.); NMR: 1.55 (6H, s), 1.2—2.3 (5H, m), 3.7—4.3 (2H, m), 5.2 (1H, br s), 7.3 (5H, br s) and 9.55 (1H, s) ppm.

Example 8

A solution containing *erythro*-5(Z)-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (140 mg.), *p*-toluenesulphonic acid (5 mg.) and phenylacetaldehyde dimethyl acetal (125 μ l.) in dry tetrahydrofuran (5 ml.) was heated at 60—65°C. for 24 hours. The cooled reaction mixture was evaporated and the residue diluted with ether (10 ml.). The solution obtained was washed with water (5 ml.), saturated aqueous sodium bicarbonate (5 ml.), water (5 ml.) and saturated brine (5 ml.) then dried (MgSO₄) and evaporated to give a yellow oil, which was purified by column chromatography, eluting with dichloromethane/methanol (19:1 v/v), to give 5(Z)-7-(2-benzyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as a pale yellow oil (100 mg.); NMR: 1.3—2.6 (9H, m), 3.0 (2H, d), 3.7—4.3 (2H, m), 4.8—5.5 (4H, m) and 7.3 (5H, br s) ppm; microanalysis, found: C, 75.7; H, 7.6%; calculated: C, 75.79; H, 7.37%.

The starting material was obtained as follows:

A solution containing 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (5.2 g.), water (20 ml.) and aqueous hydrochloric acid (2M, 3 ml.) in tetrahydrofuran (180 ml.) was heated at 60—70°C. for 3 hours and then evaporated. The residue obtained was diluted with ethyl acetate (100 ml.), washed with water (3 × 100 ml.), dried (Na₂SO₄) and evaporated to give crude *erythro*-5(Z)-9-hydroxy-8-hydroxymethyl-9-phenyl-5-nonenoic acid as a colourless oil (4.5 g.) which was used without further purification.

Example 9

Using a similar procedure to that in Example 8, but starting from cyclohexanone diethyl acetal, there was obtained 5(Z)-7-(4'-phenyl-[cyclohexanespiro-2'-1,3-dioxan]-*cis*-5-yl)heptenoic acid as a colourless oil, which solidified on standing to give material of m.p. 76—79°C.; NMR: 1.3—2.7 (19H, m), 3.7—4.3 (2H, m), 5.2—5.6 (3H, m) and 7.3 (5H, br s) ppm; m/e: 358 (M⁺).

Examples 10—22

Using a similar procedure to that described in Example 1, but starting from the appropriate aldehyde of formula II (n=1) and the ylid from (4-carboxybutyl)triphenylphosphonium bromide, the following compounds of the formula Ib (Ra=Rb=methyl)

Ex.	Ring B Subs.	m.p. (°C.)	NMR (Ring B-1H) ppm	Mass Spectrum m/e	Base/ Yield (%)
10	2-Cl	58—62	7.28 (3H, m) 7.75 (1H, m)	(M + H) 353	D/63
11	2-F	71—74	7.07 (3H, m) 7.5 (1H, m)	(M + H) 337	D/35
12	2-CF ₃	oil	7.55 (4H, m)	(M + H) 387	D/33
13	2-OMe	112—114	7.1 (4H, m) 3.7 (3H, s; OMe)	(M + H) 349	T/59
14	2-Pr ¹	oil	7.2 (3H, m) 7.3 (1H, m) 3.03 (1H, m) 1.21 (6H, d)	(M + H) 361	D/32
15	2-Et	oil	7.17 (3H, m) 7.46 (1H, m) 2.57 (2H, q) 1.16 (3H, t)	(M + H) 347	T/81
16	2,6-F ₂	oil	6.86 (3H, m) 7.19 (1H, m)	(M + H) 355	T/44
17	3-F	50—53	6.8—7.5 (4H, m)	(M—Me) 321.150	D/27
18	4-Me	94—99	7.1—7.28 (4H, m) 2.3 (3H, s; CH ₃)	(M + H) 333	T/80
19	3-CF ₃	55—58	7.4—7.58 (4H, m)	(M—Me) 386.1698	T/93
20	3-Cl	oil	7.0—7.3 (4H, m)	(M—Me) 337.120	T/60
21	4-NO ₂	oil	7.4—8.4 (4H, m)	(M) 363.1671	B/69
22	4-F	74—77	6.9—7.4 (4H, m)	(M + H) 337	T/75

Notes:

(i) NMR: determined at 90 MHz in CDCl_3 ; all the spectra contained the following additional signals: 1.55 (6H, s, CH_3), 1.3—2.6 (9H, m; CH_2CH), 3.7—4.3 (2H, m, OCH_2) and 5.1—5.5 (3H, m; $\text{CH}=\text{CH}$, OCHPh).

(ii) Bases used for generation of ylid:

D=dimethyl sodium + dimethyl sulphoxide;

T=potassium t-butoxide + tetrahydrofuran;

B=butyl lithium + tetrahydrofuran.

The solvent used for the generation of the ylid was used for the reaction between the ylid and the aldehyde of formula II.

(iii) For Ex. 21, the ylid was added to a solution of the aldehyde in tetrahydrofuran at -70°C .

The necessary starting aldehydes of formula II ($\text{Ra}=\text{Rb}=\text{CH}_3$, $n=1$) were obtained in yields of 56—95% from the corresponding derivatives of formula VII ($\text{Ra}=\text{Rb}=\text{methyl}$) in an analogous manner to that described in Example 1 starting from the appropriate ethyl 2-allyl-3-(substituted phenyl)-3-oxopropionate of formula V ($\text{R}=\text{ethyl}$). The aldehydes has the following properties:—

No.	Ring B Subs	NMR (Ring B- ^1H)	IR ($-\text{CHO}$) cm^{-1}	Physical Form
10a	2-Cl	7.25 (3H, m) 7.55 (1H, m)	1720	oil
11a	2-F	**	1720	oil
12a	2- CF_3	**	1720	oil
13a	2-OMe	**	1720	oil
14a	2- Pr^i	**	1720	oil
15a	2-Et	**	1720	oil
16a	2,6- F_2	7.12 (3H, m)	1720	solid m.p. 46—47°C
17a	3-F	**	1720	oil
18a	4-Me	**	1720	oil
19a	3- CF_3	**	1720	oil
20a	3-Cl	**	1720	oil
21a	4- NO_2	7.4—8.4 (4H, m)	1715	oil
22a	4-F	**	1720	oil

Notes:

IR: Infra-red spectra were generally determined as liquid films on rock-salt plates.

NMR: All the spectra contained the following additional signals: 1.55 (6H, s, CH_3), 2.0—3.1 (3H, m, $\text{CH}-\text{CH}_2\text{CHO}$), 3.7 (2H, m, OCH_2) and 5.2 (1H, d, $J=2\text{Hz}$, OCHPh).

** : NMR spectrum not determined; material essentially pure by thin layer chromatography (TLC) (SiO_2 :1:9 v/v ethyl acetate/chloroform).

The following intermediate (4,5-*cis*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxanes of formula VII ($\text{Ra}=\text{Rb}=\text{Methyl}$) were isolated (any isomeric (4,5-*trans*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane being removed by chromatography):—

No.	Ring B Subs	NMR (Ring B- ¹ H)	Yield (%)	Physical Form
10a	2-Cl	7.27 (3H, m) 7.61 (1H, m)	38	oil
11b	2-F	7.07 (3H, m) 7.49 (1H, m)	24	oil
12b	2-CF ₃	7.52 (4H, m)	10	oil
13b	2-OMe	7.11 (4H, m) 3.82 (3H, s, OMe)	56	Solid m.p. 77—79°C.
14b	2-Pr ⁱ		21	oil
15b	2-Et	7.17 (3H, m) 7.42 (1H, m) 1.21 (3H, m, Me)	42	oil
16b	2,6-F ₂	6.95 (2H, m) 7.31 (1H, m)	80	oil
17b	3-F	6.8—7.45 (4H, m)	28	oil
18b	4-Me	7.0—7.25 (4H, m) 2.3 (3H, s, CH ₃)	21	oil
19b	3-CF ₃	7.4—7.65 (4H, m)	30	oil
20b	3-Cl	7.1—7.35 (4H, m)	26	oil
21b	4-NO ₂	7.4—8.4 (4H, m)	33	oil
22b	4-F	6.9—7.4 (4H, m)	39	oil

Notes:

NMR: the following NMR signals were common to all the compounds: 1.55 (6H, s), 1.2—1.6 (3H, m), 3.8—4.2 (2H, m), 4.8—5.9 (3H, m) and 5.2 (1H, d, J=2.7Hz).

Yields: yields quoted are from the 2-allyl-3-(substituted phenyl)-3-oxo-propionate of formula V (Ra=Rb=methyl, R=ethyl). That quoted for No. 16b is from essentially pure *erythro*-2-allyl-1-(2,6-difluorophenyl)-1,3-propanediol and that quoted for No. 13b is from 4:1 *erythro*- to *threo*-2-allyl-1-(2-methoxyphenyl)-1,3-propanediol.

The 5-allyl-1,3-dioxane derivatives of formula VII (Ra=Rb=methyl) were themselves obtained by cyclisation of the *erythro*-form of the appropriate 2-allyl-1-(substituted phenyl)-1,3-propanediol of formula VIa (Ra=Rb=methyl) in the presence of 2,2-dimethoxypropane by analogy with the procedure in Example 1. The required *erythro*-diols of formula VIa were generally obtained, together with the corresponding *threo*-diols of formula VIb, as oils by lithium aluminium hydride or lithium borohydride reduction of the ethyl 2-allyl-3-(substituted phenyl)-3-oxopropionate of formula V and were used without special purification or characterisation.

Alternatively the *erythro*- diol of the formula VIa may be obtained essentially free of the *threo*-isomer VIb by a two stage reduction procedure using first zinc borohydride followed by lithium aluminium hydride. The latter procedure is illustrated by the production of *erythro*-2-allyl-1-(2,6-difluorophenyl)-1,3-propanediol:—

(a) A solution of anhydrous zinc chloride (1.7 g.) in anhydrous ether (20 ml.) was added to a stirred suspension of sodium borohydride (1.1 g.) in anhydrous ether (40 ml.) and the mixture stirred for 18 hours. Solid material was removed by filtration. A solution of ethyl 2-allyl-3-(2,6-difluorophenyl)-3-oxopropionate (1.4 g.) in anhydrous ether (10 ml.) was then added over 5 minutes to the filtrate which has been cooled to 0°C. The subsequent mixture was stirred at 0°C. for 45 minutes. 2M Hydrochloric acid was then added until gas evolution ceased. The organic phase was separated, washed with saturated brine, dried (MgSO₄) and evaporated. The oil (1.3 g.) obtained was purified by flash column chromatography on silica (40 g.) using 15% v/v ethyl acetate in petroleum ether (b.p. 60–80°C.) as eluent to give ethyl *erythro*-2-allyl-3-(2,6-difluorophenyl)-3-hydroxypropionate (A) (400 mg.) as an oil; NMR: 1.02 (3H, t), 2.58 (3H, m), 3.12 (1H, m), 3.90 (2H, q), 5.13 (3H, m), 5.83 (1H, m), 6.83 (2H, m) and 7.24 (1H, m) ppm.

(b) A solution of the ester (A) (340 mg.) in anhydrous ether (10 ml.) was added under nitrogen over 3 minutes to a stirred suspension of lithium aluminium hydride (120 mg.) in anhydrous ether (30 ml.) at 0°C. The mixture was heated under reflux for 30 minutes and cooled by ice-water. Ethyl acetate (2 ml.) in anhydrous ether (10 ml.) was then added, followed by saturated ammonium chloride solution (25 ml.). The mixture obtained was separated by filtration. The organic phase was washed with saturated brine, dried (MgSO₄) and evaporated to give *erythro*-2-allyl-1-(2,6-difluorophenyl)-1,3-propanediol as an oil (252 mg.); NMR: 2.30 (5H, m), 3.60 (2H, d), 5.18 (3H, m), 5.9 (1H, m), 6.95 (2H, m) and 7.30 (1H, m) ppm.

The lithium borohydride procedure is illustrated by the production of 2-allyl-1-(2-ethylphenyl)-1,3-propanediol:—

A solution of 2-allyl-3-(2-ethylphenyl)-3-oxopropionate (7.3 g.) in dry tetrahydrofuran (THF) (40 ml.) was added during 10 minutes to a stirred suspension of lithium borohydride (1.32 g.) in dry THF (40 ml.) at 0°C. under a nitrogen atmosphere. The mixture was then stirred at room temperature for 18 hours, cooled to 0–5°C. and water (40 ml.) added. The aqueous mixture was acidified to pH 2 (concentrated hydrochloric acid) and extracted with ethyl acetate (3 × 120 ml.). The combined extracts were washed with saturated brine, dried (MgSO₄) and evaporated. The residual oil (6.1 g.) was purified by chromatography on silica (180 g.) using 3:7 v/v ethyl acetate/petroleum ether (b.p. 60–80°C.) to give 2-allyl-1-(2-ethylphenyl)-propane-1,3-diol (containing approximately 4:1 *erythro*- to *threo*-forms) as an oil (4.0 g.); NMR: 1.19 (3H, m), 2.04 (5H, m), 2.59 (2H, m), 3.76 (2H, m), 5.02 (3H, m), 5.67 (1H, m), 7.17 (3H, m), and 7.47 (1H, m) ppm.

The starting ethyl 2-allyl-3-(substituted phenyl)-3-oxopropionates of formula V (R=ethyl) may be obtained as oils by allylation of the appropriate 3-(substituted phenyl)-3-oxopropionate using the general procedure of Marvel and Hager. Examples of esters of formula V obtained in this way are those wherein benzene ring B is 2-chloro-, 3-chloro-, 3-fluoro-, 2-methoxy-, 2-isopropyl-, 2-trifluoromethyl-, 3-trifluoromethyl- and 4-methyl-phenyl. The necessary starting 3-oxopropionates were made using one of the following well known, standard procedures:—

(a) reaction of the appropriate substituted benzoyl chloride with *t*-butyl ethyl malonate and magnesium ethoxide to give the corresponding *t*-butyl ethyl 2-(substituted benzoyl)malonate which is then thermolysed at 100°C. *in vacuo* in the presence of *p*-toluenesulphonic acid (e.g. those 3-oxopropionates wherein benzene ring B is 2-chloro-, 2-methoxy-, 2-isopropyl- and 2-trifluoromethyl-phenyl); or

(b) reaction of the appropriate substituted benzoyl chloride with the dilithium salt of monoethyl malonate (obtained from two molecular equivalents of butyl lithium in hexane at –70°C.) at –65°C., followed by acidification with concomitant decarboxylation at room temperature (e.g. those 3-oxopropionates wherein benzene ring B is 3-fluoro-, 3-chloro-, 3-trifluoromethyl- and 4-methyl-phenyl).

Alternatively, the starting 2-allyl-3-(substituted phenyl)-3-oxopropionates of formula V (R=ethyl) may be obtained from *t*-butyl ethyl malonate as illustrated below:—

(a) Potassium carbonate (28.0 g.) was added to a stirred solution of *t*-butyl ethyl malonate (37.6 g.) in dry *N,N*-dimethylformamide (DMF) (100 ml.). After 1 hour allyl bromide (34 ml.) was added. The mixture was heated at 70°C for 66 hours, cooled to room temperature and diluted with water (900 ml.). The mixture obtained was extracted with ethyl acetate (3 × 200 ml.). The extracts were dried (MgSO₄) and evaporated. The oil obtained was purified by flash column chromatography eluting with 1:15 v/v ethyl acetate/petroleum ether (b.p. 60–80°C.) to give *t*-butylethyl 2-allylmalonate as a colourless oil (15.6 g.), b.p. 70–72°C. at 0.2 mmHg; NMR: 1.21 (3H, t), 1.42 (9H, s), 2.66 (2H, m), 3.28 (1H, m), 4.16 (2H, q), 5.06 (2H, m) and 5.76 (1H, m) ppm.

(b) Sodium hydride (2.8 g., 50% w/w dispersion in mineral oil) was added over 15 minutes to an ice cooled solution of *t*-butyl ethyl 2-allylmalonate (13.4 g.) in dry DMF (120 ml.) under nitrogen. The mixture was stirred at room temperature for 45 minutes and cooled to 0°C. 2-Ethylbenzoyl chloride (10.1 g.) was added over 2 minutes and the mixture stirred at room temperature for 18 hours. The DMF was evaporated and the residue shaken with water (100 ml.) and ethyl acetate (200 ml.). The ethyl acetate phase was separated, washed with saturated brine, dried (MgSO₄) and evaporated. The oil obtained (21.8 g.) was purified by flash column chromatography on silica (650 g.) using toluene as eluant to give *t*-butyl ethyl 2-allyl-2-(2-ethylbenzoyl)malonate (14.3 g.) as an oil; NMR: 1.25 (15H, m), 2.7 (2H, q), 2.9 (2H, d), 4.12 (2H, q), 5.31 (2H, m), 6.05 (1H, m) and 7.35 (4H, m) ppm.

(c) A mixture of *t*-butyl ether 2-allyl-2-(2-ethylbenzoyl)malonate (14.3 g.), acetic anhydride (4 ml.) and *p*-toluenesulphonic acid (100 mg.) in acetic acid (200 ml.) was heated at 140°C. under nitrogen for 75 minutes and then evaporated. The residue was shaken with a mixture of saturated sodium bicarbonate solution (100 ml.) and ethyl acetate (100 ml.). The organic phase was dried (MgSO₄) and evaporated. The oil

obtained (9.3 g.) was purified by flash column chromatography (280 g.) using toluene as eluant to give ethyl 2-allyl-3-(2-ethylphenyl)-3-oxopropionate (7.4 g.) as a pale yellow oil; NMR: 1.19 (6H, m), 2.74 (4H, m), 4.15 (3H, m), 5.05 (2H, m), 5.79 (1H, m), 7.30 (3H, m) and 7.61 (1H, m) ppm.

An analogous procedure to (a)-(c) above was used in addition for the preparation of:—

(i) ethyl 2-allyl-3-(2,6-difluorophenyl)-3-oxopropionate, obtained as an oil; NMR: 1.2 (3H, t), 2.70 (2H, m), 4.17 (3H, m), 4.92 (2H, m), 5.73 (1H, m), 6.95 (2H, m) and 7.26 (1H, m) ppm; and

(ii) ethyl 2-allyl-3-(2-fluorophenyl)-3-oxopropionate, obtained as an oil; NMR: 1.23 (3H, t), 2.67 (2H, m), 4.20 (3H, m), 5.04 (2H, m), 5.83 (1H, m), 7.09 (2H, m), 7.37 (1H, m) and 7.73 (1H, m) ppm.

Characteristic NMR data for other representative 2-allyl-3-oxopropionates of formula V (R=ethyl) obtained as oils by direct sodium ethoxide allylation of the corresponding ethyl 3-(substituted phenyl)-3-oxopropionate are as follows:—

(i) ethyl 2-allyl-3-(2-trifluoromethylphenyl)-3-oxopropionate; NMR: 1.21 (3H, m), 2.75 (2H, m), 4.14 (3H, m), 5.04 (2H, m), 5.90 (1H, m) and 7.59 (4H, m) ppm;

(ii) ethyl 2-allyl-3-(2-chlorophenyl)-3-oxopropionate; NMR: 1.20 (3H, m), 2.71 (2H, m), 4.18 (3H, m), 4.93 (2H, m), 5.73 (1H, m) and 7.34 (4H, m) ppm; and

(iii) ethyl 2-allyl-3-(2-methoxyphenyl)-3-oxopropionate; NMR: 1.17 (3H, m), 2.69 (2H, m), 4.10 (6H, m), 5.00 (2H, m), 5.81 (1H, m), 6.95 (2H, m), 7.38 (1H, m) and 7.51 (1H, m) ppm.

Examples 23—24

Using a similar procedure to that described in Example 1 the following acids of formula I were obtained:—

Example 23

5(Z)-7-[(2,4,5-*cis*)-2-methyl-4-phenyl-1,3-dioxan-5-yl]heptenoic acid, as a solid in 55% yield, m.p. 31—32°C.; NMR: 1.0—2.4 (12H, m), 3.7—4.3 (2H, m), 4.7—5.0 (2H, m), 5.1—5.5 (2H, m) and 7.1—7.5 (5H, m) ppm; starting from [(2,4,5-*cis*)-2-methyl-4-phenyl-1,3-dioxan-5-yl]acetaldehyde and using potassium *t*-butoxide and tetrahydrofuran instead of dimethyl sodium and dimethyl sulphoxide;

Example 24

5(Z)-7-(2,2-dipropyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as an oil in 60% yield; NMR: 0.8—2.8 (23H, m), 3.6—4.3 (2H, m), 5.0—5.6 (3H, m), 7.1—7.6 (5H, m) and 9.3 (1H, br s) ppm, starting from (2,2-dipropyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde.

The starting acetaldehyde for 23 was obtained as an oil [NMR: 1.45 (3H, d, $J=5.0$ Hz), 2.1—3.1 (3H, m), 4.05 (2H, s), 4.7—5.1 (2H, m), 7.1—7.5 (5H, m) and 9.55 (1H, s) ppm] in 89% yield by oxidation of (2,4,5-*cis*-5-allyl-2-methyl-4-phenyl-1,3-dioxane, itself obtained as an oil [NMR: 1.45 (3H, d, $J=5.0$ Hz), 1.5—2.6 (3H, m), 3.7—4.3 (2H, m), 4.8—5.1 (4H, m), 5.3—5.8 (1H, m) and 7.1—7.5 (5H, m) ppm] in 79% yield by cyclisation of the *erythro*-form of 2-allyl-1-phenyl-1,3-propanediol with acetaldehyde, using analogous procedures to those described for Example 1.

The starting acetaldehyde for 24 was obtained as an oil in 95% yield by oxidation of (4,5-*cis*)-5-allyl-2,2-dipropyl-4-phenyl-1,3-dioxane using a similar procedure to that described in Example 4. The latter dioxane was itself obtained as an oil; NMR: 0.7—2.7 (17H, m), 3.7—4.2 (2H, m), 4.7—5.8 (4H, m) and 7.0—7.4 (5H, m) ppm, in 42% yields by reaction of *erythro*-2-allyl-1-phenyl-1,3-propanediol with 4-heptanone using a similar procedure to that described for the analogous compound in Example 4.

Examples 25—29

A mixture of cyclopentanone (0.165 ml.), *erythro*-5(Z)-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (0.52 g.), triethyl orthoformate (0.4 ml.) and *p*-toluenesulphonic acid (5 mg.) was stirred for 3 hours. Ether (25 ml.) was then added and the solution was extracted with a solution of potassium hydroxide (0.21 g.) in water (10 ml.). The basic extract was washed with ether (10 ml.) and then acidified to pH 4 (2M hydrochloric acid). The resultant emulsion was extracted with ether (2 × 30 ml.). The combined extracts were washed with water (3 × 20 ml.) and saturated brine (20 ml.), then dried ($MgSO_4$) and evaporated. The yellow oil obtained was purified by flash column chromatography, using 80:20:2 v/v toluene/ethyl acetate/acetic acid to give 5(Z)-7-(4'-phenyl-[cyclopentanespiro-2'-1,3-dioxan]-*cis*-5-yl)heptenoic acid (Example 25) as a colourless oil (400 mg.); NMR: 1.4—2.5 (17H, m), 3.7—4.2 (2H, m), 5.1 (1H, d, $J=2$ Hz), 5.2—5.5 (2H, m) and 7.1—7.5 (5H, m); m/e : 344 (M^+).

Using a similar procedure, but starting from the appropriate ketone, the following acids of formula Ib wherein benzene ring B is unsubstituted were obtained:—

Example 26

Ra + Rb = trimethylene; as an oil in 37% yield; NMR: 1.3—2.7 (15H, m), 3.7—4.1 (2H, m), 5.0 (1H, d, $J=2$ Hz), 5.1—5.5 (2H, m), 7.1—7.4 (5H, m) and 9.0 (1H, br s) ppm; m/e : 330 M^+ .

Example 27

Ra + Rb = hexamethylene; as an oil in 42% yield; NMR: 1.2—2.6 (21H, m), 3.6—4.2 (2H, m), 5.1—5.5 (3H, m) and 7.1—7.5 (5H, m) ppm; m/e : 372 M^+ .

Example 28

Ra=Rb=butyl; as an oil in 10% yield; NMR: 0.7—2.6 (27H, m), 3.7—4.2 (2H, m), 5.1—5.4 (3H, m) and 7.1—7.4 (5H, m) ppm.

Example 29

Ra=phenyl Rb=methyl; as an oil in 40% yield; NMR: 1.65 (3H, s), 7.0—7.6 (10H, m) and 7.7—8.7 (1H, br s) ppm; m/e: 380 (M⁺).

Examples 30—32

Using a similar procedure to that described in Example 8 but replacing phenylacetaldehyde dimethyl acetal by:—

(a) 1,1-dimethoxyheptane, there was obtained 5(Z)-7-[(2,4,5-*cis*)-2-hexyl-4-phenyl-1,3-dioxan-5-yl]-heptenoic acid (Example 30) as a solid, m.p. 60—62°C. in 74% yield; NMR: 0.9 (3H, t), 1.1—2.6 (17H, m), 3.7—4.2 (2H, m), 2.7 (1H, t, J=4.0 Hz), 4.9 (1H, d, J=3.0 Hz), 5.1—5.5 (2H, m) and 7.1—7.4 (5H, m) ppm; and

(b) 1,1-diethoxypropane, there was obtained 5(Z)-7-[(2,4,5-*cis*)-2-ethyl-4-phenyl-1,3-dioxan-5-yl]-heptenoic acid (Example 31) as an oil in 63% yield; NMR: 1.0 (3H, m), 1.3—2.6 (11H, m), 3.7—4.3 (2H, m), 4.7 (1H, t, J=5.0 Hz), 4.9 (1H, d, J=3.0 Hz), 5.1—5.5 (2H, m), 7.1—7.4 (5H, m) and 8.2 (1H, br s) ppm.

Similarly, by using the procedure of Example 8 with *erythro*-5(Z)-9-hydroxy-8-hydroxymethyl-9-(2-methylphenyl)nonenoic acid (A) and 3,3-dimethoxypentane, there was obtained 5(Z)-7-(2,2-diethyl-4-(2-methylphenyl)-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 32) as an oil in 65% yield; NMR: 0.7—1.3 (6H, m), 1.4—2.6 (13H, m), 2.13 (3H, s), 3.6—4.2 (2H, m), 4.9—5.4 (3H, m) and 7.0—7.6 (4H, m).

The necessary starting acid (A) was obtained as an oil in a similar manner to the 9-phenyl analogue described for Example 8, but starting from 5(Z)-7-[2,2-dimethyl-4-(2-methylphenyl)-1,3-dioxan-*cis*-5-yl]-heptenoic acid; NMR: 1.1—2.5 (9H, m), 2.3 (3H, s), 3.8 (2H, d, J=5.0 Hz), 4.6—5.6 (3H, m) and 7.0—7.7 (4H, m) ppm.

Example 33

5(Z)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (191 mg, 0.6 mM) was dissolved in dry toluene (10 ml.), and freshly-distilled benzaldehyde (212 mg., 1.2 mM) and *p*-toluenesulphonic acid (3 mg.) were added. The mixture was heated at 100°C., with stirring, while being protected from the atmosphere (drying tube), for 1—2 hours until thin layer chromatography (TLC) indicated completion of the reaction. The cooled reaction mixture was purified by flash column chromatography on silica (20 g.) eluting with 5% v/v methanol in methylene chloride. There was thus obtained 5(Z)-7-[(2,4,5-*cis*)-2,4-diphenyl-1,3-dioxan-5-yl]heptenoic acid as a viscous oil (254 mg.); NMR: 1.4—2.8 (9H, m), 4.1—4.3 (2H, m), 5.1—5.5 (3H, m), 5.75 (1H, s), 7.2—7.7 (10H, m) ppm; m/e: 366 (M⁺), 348 (M—H₂O), 279 [M—(CH₂)₃.CO₂H], 260 (M—PhCHO).

Examples 34—64

Using a similar procedure to that described in Example 33 but replacing benzaldehyde by the appropriate substituted aldehyde of the formula Ra.CHO, the following acids of formula Ib (benzene ring B is unsubstituted, Rb=H) were obtained in yields of 37—92% using either 10% v/v methanol in methylene chloride, 40% v/v acetone in methylene chloride, or 40:10:1 by (volume) toluene/ethyl acetate/acetic acid as the eluant for the flash chromatography.

Ex.	Ra.	Form	¹ H NMR (ppm)	Mass Spectrum (m/e M ⁺)
34	4Cl-Ph	oil	7.2—7.7 (9H, m) 5.70 (1H, s)	400, 402 (3:1)
35	4F-Ph	oil	6.95—7.65 (9H, m) 5.70 (1H, s)	384
36	2Cl-Ph	oil	7.8—8.0 (1H, m) 7.25—7.6 (8H, m) 6.17 (1H, s)	400, 402 (3:1)
37	3Cl-Ph (iii)	oil	7.0—7.6 (9H, m) 5.7 (1H, s)	400, 402 (3:1)
38	3Cl-Ph (iv)	oil	7.0—7.6 (9H, m) 5.7 (1H, s)	400, 402 (3:1)
39	3Cl-Ph (v)	oil	7.0—7.6 (9H, m) 5.7 (1H, s)	400—402 (3:1)
40	2Me-Ph	oil	7.7 (1H, dd; J10, 3) 7.0—7.5 (8H, m) 5.85 (1H, s) 2.5 (3H, s)	380
41	4Me-Ph	solid m.p. 93—95°C.	7.0—7.5 (9H, m) 5.65 (1H, s) 2.35 (3H, s)	380
42	4NO ₂ -Ph	oil	8.25 (2H, d; J8) 7.7 (2H, d; J8) 7.25 (5H, s) 5.75 (1H, s)	429*
43	4MeO-Ph	oil	7.6—8.2 (1H, CO ₂ H) 7.5 (2H, d; J8.5) 7.35 (5H, s) 6.9 (2H, d; J8.5) 5.6 (1H, s) 3.8 (3H, s)	396

Ex.	Ra.	Form	¹ H NMR (ppm)	Mass Spectrum (m/e M ⁺)
44	3Br-Ph	oil	7.15—8.2 (10H, m; aromatic + CO ₂ H) 5.65 (1H, s)	462, 464* (1:1)
45	1-naphth	oil	8.25 (1H, m) 8.0—7.7 (3H, m) 7.2—7.7 (9H, m; aromatic + CO ₂ H)	416
46	2-naphth	solid m.p.	7.0—8.0 (13H, m; aromatic + CO ₂ H)	416
47	3Me-Ph	oil	118—119°C. 5.85 (1H, s) 7.1—7.5 (10H, m; aromatic + CO ₂ H) 5.85 (1H, s)	380
48	3,4Cl ₂ -Ph	oil	7.1—8.5 (9H, m; aromatic + CO ₂ H) 5.65 (1H, s)	452, 454 456*
49	4CF ₃ -Ph	oil	7.75 (4H, S) 7.3 (5H, s) 5.8 (1H, s)	434
50	3-CF ₃ -Ph	oil	7.0—8.8 (10H, m; aromatic + CO ₂ H) 5.75 (1H, s)	452*
51	3MeO-Ph	oil	9.0—10.0 (1H; br CO ₂ H) 7.05—7.5 (8H, m) 6.85 (1H, dd; J8, 2) 5.7 (1H, s) 3.8 (3H, s)	396

Ex.	Ra.	Form	¹ H NMR (ppm)	Mass Spectrum (m/e M ⁺)
52	2F-Ph	oil	8.0—9.4 (1H, br CO ₂ H) 7.75 (1H, m) 6.95—7.5 (8H, m)	402*
53	2MeO-Ph	oil	6.05 (1H, s) 7.8 (1H, dd; J8, 2) 7.2—7.5 6H, m) 7.05 (1H, dt; J1.5, 8)	396
54	4Br-Ph	oil	6.9 (1H, dd; J1.5, 8) 6.07 (1H, s) 3.85 (3H, s) 7.5 (4H, m) 7.2 (5H, m) 5.7 (1H, s)	462, 464*
55	4CN-Ph	oil	8.0—9.2 (1H; br CO ₂ H) 7.7 (4H, m) 7.3 (5H, m) 5.75 (1H, s)	409*
56	3F-Ph	oil	8.0—9.0 (1H, br CO ₂ H) 6.8—7.4 (9H, m) 5.7 (1H, s)	384
57	2Cl ₃ -Ph	oil	7.3—8.7 (1H; br CO ₂ H) 8.1 (1H; d, J8) 7.2—7.8 (8H, m)	452*
58	4MeS-Ph	oil	6.05 (1H, s) 8.3—9.2 (1H, br CO ₂ H) 7.5 (d, J8) 7.35 (s) 7.25 (d, J8) } 9H 5.7 (1H, s) 2.5 (3H, s)	412

Ex.	Ra.	Form	¹ H NMR (ppm)	Mass Spectrum (m/e M ⁺)
59	3HO-Ph	oil	6.65—7.5 (9H, m) 6.0—6.65 (2H, br s)	382
60	4AcNH-Ph	solid m.p. 157—159°C.	8.9 (1H, br NH) 7.4—7.7 (4H, m) 7.1—7.4 (5H, m) 5.65 (1H, s) 2.1 (3H, s)	441*
61	F ₅ -Ph	oil	10.2—10.6 (1H, br CO ₂ H) 7.1—7.6 (5H, m)	456
62	3,4-OCH ₂ O-Ph	oil	6.1 (1H, s) 7.2—7.4 (5H, m) 7.1 (1H, br s) 7.05 (1H, dd; J8, 2) 6.8 (1H, dd; J8, 2) 5.95 (2H, s) 5.65 (1H, s)	410
63	2,4-Me ₂ Ph	oil	7.55 (1H, d, J8) 7.2—7.4 (5H, m) 7.05 (1H, dd, J8, 2) 7.0 (1H, br s) 5.8 (1H, s) 2.4 (3H, s) 2.3 (3H, s)	394
64	3,4-(CH ₂ -OCH ₂)-Ph	oil	7.1—7.6 (8H, m) 5.75 (1H, s) 5.2 (4H, s)	408

Notes:

(i) NMR: all proton NMR were determined in CDCl₃ at 90 MHz except Ex. 60 which was determined in d₆-acetone; signals are given in the Table for ring B protons and the fragment Ra.CH, but the spectra additionally contain signals at 1.4—2.8 (9H, m), 4.1—4.3 (2H, m) and 5.1—5.5 (3H, m) ppm; coupling constants (J) are given in Hz;

(ii) MS: all mass spectra contained additional characteristic signals corresponding to m/e = M—Ra.CHO; those marked with an asterisk (*) were determined by chemical ionisation

using ammonia and corresponding to $m/e = M + NH_4$ rather than $m/e = M$; relative strengths of isotopic values are given in parentheses;

(iii) racemic ($\pm$) form;

(iv) dextrorotatory (+) enantiomer; $[\alpha]_D^{20} = +88^\circ$ (c. 2.05, MeOH);

(v) laevorotatory (-) enantiomer; $[\alpha]_D^{20} = -92^\circ$ (c. 1.52, MeOH);

The aldehyde starting material for Example 64 was obtained as follows:—

To a solution of 1,3-dihydro(5-benzo[c]furyl)methanol (1.265 g.) in dry methylene chloride (10 ml.) was added pyridinium dichromate (3.23 g.) in one portion. The dark mixture was stirred for 90 minutes and diluted with ether (100 ml.). The suspension obtained was separated by filtration through diatomaceous earth. The residue was washed with ether (50 ml.) and the combined filtrate and washings evaporated. The residual oil was purified by flash column chromatography, eluting with 40% v/v ethyl acetate/hexane to give 1,3-dihydro(5-benzo[c]furyl)carboxaldehyde as a semi-solid mass (0.66 g.); NMR: 9.95 (1H, s); 7.7—7.8 (2H, m); 7.3 (1H, d, $J=8$ Hz) and 5.1 (4H, s) ppm.

Examples 65—69

Using a similar procedure to that described for Example 33 but starting from the appropriate aldehydes of formula $R_a.CHO$, the following acids of formula Ib were obtained in yields of 30—80%:—

Example 65

R_a =isopropyl, R_b =H, benzene ring B is unsubstituted; as an oil; NMR: 10.0 (1H, br s), 7.1—7.5 (5H, m), 5.0—5.6 (2H, m), 4.9 (1H, d, $J=1$ Hz), 4.5 (1H, d, $J=3$ Hz), 3.8—4.2 (2H, m), 1.3—2.7 (10H, m) and 1.05 (6H, d, $J=8$ Hz) ppm; m/e : 331 ($M^+ + H$); using isobutyraldehyde in place of benzaldehyde at room temperature for 3 days;

Example 66

R_a =pentyl, R_b =H, benzene ring B is unsubstituted; as an oil; NMR: 7.2—7.4 (5H, m), 5.2—5.5 (2H, m), 4.9 (1H, d, $J=2$ Hz), 4.7 (1H, t, $J=3$ Hz), 3.7—4.2 (2H, m) and 0.7—2.6 (20H, m) ppm; m/e : 359 ($M^+ + H$); using hexanal in place of benzaldehyde;

Example 67

R_a =octyl, R_b =H, benzene ring B is unsubstituted; as an oil; NMR: 7.1—7.4 (5H, m), 5.1—5.5 (2H, m), 4.9 (1H, d, $J=1$ Hz), 4.75 (1H, t, $J=3$ Hz), 3.7—4.2 (2H, m), 1.05—2.6 (23H, m) and 0.85 (3H, br t) ppm; m/e : 403 ($M^+ + H$); starting from 1-nonanal in place of benzaldehyde;

Example 68

R_a = 2-chlorophenyl, R_b =H, benzene ring B is 2-fluorophenyl; as an oil; NMR: 1.4—2.8 (9H, m), 4.1—4.3 (2H, m), 5.1—5.5 (3H, m), 6.05 (1H, s), 7.22 (7H, m) and 7.82 (1H, m) ppm; starting from 2-chlorobenzaldehyde and 5(Z)-7-[2,2-dimethyl-4-(2-fluorophenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid;

Example 69

R_a = 2-methylphenyl, R_b = H, benzene ring B is 2-methoxyphenyl; as an oil; NMR: 1.4—2.8 (9H, m), 2.44 (3H, s), 3.85 (3H, s), 4.0—4.3 (2H, m), 5.1—5.5 (3H, m), 5.87 (1H, s) and 7.28 (8H, m) ppm; starting from 2-methylbenzaldehyde and 5(Z)-7-[2,2-dimethyl-4-(2-methoxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid.

Example 70

Using a similar method to that described in Example 4, there was obtained 5(Z)-7-[2,2-diethyl-4-(2-fluorophenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid; NMR: 0.7—1.2 (6H, m), 1.3—2.6 (13H, m), 3.7—4.3 (2H, m), 5.1—5.5 (3H, m), 7.11 (3H, m) and 7.52 (1H, m) ppm; as an oil in 54% yield starting from [2,2-diethyl-4-(2-fluorophenyl)-1,3-dioxan-*cis*-5-yl]acetaldehyde, itself obtained in 64% yield as an oil with IR absorption at 1720 cm^{-1} by oxidation of (4,5-*cis*)-5-allyl-2,2-diethyl-4-(2-fluorophenyl)-1,3-dioxane. The latter compound showed significant NMR aromatic proton signals at 7.15 (3H, m) and 7.58 (1H, m) ppm and was obtained in 23% yield from *erythro*-2-allyl-1-(2-fluorophenyl)-1,3-propanediol using an analogous procedure to that described for the corresponding starting material in Example 4, but starting from (4,5-*cis*)-5-allyl-2,2-diethyl-4-(2-fluorophenyl)-1,3-dioxane.

Example 71

In a similar manner to example 1, but starting from [2,2-bis(trifluoromethyl)-4-phenyl-1,3-dioxan-*cis*-5-yl]acetaldehyde, there was obtained 5(Z)-7-[2,2-bis(trifluoromethyl)-4-phenyl-1,3-dioxan-*cis*-5-yl]heptenoic acid as a colourless oil in 65% yield; NMR: 1.3—2.6 (9H, m), 4.0—4.5 (2H, m), 4.9—5.6 (3H, m) and 7.1—7.5 (5H, m) ppm; m/e : 426 (M^+).

The starting material was obtained as follows:—

(a) A solution of *p*-toluenesulphonyl chloride (15.8 g.) in methylene chloride (50 ml.) was added over an

hour to a stirred solution of crude *erythro*-2-allyl-1-phenyl-1,3-propanediol (15.4 g.) in methylene chloride (150 ml.) containing triethylamine (12.0 ml.) and kept at 4°C. The mixture was stirred a further 1 hour at 4°C. and then for 64 hours at room temperature before being diluted with ether (500 ml.). The subsequent mixture was washed successively with water (100 ml.) 5% w/v sodium hydrogen carbonate solution (100 ml.), water (2 × 100 ml.) and saturated brine solution (100 ml.), then dried (MgSO₄) and concentrated to give an oil which on column chromatography, eluting with 10% v/v ethyl acetate/hexane, gave 3-*(erythro*-2-allyl-1-phenyl-1,3-propanediol) *p*-toluenesulphonate ester (X), as a colourless oil in 69% yield; NMR: 1.8—2.3 (4H, m), 2.4 (3H, s), 3.7—4.2 (2H, m), 4.7—5.0 (3H, m), 5.35—5.8 (1H, m), 7.2—7.4 (7H, m) and 7.75 (2H, d, J=8Hz) ppm.

(b) A solution of the ester (X) (3.46 g.) in dry ether (10 ml.) containing anhydrous *p*-toluenesulphonic acid (5 mg.) was added over 10 minutes to a stirred solution of hexafluoroacetone (prepared from 3.0 ml. of the sesquihydrate) at -70°C. The mixture was stirred for 2½ hours at -70°C. and then allowed to warm to room temperature with stirring for 16 hours. The solvent was evaporated and the residual oil dissolved in anhydrous ether (50 ml.) and sodium hydride (0.36 g.) was added in portions. The stirred mixture was heated under reflux for 1 hour, cooled, and treated with ethanol (2 ml.) and ether (50 ml.). This mixture was washed with water (4 × 15 ml.), dried (MgSO₄) and evaporated. The residual oil gave, on column chromatography eluting with 1.5% v/v ethyl acetate/hexane, (4,5-*cis*)-5-allyl-2,2-bis(trifluoromethyl)-4-phenyl-1,3-dioxane (Y) as a crystalline solid (61%); m.p. 34—35°C. NMR: 1.6—2.5 (3H, m), 4.1—4.5 (2H, m), 4.8—5.7 (4H, m) and 7.1—7.4 (5H, m) ppm; m/e: 340 (M⁺).

(c) Ozone was passed through a solution of the dioxane (Y) (1.70 g.) in ethyl acetate (100 ml.) at -78°C. until a permanent blue colour developed. The solution was then flushed with argon until colourless. A solution of triphenylphosphine (1.97 g.) in ethyl acetate (20 ml.) was then added and the mixture was stirred for 1 hour at -78°C. and the overnight at 4°C. This mixture was evaporated and the residue was purified by column chromatography, eluting with 15% v/v ethyl acetate/hexane to give [2,2-bis(trifluoromethyl)-4-phenyl-1,3-dioxan-*cis*-5-yl]acetaldehyde as a crystalline solid, m.p. 52.5—53.5°C. in 93% yield; NMR: 2.15—3.1 (3H, m), 4.0—4.7 (2H, m), 5.55 (1H, br s), 7.15—7.55 (5H, m) and 9.55 (1H, s) ppm; m/e: 342 (M⁺).

Examples 72—73.

In a similar manner to that described in Example 71, there were prepared:—

5(Z)-7-[(2,4,5-*cis*)-2-trifluoromethyl-4-phenyl-1,3-dioxane-5-yl]heptenoic acid (Example 72) as a crystalline solid, m.p. 87.5—88.5°C., in 76% yield; NMR: 1.2—2.7 (9H, m), 3.8—4.3 (2H, m), 4.95—5.6 (4H, m), 7.1—7.4 (5H, m) and 9.25 (1H, br s) ppm; m/e: 357 (M⁺-H); and

5(Z)-7-[(2,4-*trans*,4,5-*cis*)-2-trifluoromethyl-4-phenyl-1,3-dioxane-5-yl]heptenoic acid (Example 73) as a crystalline solid, m.p. 62—64°C., in 96% yield; NMR: 1.5—2.6 (9H, m), 3.85—4.5 (2H, m), 5.05—5.6 (4H, m), 7.1—7.5 (5H, m) and 9.85 (1H, br s) ppm; m/e: 358 (M⁺).

The following intermediates were obtained:—

(i) [2,4,5-*cis*]-2-trifluoromethyl-4-phenyl-1,3-dioxan-5-yl]acetaldehyde as an oil in 96% yield; NMR: 2.15—3.2 (3H, m), 4.0—4.2 (2H, m), 5.0—5.2 (2H, m), 7.15—7.5 (5H, m) and 9.6 (1H, s) ppm; m/e: 274 (M⁺); and

(ii) [(2,4-*trans*,4,5-*cis*)-2-trifluoromethyl-4-phenyl-1,3-dioxan-5-yl]acetaldehyde as a crystalline solid, m.p. 62—63°C., in 92% yield; NMR: 2.2—3.05 (3H, m), 3.8—4.65 (2H, m), 5.1—5.55 (2H, m), 7.15—7.5 (5H, m) and 9.6 (1H, s) ppm.

These aldehydes were obtained by oxidation of the corresponding 5-allyl-1,3-dioxanes as described for example 71. These dioxanes were obtained together by substituting trifluoroacetaldehyde for hexafluoroacetone in procedure (b) of Example 71, followed by chromatographic separation on silica using 2% v/v ethyl acetate/hexane as eluant, resulting in the isolation of:—

(iii) [2,4,5-*cis*]-5-allyl-2-trifluoromethyl-4-phenyl-1,3-dioxane in 49% yield as a crystalline solid, m.p. 60—61°C.; NMR: 1.6—1.95 (2H, m), 2.1—2.6 (1H, m), 3.9—4.4 (2H, m), 4.8—5.15 (4H, m), 5.3—5.8 (1H, m) and 7.2—7.4 (5H, m) ppm; m/e: 272 (M⁺); and

(iv) [2,4-*trans*,4,5-*cis*]-5-allyl-2-trifluoromethyl-4-phenyl-1,3-dioxane in 15% yield as a crystalline solid m.p. 78—79°C.; NMR: 1.65—2.45 (3H, m), 3.9—4.5 (2H, m), 4.8—5.8 (5H, m) and 7.25—7.45 (5H, m) ppm; m/e 272 (M⁺).

Example 74

To a solution of methyl 5(Z)-7-[(2,4,5-*cis*)-2-chloromethyl-4-phenyl-1,3-dioxan-5-yl]heptenoate (300 mg.) in methanol (10 ml.) was added aqueous potassium hydroxide (2M, 2.6 ml.). The mixture was stirred for 4½ hours and diluted with water (50 ml.), then extracted with ether (2 × 20 ml.) and the extracts discarded. The aqueous layer was acidified to pH 5 (2M hydrochloric acid) and extracted with ether (3 × 20 ml.). The extracts were dried (MgSO₄) and evaporated to give an oil which on column chromatography, eluting with 85:12:2 (by volume) toluene/ethyl acetate/acetic acid gave 5(Z)-7-[(2,4,5-*cis*)-2-chloromethyl-4-phenyl-1,3-dioxan-5-yl]heptenoic acid in 92% yield as a crystalline solid; m.p. 58—61°C.; NMR: 1.4—2.7 (9H, m), 3.65 (2H, d, J=4 Hz), 3.85—4.3 (2H, m), 4.85—5.55 (4H, m), 7.2—7.4 (5H, m) and 8.4 (1H, br s) ppm.

26

Example 75

A solution containing methyl 5(Z)-*erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonenoate (584 mg.), *p*-toluenesulphonic acid (10 mg.) and 2-chloro-1,1-dimethoxyethane (2 ml.) was heated at 100°C. for 18 hours. The cooled reaction mixture was diluted with ether (80 ml.) and successively washed with 5% w/w sodium hydrogen carbonate solution (2 × 10 ml.), water (3 × 10 ml.) and saturated sodium chloride solution (1 × 10 ml.), then dried (MgSO₄) and evaporated to give an oil, which on column chromatography, using 2% v/v ethyl acetate/toluene as eluant, gave methyl 5(Z)-7-([2,4,5-*cis*]-2-chloromethyl-4-phenyl-1,3-dioxan-5-yl)heptenoate as a colourless oil in 52% yield; NMR: 1.4—2.65 (9H, m), 3.6—3.8 (5H, m), 3.8—4.25 (2H, m), 4.85—5.55 (4H, m) and 7.2—7.45 (5H, m) ppm; m/e: 351 (M⁺—H).

The starting material was obtained as follows:—

An ethereal solution of diazomethane was added to a solution of 5(Z)-*erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (3.99 g.) in dry ether (50 ml.) at 4°C., until a yellow colour persisted in the mixture. A few drops of acetic acid were then added until effervescence had ceased. The mixture was evaporated to give an oil which on column chromatography using 70:30:2 (by volume) toluene/ethyl acetate/acetic acid as eluant, gave methyl 5(Z)-*erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonenoate as a colourless oil in 81% yield; NMR: 1.4—2.4 (9H, m), 2.6—3.1 (2H, br s), 3.55—3.8 (5H, m), 4.9—5.55 (3H, m) and 7.15—7.45 (5H, m) ppm.

Examples 76—79

Using a similar procedure to that described in Example 74, the following compounds were obtained by hydrolysis of the corresponding methyl esters:—

Example 76

5(Z)-7-([2,4,5-*cis*]-2-chloroethyl-4-phenyl-1,3-dioxan-5-yl)heptenoic acid as a crystalline solid, m.p. 54—54.5°C. in 92% yield; NMR: 1.4—2.6 (11H, m), 3.75 (2H, t, J=7Hz), 3.8—4.2 (2H, m), 4.9—5.55 (4H, m), 7.2—7.4 (5H, m) and 9.8 (1H, br s) ppm;

Example 77

5(Z)-7-(4'-phenyl-[4-methylcyclohexanespiro-2'-1,3-dioxan]-*cis*-5'-yl)heptenoic acid (isomer A*) as a colourless oil in 81% yield; NMR: 0.7—2.9 (21H, m), 3.6—4.2 (2H, m), 4.9—5.6 (3H, m) and 7.1—7.5 (5H, m) ppm; m/e: 372 (M⁺); and

Example 78

5(Z)-7-(4'-phenyl-[4-methylcyclohexanespiro-2'-1,3-dioxan]-*cis*-5'-yl)heptenoic acid (isomer B*) as a colourless oil in 53% yield; NMR: 0.7—2.9 (21H, m), 3.6—4.4 (2H, m), 5.0—5.5 (3H, m) and 7.1—7.5 (5H, m) ppm; m/e: 372 (M⁺); [*Isomers A and B were obtained, respectively, by hydrolysis of the less polar and more polar isomers of methyl 5(Z)-7-(4'-phenyl-[4-methylcyclohexanespiro-2'-1,3-dioxan]-*cis*-5'-yl)-heptenoate, as seen on TLC analysis on 10% v/v ethyl acetate/hexane.]

Example 79

5(Z)-7-([2,4,5-*cis*]-2-vinyl-4-phenyl-1,3-dioxan-5-yl)heptenoic acid as a solid, m.p. 40—43°C., in 80% yield; NMR: 1.4—2.7 (9H, m), 3.8—4.3 (2H, m), 5.05 (1H, d, J=3Hz), 5.1—5.55 (4H, m), 5.6—5.7 (1H, m), 5.8—6.3 (1H, m), 7.2—7.4 (5H, m) and 7.7 (1H, br s) ppm; m/e: 316 (M⁺).

Examples 80—82

Using a similar procedure to that described in Example 75, the following esters were obtained from methyl 5(Z)-*erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonenoate:—

Example 80

methyl 5(Z)-7-([2,4,5-*cis*]-2-chloroethyl-4-phenyl-1,3-dioxan-5-yl)heptenoate as a colourless oil in 63% yield; NMR: 1.4—2.6 (11H, m), 3.55—4.3 (7H, m), 4.85—5.5 (4H, m) and 7.15—7.45 (5H, m) ppm; by replacing 2-chloro-1,1-dimethoxyethane with 3-chloro-1,1-dimethoxypropane, carrying out the reaction at room temperature for 16 hours, and purification by column chromatography on silica using 10% v/v ethyl acetate/hexane as eluant;

Example 81

methyl 5(Z)-7-(4'-phenyl-[4-methylcyclohexanespiro-2'-1,3-dioxan]-*cis*-5'-yl)heptenoate (less polar isomer on TLC: SiO₂, 10% v/v ethyl acetate/hexane), as a colourless oil in 38% yield; NMR: 0.9 (3H, d), 1.0—2.7 (18H, m), 3.6 (3H, s), 3.8 (1H, m), 4.05 (1H, m), 5.1—5.4 (3H, m) and 7.1—7.4 (5H, m) ppm;

Example 82

methyl 5(Z)-7-(4'-phenyl-[4-methylcyclohexanespiro-2'-1,3-dioxan]-*cis*-5'-yl)heptenoate (more polar isomer on TLC: SiO₂, 10% v/v ethyl acetate/hexane) as a colourless oil in 28% yield; NMR: 0.9 (3H, d), 1.0—2.7 (18H, m), 3.6 (3H, s), 3.7 (1H, d), 4.2 (1H, d), 5.15 (1H, d), 5.2 (1H, m), 5.3 (1H, m) and 7.2—7.4 (5H, m) ppm;

[Both Example 81 and 82 were obtained in the same reaction by replacing 2-chloro-1,1-dimethoxyethane with 4-methylcyclohexanone (0.27 ml.) and trimethyl orthoformate (0.29 ml.), carrying out the reaction at room temperature for 2 hours, and purifying the crude product by column chromatography using 10% v/v ethylacetate/hexane as eluant.].

Example 83

A solution containing 5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoate (222 mg.), *p*-toluenesulphonic acid (5 mg.) and 3,3-dimethoxy-1-propene (0.2 ml.) in toluene (1 ml.) was stirred for 3 hours. Water (20 ml.) was added and the mixture was extracted with ether (3 x 10 ml.). The combined organic extracts were washed successively with water (2 x 10 ml.) and saturated brine solution (1 x 50 ml.), dried (MgSO₄) and evaporated to give an oil which on column chromatography, using 20% v/v ethyl acetate/hexane as eluant, gave methyl 5(Z)-7-[(2,4,5-*cis*)-2-vinyl phenyl-1,3-dioxan-5-yl]heptenoate as a colourless oil in 48% yield, essentially pure by TLC analysis.

Example 84

A solution containing 5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-(2-methylphenyl)nonenoic acid (2.75 g.) and powdered potassium hydroxide (4.19 g) in dimethyl sulphoxide (23 ml.) was treated with dibromomethane (3.26 g.) with stirring under argon. Stirring was continued overnight. The mixture was then poured into ice-water (70 ml.), acidified to pH 5 (2M hydrochloric acid), and extracted with ethyl acetate (3 x 50 ml.). The combined extracts were washed with water and saturated brine, dried (MgSO₄) and evaporated to give an oil (2.8 g.) which was purified by column chromatography using 80:20:2 by (volume) toluene/ethyl acetate/acetic acid to give 5(Z)-4-[2-methylphenyl]-1,3-dioxan-*cis*-5-yl]heptenoic acid (1.0 g.) as an oil which solidified on standing to give a crystalline solid, m.p. 83–86°C.; NMR: 7.1–7.5 (4H, m), 4.9–5.4 (5H, m), 3.8–4.1 (2H, m), 1.5–2.65 (9H, m) and 2.25 (3H, s) ppm.

Example 85

A solution containing sodium ethoxide (from sodium metal, 0.095 g.) in ethanol (20 ml.) was treated with a solution of 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (0.12 g.) in ethanol (20 ml.) and the mixture was stirred for 2 hours. The solvent was evaporated to leave a white powder which on crystallisation from dichloromethane/hexane gave sodium 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoate as white crystals, m.p. 160–169°C. (decomposition); microanalysis found: C, 66.1; H, 7.5%; Calculated (C₁₉H₂₅O₄Na + ½ H₂O): C, 66.2; H, 7.4%.

Examples 86–92

A solution containing 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (318 mg.), 4-dimethylaminopyridine (122 mg.) and methanesulphonamide (95 mg.) in dry dichloromethane (20 ml.) was treated with a solution of dicyclohexylcarbodiimide (206 mg.) in dichloromethane (2 ml.). The mixture was stirred overnight, filtered, and the filtrate was evaporated. The residual oil was partitioned between saturated aqueous sodium carbonate solution (50 ml.) and ether (50 ml.), and the aqueous phase was washed with more ether (2 x 25 ml.). The aqueous phase was acidified with hydrochloric acid (2M) and extracted with ethyl acetate (3 x 25 ml.). The combined extracts were washed with saturated brine, dried (MgSO₄) and evaporated to give an oil which on column chromatography, eluting with toluene/ethyl acetate/acetic acid (80:20:2 v/v) gave N-methanesulphonyl-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenamide, as a colourless oil (100 mg.); NMR: 1.2–2.5 (9H, m), 1.55 (6H, s), 3.25 (3H, s), 3.7–4.3 (2H, m), 5.1–5.5 (3H, m), 7.1–7.4 (5H, br. s) and 8.4 (1H, br. s) ppm.

Using a similar procedure the following N-alkanesulphonyl-heptenamides may be obtained starting from the appropriate heptenoic acid of formula Ib:—

Example 87

N-methanesulphonyl-5(Z)-7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenamide, as a solid, m.p. 85–87°C. in 71% yield; NMR: 1.2–2.5 (9H, m), 3.25 (3H, s), 3.7–4.3 (2H, m), 4.8–5.5 (5H, m), 7.1–7.4 (5H, br s) and 8.4 (1H, br s) ppm; m/e: 368 (M⁺ + H);

Example 88

N-methanesulphonyl-5(Z)-7-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenamide, as an oil in 70% yield; NMR: 0.7–1.3 (6H, m), 1.2–2.5 (13H, m), 3.25 (3H, s), 3.7–4.3 (2H, m), 5.1–5.5 (3H, m), 7.1–7.4 (5H, br s) and 8.5 (1H, br s) ppm; m/e: 424 (M⁺ + H);

Example 89

N-ethanesulphonyl-5(Z)-7-[4-(2-fluorophenyl)-2,2-dimethyl-1,3-dioxan-*cis*-5-yl]heptenamide, as an oil in 77% yield; NMR: 1.35 (3H, t), 2.15 (15H, m), 3.45 (2H, q), 4.03 (2H, m), 5.34 (3H, m), 7.12 (4H, m) and 7.50 (1H, m) ppm; m/e: 428 (M⁺ + H);

Example 90

N-ethanesulphonyl-5(Z)-7-[4-(2-ethylphenyl)-2,2-dimethyl-1,3-dioxan-*cis*-5-yl]heptenamide, as an oil

in 74% yield; NMR: 1.32 (6H, m), 1.64 (8H, m), 2.33 (9H, m), 3.46 (2H, q), 4.07 (2H, m), 5.30 (3H, m), 7.23 (4H, m) and 7.50 (1H, m) ppm; m/e: 438 ($M^+ + H$);

Example 91

N-methanesulphonyl-5(Z)-7-[4-(2-ethylphenyl)-2,2-dimethyl-1,3-dioxan-*cis*-5-yl]heptenamide, as an oil in 81% yield; NMR: 1.13 (3H, t), 2.05 (17H, m), 3.16 (1H, s), 3.83 (2H, m), 5.15 (3H, m), 7.1 (4H, m) and 7.37 (1H, m) ppm; m/e: 424 ($M^+ + H$);

Example 92

N-(1-methylethanesulphonyl)-5(Z)-[4-(2-ethylphenyl)-2,2-dimethyl-1,3-dioxan-*cis*-5-yl]heptenamide, as an oil in 73% yield; NMR: 1.4 (15H, m), 2.27 (11H, m), 3.83 (3H, m), 5.18 (3H, m), 7.10 (4H, m) and 7.46 (1H, m) ppm; m/e: 452 ($M^+ + H$).

Example 93

A solution containing *erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonanoic acid (250 mg.), 2,2-dimethoxypropane (93 mg.) and *p*-toluenesulphonic acid (3 mg) in dry THF (10 ml.) was stirred for 30 minutes and then allowed to stand overnight. Triethylamine (2 drops) was added and the mixture was partitioned between ether (50 ml.) and water (50 ml.). The organic layer was washed with saturated brine (20 ml.), dried ($MgSO_4$) and evaporated to give an oil. Column chromatography, eluting with 80:20:2 (by volume) toluene/ethyl acetate/acetic acid gave 7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptanoic acid (180 mg.) as a colourless oil; NMR: 1.55 (6H, d), 0.9—2.4 (13H, m), 3.7—4.3 (2H, m), 5.15 (1H, br s) and 7.3 (5H, br s) ppm.

The starting material was obtained as follows:

Hydrogenation of a solution of 5(Z)-*erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (320 mg.) in ethyl acetate (20 ml.) using Adam's catalyst (30 mg.) for 2 hours at atmospheric pressure, followed by filtration and evaporation gave *erythro*-9-hydroxy-8-hydroxymethyl-9-phenylnonanoic acid (317 mg.) as an oil, which was essentially pure by TLC analysis and was used without characterisation.

Example 94

A portion (2.1 ml.) of a 0.5 M solution of sodium thioethoxide in N,N-dimethylformamide was added under nitrogen to 5(Z)-7-[2,2-dimethyl-4-(2-methoxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid (104 mg.). The mixture was heated under reflux for 1.1 hours and then diluted with ice-water to a total volume of 25 ml. The aqueous mixture was acidified to pH 4 with acetic acid and extracted with ethyl acetate (2 × 15 ml.). The extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated. The oil obtained was purified by column chromatography on silica (12 g.) eluting with 80:20:3 (by volume) toluene/ethyl acetate/acetic acid to give 5(Z)-7-[2,2-dimethyl-4-(2-hydroxyphenyl)-1,3-dioxan-*cis*-5-yl]heptenoic acid as an oil (25 mg.); NMR: 1.50 (6H, s), 2.22 (9H, m), 3.97 (2H, m), 5.31 (3H, m), 6.98 (4H, m) and 8.38 (2H, s) ppm.

Example 95

Potassium *t*-butoxide (7.4 g.) was added to a stirred mixture of (4-carboxybutyl)triphenyl phosphonium bromide (14.7 g.) and THF (170 ml.) at 0—5°C. under nitrogen. This mixture was added dropwise during 10 minutes to a stirred solution of (2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (3.1 g.) in THF (50 ml.) at 0—5°C. The mixture was stirred for 18 hours, poured onto ice (400 g.) and the solvent evaporated. The aqueous residue was washed with ethyl acetate and insoluble material removed by filtration through diatomaceous earth. The filtrate was cooled to 0°C. and acidified to pH 4 by addition of a saturated solution of sodium hydrogen tartrate (160 ml.). The resultant emulsion was extracted with a 1:1 v/v mixture of ether and pentane.

The combined extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated to give an oil which was purified by chromatography using a 3:1 v/v mixture of hexane and ether as eluant to give 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as an oily solid (2.6 g.) mp. 79—85°C., which was crystallised from hexane (3 times) to give material of m.p. 86—86.5°C.; 1H -NMR: 1.55 (6H, s), 1.4—2.7 (9H, m), 3.80 (1H, dd), 4.15 (1H, br d), 5.0—5.5 (3H, m), 7.30 (5H, s) and 11.0 (1H, br s) ppm; and ^{13}C -NMR ($CDCl_3$, 22.5 MHz): 19.02 (axial CH_3), 21.67 ($C7^*$, *cis*), 24.49 ($C3^*$), 26.28 ($C4^*$, *cis*), 29.64 (equatorial CH_3), 33.37 ($C2^*$), 39.66 (dioxan- $C5$), 62.52 (dioxan- $C6$), 73.08 (dioxan- $C4$), 76.93 ($CDCl_3$), 98.98 (dioxan- $C2$), 125.31 (phenyl- $C2$), 126.72 (phenyl- $C4$), 127.96 (phenyl- $C3$), 128.99 ($C6^*$), 130.18 ($C5^*$), 140.80 (phenyl- $C1$) and 179.05 (Cl^* , CO_2H) ppm (relative to TMS). [* refer to heptenoic acid carbon atoms]; i.e. essentially free from 5(E) isomer.

The starting aldehyde was obtained as follows:—

A solution of osmium tetroxide (47 mg.) in water (6.0 ml.) was added to a stirred solution of (4,5-*cis*)-5-allyl-4-phenyl-1,3-dioxane (3.6 g.) in THF (160 ml.). When the solution had become brown (5 minutes), it was treated dropwise during 30 minutes with a solution of sodium periodate (13.7 g.) in water (90 ml.). The mixture was further stirred for 2 hours and the solid removed by filtration. The filter cake was washed first with THF (15 ml.) and then with hexane (200 ml.). The aqueous phase of the filtrate was washed with hexane and the hexane washings combined with the organic phase of the filtrate. The solution obtained

was concentrated *in vacuo* to low volume and the residual material diluted with further hexane. The solution obtained was washed with 10% w/v sodium sulphide solution, then with saturated brine and then dried (Na_2SO_4) and evaporated. The residual oil was purified by column chromatography using 1:1 v/v hexane and ether as eluant. There was thus obtained (2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a solid, m.p. 69–70°C. (after recrystallisation from hexane); NMR: 1.56 (6H, s), 2.09–2.45 (2H, m), 2.87 (1H, m), 3.80 (1H, dd), 4.33 (1H, dt), 5.24 (1H, d), 7.33 (5H, s) and 9.59 (1H, s) ppm.

Examples 96–97

Using a similar procedure to that described in Example 95, but starting from (+)-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde, there was obtained (+)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 96) as a syrup in 62% yield, $[\alpha]_D^{20} +99.5^\circ$ (c, 4.00, MeOH), having an identical NMR spectrum to that described for the racemic form in Example 95, and containing approximately 4% of the 5(E) isomer as judged by ^{13}C -NMR spectroscopy.

Similarly, (–)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 97) was obtained as a syrup in 65% yield, $[\alpha]_D^{20} -101^\circ$ (c, 4.24, MeOH), having an identical NMR spectrum to that described for the racemic form in Example 95, and containing about 5% of the 5(E) isomer by ^{13}C -NMR spectroscopy starting from (–)-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde.

The starting enantiomeric aldehydes were obtained as follows:—

(i) A solution of recrystallised (±)-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (14.0 g., m.p. 69–70°C.) and (–)-ephedrine (9.9 g.) in benzene (200 ml.) was heated under reflux for 2.5 hours using a Dean and Stark apparatus for azeotropic removal of water. The solution was then evaporated and the residual oil triturated with hexane to give solid which was recrystallised from hexane and petroleum ether (b.p. 30–40°C.) to give (–)-[2,4,5-*cis*]-3,4-dimethyl-2-[(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)methyl]-5-phenyloxazolidine (A) as a crystalline solid (5.9 g.), m.p. 104–105°C., $[\alpha]_D^{20} -46^\circ$ (c, 4.23, acetone); microanalysis, found: C, 75.5; H, 8.3; N, 3.7%; $\text{C}_{24}\text{H}_{31}\text{NO}_3$ requires: C, 75.5; H, 8.2; N, 3.7%; m/e: 382 ($\text{M}^+ + \text{H}$).

(ii) A solution of anhydrous (+)-tartaric acid (2.98 g.) in acetone (299 ml.) containing 1% v/v of water was added to a solution of the (–)-enantiomer (A, above) (7.6 g.) in acetone (50 ml.). The mixture was stirred for 18 hours and the precipitate of ephedrine tartrate separated by filtration. The residue was washed with acetone and the combined washings and filtrate were evaporated. This residue was partitioned between ether and water. The ethereal phase was dried (Na_2SO_4) and evaporated. The resultant oil was purified by column chromatography using 3:1 v/v hexane and ether as eluant. There was thus obtained (–)-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a syrup (4.3 g.), $[\alpha]_D^{20} -58^\circ$ (c, 4.20, MeOH), having an NMR spectrum identical with that described for the racemic aldehyde in Example 95.

(iii) Using a similar procedure to (i) above but using (+)-ephedrine and starting from 12.9 g. of the racemic aldehyde, there was obtained (+)-[2,4,5-*cis*]-3,4-dimethyl-2-[(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)methyl]-5-phenyloxazolidine (B) as a crystalline solid (4.5 g.) m.p. 104–105°C., $[\alpha]_D^{20} +46^\circ$ (c, 4.02, acetone); microanalysis, found: C, 75.9; H, 8.0; N, 3.8%; $\text{C}_{24}\text{H}_{31}\text{NO}_3$ requires: C, 75.5; H, 8.2; N, 3.7%; m/e: 382 ($\text{M}^+ + \text{H}$).

(iv) Using a similar procedure to (ii) above but using (+)-tartaric acid and the (+)-enantiomer (B, above) (7.9 g.), there was obtained (+)-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde as a syrup (4.4 g.), $[\alpha]_D^{20} +57^\circ$ (c, 4.20, MeOH), having an NMR spectrum identical with that described for the racemic aldehyde in Example 95.

Examples 98–99

A solution of (±)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (6.0 g., m.p. 84–84.5°C.) and (–)- α -methylbenzylamine (1.14 g.) in ether (100 ml.) was seeded with crystals of salt X (see below). The crystals which separated were collected by filtration and the mother liquor (A) retained.

The crystals, $[\alpha]_D^{21} +45^\circ$ (c, 3.08, MeOH) were recrystallised by dissolution in the minimum volume of boiling methanol followed by addition of ether (30 ml./g. of crystals). After four recrystallisations pure salt X was obtained as needles (B) (1.6 g.) of constant specific rotation $[\alpha]_D^{20} +68.8^\circ$ (c, 3.14, MeOH) and m.p. 123–128°C. The recrystallisation mother liquors gave further crops of salt X of varying purity $[\alpha]_D^{20} +44$ to $+68^\circ$ and mother liquors (C).

The combined mother liquors (A) and (C) were evaporated. The residue was dissolved in the minimum volume of cold methanol. The solution obtained was diluted with ether, washed three times with McIlvaine buffer of pH 4.0, five times with water, dried (Na_2SO_4) and evaporated. The residual oily solid [4.0 g., $[\alpha]_D^{20} -29.9^\circ$ (c, 3.60, MeOH)] was dissolved in ether (100 ml.) containing [+-]- α -methylbenzylamine (1.0 g.). The solution was seeded with salt Y (see below). The crystals [3.2 g., $[\alpha]_D^{21} -55.3^\circ$ (c, 3.05, MeOH)], which separated were recrystallised four times as described for salt X above to give pure salt Y as needles (D) (1.72 g.) of constant specific rotation $[\alpha]_D^{20} -68.7^\circ$ (c, 3.10, MeOH) and m.p. 123–128°C.

Needles D (1.7 g., salt Y) were dissolved in the minimum volume of methanol and the solution diluted with ether. The solution was then washed three times with McIlvaine buffer of pH 4.0, five times with water, dried (Na_2SO_4) and evaporated. A solution of the residue in pentane (15 ml.) was then percolated through silica (0.6 g.). The filtrate and washings were combined and evaporated to give (–)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 98) as a syrup (1.02 g.), $[\alpha]_D^{20} -105^\circ$ (c, 3.99, MeOH),

having an identical NMR spectrum with that of the racemic acid described in Example 95.

Similar treatment of needles B (1.6 g., salt X) yielded (+)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 99) as a syrup (0.95 g), $[\alpha]_D^{20} +106^\circ$ (c, 4.1, MeOH), having an identical NMR spectrum to that of the racemic acid described in Example 95.

5 The starting seed crystals were obtained as follows:—

A solution the (+)-acid (Example 96) (163 mg.) and (–)- α -methylbenzylamine (62 mg.) in ether (2 ml.) deposited the corresponding salt X as prisms (201 mg.), m.p. 123–128°C. (indefinite), $[\alpha]_D^{20} +67.8^\circ$ (c, 3.17, MeOH).

10 Similarly, a solution of the (–)-acid (Example 97) (187 mg.) and (+)- α -methylbenzylamine (71 mg.) in ether (2 ml.) deposited the corresponding salt Y as prisms (221 mg.), m.p. 123–128°C. (indefinite), $[\alpha]_D^{20} -67.9^\circ$ (c, 2.78, MeOH).

Examples 100–101

15 A mixture of (–)-5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (1.2 g.), 3,3-diethoxypentane (5 ml.), and p-toluenesulphonic acid monohydrate (one crystal) was stirred for 18 hours. The mixture was diluted with ether, treated with triethylamine (2 drops) and evaporated *in vacuo*. An ethereal solution of the residue was washed three times with water, dried (Na_2SO_4) and evaporated to give an oil (1.4 g.). This was chromatographed on silica. Elution of the column with mixtures of hexane and ether (10:1 to 3:1) yields (–)-5(Z)-7-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 100) as an oil (0.68 g.), $[\alpha]_D^{20} -82.5^\circ$ (c, 4.22, MeOH) (containing 2.8% of the corresponding 5(E) isomer by ^{13}C NMR spectroscopy); ^1H -NMR: 0.86 (3H, s), 1.08 (3H, s), 1.45–1.95 (10H, m), 2.23 (2H, t), 2.45 (1H, m), 3.80 (1H, dd), 4.13 (1H, br d), 5.10 (1H, d), 5.02–5.52 (2H, m), 7.32 (5H, s) and 10.05 (1H, br s) ppm.

20 Using a similar procedure starting from (+)-5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid (0.6 g.) there was obtained (+)-5(Z)-7-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (Example 101) as an oil (0.4 g.), $[\alpha]_D^{20} +82.7^\circ$ (c, 4.26, MeOH) (containing less than 3% of the corresponding 5(E) isomer by ^{13}C -NMR spectroscopy) and having an essentially identical ^1H -NMR spectrum to that of Example 100 above.

The necessary starting materials were obtained as follows:—

30 (i) A solution of (–)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (1.45 g.) in a mixture of THF (45 ml.) and 1 M hydrochloric acid (1.1 ml.) was left at ambient temperature for 18 hours and then evaporated. An ethereal solution of the residue was washed repeatedly with water until no ionic chloride was present in the washings, dried (Na_2SO_4) and evaporated to give (–)-5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid as a syrup (1.23 g.) $[\alpha]_D^{20} -32^\circ$ (c, 2.14, methanol). ^1H -NMR: 1.4–2.2 (7H, m), 2.86 (2H, t, $J=7$ Hz), 3.68 (2H, d), 4.8 (3H, br), 4.99 (1H, d, $J=3.6$ Hz), 5.2–5.6 (2H, m) and 7.33 (5H, s) ppm.

35 (ii) In a similar manner but starting from (+)-5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (1.26 g.), there was obtained (+)-5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid as a syrup (1.1 g.), $[\alpha]_D^{20} +32^\circ$ (c, 2.16, MeOH), having an essentially identical ^1H -NMR spectrum to that of the (–) isomer in (i) above.

40 The above procedures were also used to obtain the racemic ($\pm$) form of 5(Z)-7-(2,2-diethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid having an identical ^1H -NMR spectrum to that of the (–) or (+)-enantiomers (Examples 100, 101), starting from racemic 5(Z)-erythro-9-hydroxy-8-hydroxymethyl-9-phenylnonenoic acid.

Example 102

45 A solution of 5(Z)-7-[2,4,5-*cis*]-2-methyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (500 mg.) in absolute ethanol (10 ml.) containing 5% w/w palladium on charcoal catalyst (100 mg.) was stirred under an atmospheric pressure of hydrogen for 3 hours. The catalyst was separated by filtration through kieselguhr and the filtrate was evaporated to give 7-[2,4,5-*cis*]-2-methyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptanoic acid as a colourless oil in 99% yield; NMR: 0.8–1.8 (14H, m), 2.2 (2H, t, $J=8$ Hz), 3.8–4.25 (2H, m), 4.75–5.0 (2H, m), 7.14–7.4 (5H, m) and 8.5–9.3 (1H, br) pm; m/e: 307 ($\text{M}^+ + \text{H}$).

Example 103

55 Aqueous potassium hydroxide (34 ml. of 40% w/v solution) was added to a stirred solution of 5(E)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenonitrile (831 mg.) in freshly distilled ethylene glycol (34 ml.) under an argon atmosphere and the mixture heated under reflux for 3.5 hours. The cooled mixture was diluted with water (100 ml.) and methylene chloride (100 ml.), and then stirred and acidified to pH 5 (2 M hydrochloric acid). The organic phase was separated, dried (MgSO_4) and evaporated. The residue was purified by flash chromatography eluting with 1:99 v/v acetic acid and ethyl acetate to give 5(E)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid as an oil (454 mg.): ^1H -NMR: 8.7–9.6 (1H, br, CO_2H) m 7.0–7.5 (5H, m), 4.85–5.5 (3H, m), 4.0 (2H, q, $J=12$ Hz) and 1.35–2.55 (15H, m; including s at 1.52 and 1.54) ppm; ^{13}C -NMR: (CDCl_3 ; 22.5 MHz) 178.94 (C^*), 140.80 (pH, Cl), 130.78 (C^*), 129.70 (C^*), 128.02 (C^*), 128.02 (Ph, C3), 126.77 (Ph, C4), 125.42 (Ph, C2), 99.03 (dioxane, C2), 78.39 + 76.93 + 75.52 (CDCl_3), 73.08 (dioxane, C4), 62.63 (dioxane, C6), 39.55 (dioxane, C5), 33.21 (C^*), 31.70 (C^*), 29.58 (equatorial CH_3), 27.09 (C^*), 24.38 (C^* and 19.13 (axial CH_3) ppm [Note: asterisk values refer to the heptenoic acid moiety];

m/e: 318 (M^+), 303 ($M-CH_3$) and 260 [$M-(CH_3)_2CO$].

The starting material was obtained as follows:—

A solution of 2-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (518 mg.) in dry THF (10 ml.) was added over 30 minutes to a stirred solution of vinyl magnesium bromide (3.4 ml of 1.3 M solution in tetrahydrofuran) in tetrahydrofuran (5 ml.), at 0°C. under an atmosphere of Argon. After further stirring at 0°C. for 1 hr, saturated ammonium chloride solution was added to quench the reaction. The mixture obtained was separated and the aqueous phase was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting with 1:1 v/v ethyl acetate/hexane to give an epimeric mixture of 3-hydroxy-4-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)-but-1-ene (A), as an oil (564 mg.) NMR: 7.3 (5H, s); 5.35—5.9 (1H, m); 4.8—5.3 (3H, m); and 0.8—2.2 (10H, m), including 2 s at 1.55 m + OH) ppm.

Propionic acid (7.4 micromole) was added to a solution of (A; 433 mg.) in triethyl orthoacetate (2.2 ml.). The mixture was stirred at 140—145°C. with removal of ethanol by distillation during 1 hour. The cooled reaction mixture was evaporated and the residue purified by flash chromatography, eluting with 15:85 v/v ethyl acetate/hexane to give ethyl 4(E)-6-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)hexenoate (B) as an oil (329 mg.); NMR: 7.3 (5H, s), 5.1—5.5 (3H, m), 3.75—4.2 (4H, m; including q at 4.1, $J=7$ Hz), 2.0—2.6 (6H, m), 1.4—1.8 (7H, m; including s at 1.55) and 1.25 (3H, t, $J=7$ Hz) ppm.

A solution of B (2.593 g.) in anhydrous ether (15 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (297 mg.) in anhydrous ether (60 ml) cooled to 5°C. The mixture was stirred at 5°C. for a further 1 hour. Water (40 ml.) was then added cautiously. The mixture was separated and the aqueous phase was extracted with ether (4 x 60 ml.). The combined ethereal phases were dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography, eluting with 3:2 v/v ethyl acetate/hexane to give 4(E)-6-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)hexenol (C) as an oil (2.22 g.) NMR: 7.1—7.45 (5H, m), 5.0—5.6 (3H, m), 3.95 (2H, q, $J=12$ Hz), 3.05 (2H, t, $J=9$ Hz), 1.8—2.6 (4H, m) and 1.4—1.8 (10H, m) ppm.

Methanesulphonyl chloride (0.57 ml.) was added dropwise to a stirred solution of triethylamine (1.0 m.) and C (2.083 g.) in methylene chloride (25 ml. freshly filtered through a short column of basic alumina) cooled to 5°C. The stirred mixture was then allowed to warm up to room temperature during 2 hours. Ether (100 ml.) was then added. The mixture was washed successively with water, and saturated brine, and was then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using 3:2 v/v ethyl acetate/hexane to give 4(E)-6-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)hexenol *O*-methanesulphonate as an oil (D) (2.176 g.) NMR: 7.3 (5H, s), 5.0—5.55 (3H, m), 4.15 (2H, t, $J=6$ Hz) 3.85 (2H, q, $J=12$ Hz), 2.95 (3H, s) and 1.4—2.65 (13H, m; including 2 s at 1.55) ppm.

Potassium cyanide (405 mg.) was added in portions to a solution of D (1.115 g.) in anhydrous dimethyl sulphoxide (20 ml.) under argon. The mixture was stirred at 75°C. for 2 hours, then diluted with water (15 ml.). The resultant mixture was extracted with ether. The extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using 3:7 v/v ethyl acetate/hexane as eluant to give 5(E)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenonitrile as an oil (687 mg.); NMR: 7.3 (5H, s), 5.0—5.5 (3H, m), 4.0 (2H, q, $J=11$ Hz), 1.9—2.5 (5H, m) and 1.3—1.9 (10H, m, including 2 s at 1.50) ppm.

Example 104

The preparation of an oral dosage form is illustrated by the following tablet formulation:

5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (300 parts);

lactose (56 parts);

maize starch (30 parts);

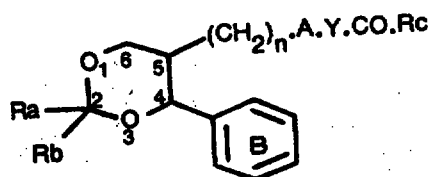
polyvinylpyrrolidone (10 parts); and

magnesium stearate (4 parts)

obtained using a standard wet granulation and compression procedure [all parts by weight]. The lactose may be replaced by an alternative filler such as calcium phosphate, the maize starch by an alternative disintegrant such as calcium carboxymethylcellulose, and the polyvinylpyrrolidone by an alternative binder such as gelatine, if desired.

Similarly the active ingredient may be replaced by another compound of formula I described herein. The tablets may be enteric coated by conventional means, for example to incorporate a coating of cellulose acetate phthalate.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A 4-phenyl-1,3-dioxan-*cis*-5-ylalkenoic acid derivative of the formula I:—

wherein Ra and Rb are independently hydrogen, (2—6C)alkenyl, (1—8C)alkyl optionally bearing up to three halogeno substituents, pentafluorophenyl, aryl or aryl(1—4C)alkyl, the latter two of which may optionally bear up to three substituents selected from halogeno, (1—6C)alkyl, (1—6C)alkoxy, (1—4C)alkylenedioxy, trifluoromethyl, cyano, nitro, hydroxy, (2—6C)alkanoyloxy, (1—6C)alkylthio, (1—6C)alkanesulphonyl, (1—6C)alkanoylamino, and oxapolyethylene of 2 to 4 carbon atoms, provided that when both Ra and Rb are alkyl or alkenyl, the total number of carbon atoms in Ra and Rb taken together is 8 or less; or Ra and Rb together form polymethylene of 2 to 7 carbon atoms, optionally bearing one or two (1—4C)alkyl substituents; Rc is hydroxy, (1—6C)alkoxy or (1—6C)alkanesulphonamido; n is the integer 1 or 2; A is ethylene or vinylene; Y is polymethylene of 2 to 5 carbon atoms optionally bearing (1—4C)alkyl as a substituent; benzene ring B optionally bears one or two substituents selected from halogeno, (1—6C)alkyl, (1—6C)alkoxy, hydroxy, (2—6C)alkanoyloxy, (1—6C)alkanoylamino, trifluoromethyl and nitro; and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry; or for those compounds wherein Rc is hydroxy, a salt thereof with a base affording a physiologically acceptable cation.

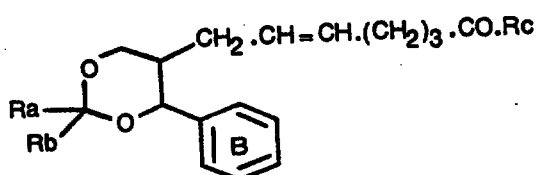
2. A compound as claimed in claim 1 wherein Ra and Rb are, independently, hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, vinyl, allyl, 2-methylallyl, chloromethyl, trifluoromethyl or 2,2,2-trifluoroethyl, pentafluorophenyl, 1-naphthyl, 2-naphthyl, benzyl, 1-phenylethyl, 2-phenylethyl or phenyl, the latter six of which may optionally bear up to three substituents selected from: fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, methylenedioxy, ethylenedioxy, isopropylidenedioxy, trifluoromethyl, cyano, nitro, methylthio, ethylthio, methanesulphonyl, ethanesulphonyl, formamido, acetamido, propionamido, hydroxy, acetoxy, propionyloxy, methyleneoxy, methylene and ethyleneoxymethylene; provided that when both Ra and Rb are alkyl or alkenyl, the total number of carbon atoms in Ra and Rb taken together is 8 or less; or Ra and Rb together constitute ethylene, trimethylene, tetramethylene, pentamethylene or hexamethylene, any of which may bear an optional methyl substituent; Rc is hydroxy, methoxy, ethoxy, methanesulphonamido, ethanesulphonamido or 1-methylethanesulphonamido; n is the integer of 1 or 2; A is ethylene or vinylene; Y is ethylene, trimethylene or tetramethylene, any of which may optionally bear a methyl substituent; and benzene ring B optionally bears one or two substituents selected from fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, propyl, methoxy, ethoxy, propoxy, hydroxy, acetoxy, propionyloxy, formamido, acetamido, propionamido, trifluoromethyl and nitro.

3. A compound as claimed in claim 1 or 2 wherein Ra and Rb are, independently, hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, octyl, vinyl, allyl, 2-methylallyl, trifluoromethyl, chloromethyl, 2-chloroethyl, phenyl optionally bearing a fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, methylthio, methanesulphonyl, nitro, hydroxy, cyano, acetamido, methylenedioxy or a methyleneoxy-methylene ($-\text{CH}_2\text{OCH}_2-$) substituent, dichlorophenyl, dimethylphenyl, pentafluorophenyl, 1-naphthyl, 2-naphthyl or benzyl; or together form trimethylene, pentamethylene or hexamethylene, optionally bearing a methyl substituent; provided that when both Ra and Rb are alkyl or alkenyl the total number of carbon atoms in Ra and Rb taken together is 8 or less; and benzene ring B is phenyl, 2-methylphenyl, 2-ethylphenyl, 2-isopropylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-fluorophenyl, 4-methylphenyl or 2,6-difluorophenyl.

4. A compound as claimed in claim 1, 2 or 3 wherein benzene ring B is unsubstituted; *ortho*-substituted by fluoro, chloro, methyl, hydroxy, methoxy, ethyl or isopropyl, or *meta*-substituted by fluoro or chloro.

5. A compound as claimed in any one of claims 1—4 wherein Rc is hydroxy, methoxy, ethoxy, methanesulphonamido or ethanesulphonamido.

6. A 7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid derivative of the formula Ia:—



wherein Ra and Rb are:—

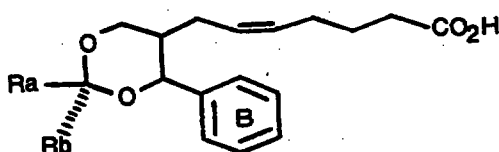
- (i) independently hydrogen or (1—4C)alkyl, optionally bearing 1 to 3 halogeno substituents;
- (ii) one of the two is hydrogen or (1—4C)alkyl, and the other is phenyl, naphthyl or phenyl-(1—4C)alkyl, optionally bearing 1 or 2 substituents selected from halogeno, (1—4C)alkyl, (1—4C)alkoxy, (1—4C)alkylene-dioxy, trifluoromethyl, cyano, nitro, hydroxy, (2—4C)alkanoyloxy, (1—4C)alkylthio, (1—4C)alkanesulphonyl, (1—4C)alkanoylamino and oxapolymerethylene of 2 to 4 carbon atoms, or pentafluorophenyl;
- (iii) one of the two is hydrogen and the other is (5—8C)alkyl or (2—6C)alkenyl; or
- (iv) both together form polymethylene of 2 to 7 carbon atoms optionally bearing a (1—4C)alkyl substituent;

Rc is hydroxy, (1—4C)alkoxy or (1—4C)alkanesulphonamido; and benzene ring B optionally bears a single substituent located at the 2-position selected from halogeno, (1—4C)alkyl, (1—4C)alkoxy, hydroxy, (2—4C)alkanoyloxy, (1—4C)alkanoylamino and trifluoromethyl, or bears a 3-halogeno substituent; and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry; or for those compounds wherein Rc is hydroxy, a salt thereof with a base affording a physiologically acceptable cation.

7. A compound as claimed in claim 6 wherein:—

- (i) Ra and Rb are both hydrogen, methyl, ethyl, propyl, butyl or trifluoromethyl;
- (ii) one of Ra and Rb is hydrogen and the other is trifluoromethyl, chloromethyl, benzyl, isopropyl, hexyl, octyl, phenyl (optionally bearing 1 or 2 fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, hydroxy, cyano, methylthio or acetamido), phenyl bearing methylenedioxy or methyleneoxymethylene (—CH₂OCH₂—), pentafluorophenyl, 1-naphthyl or 2-naphthyl; or
- (iii) Ra and Rb together form trimethylene, tetramethylene, pentamethylene, hexamethylene or a group of the formula: —CH₂CH₂·CHCH₃·CH₂CH₂—; and benzene ring B is phenyl; 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-methylphenyl, 2-ethylphenyl, 2-isopropylphenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 3-fluorophenyl or 3-chlorophenyl; and Rc is hydroxy, methanesulphonamido or ethanesulphonamido.

8. A 5(Z)-7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid of the formula Ib:—



Ib

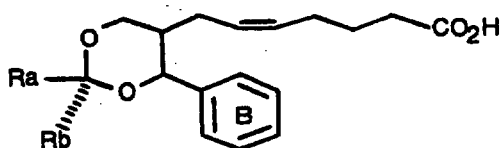
wherein:—

- (i) Ra and Rb are both hydrogen, methyl, ethyl, propyl, butyl or trifluoromethyl.
 - (ii) Ra and Rb together form trimethylene, tetramethylene, pentamethylene, hexamethylene or a group of the formula: —CH₂CH₂·CHCH₃·CH₂CH₂—; or
 - (iii) Ra is (3—8C)alkyl, trifluoromethyl, chloromethyl, 2-chloroethyl, pentafluorophenyl, or phenyl, benzyl or naphthyl, the last three of which may optionally bear 1 or 2 halogeno, (1—4C)alkyl, (1—4C)alkoxy, trifluoromethyl, hydroxy, cyano, (1—4C)alkylthio or (1—4C)alkanoylamino substituents, or a methylenedioxy or methyleneoxymethylene substituent, and Rb is hydrogen;
- benzene ring B is unsubstituted or is 2-halogeno-, 2-(1—4C)alkyl-, 2-(1—4C)alkoxy-, 2-hydroxy- or 3-halogeno-phenyl;

Ra and the substituents at the 4 and 5-positions of the dioxane ring have *cis*-relative stereochemistry; and the carbon atoms adjacent to the vinylene group have the indicated *cis*-relative stereochemistry; or a salt thereof with a base affording a physiologically acceptable cation; or a methyl or ethyl ester thereof; or a methanesulphonamido, ethanesulphonamido or 1-methylethanesulphonamido derivative thereof.

9. A compound as claimed in claim 8 wherein Ra and Rb have the meanings defined in (i) and (ii) of claim 8; or Ra is isopropyl, butyl, hexyl, octyl, trifluoromethyl, chloromethyl, 2-chloroethyl, pentafluorophenyl, benzyl, naphthyl or phenyl (optionally bearing 1 or 2 fluoro, chloro, bromo, methyl, methoxy, trifluoromethyl, hydroxy, cyano, methylthio or acetamido substituents, or bearing a methylenedioxy or methyleneoxymethylene substituent), and Rb is hydrogen; and benzene ring B is unsubstituted or bears a 2-fluoro, 2-chloro, 2-bromo, 3-fluoro, 3-chloro, 2-methyl, 2-ethyl, 2-isopropyl, 2-methoxy, or 2-hydroxy substituent.

10. A 5(Z)-7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid of the formula Ib:—



Ib

wherein Ra, Rb and benzene ring B are selected from the following combinations:—

No.	Ra	Rb	Benzene Ring B
1	methyl	methyl	3-fluorophenyl
2	methyl	methyl	3-chlorophenyl
3	methyl	methyl	2-methoxyphenyl
4	methyl	methyl	2-methylphenyl
5	methyl	H	phenyl
6	trifluoromethyl	H	phenyl
7	isopropyl	H	phenyl
8	ethyl	ethyl	phenyl
9	ethyl	ethyl	2-fluorophenyl
10	2-chlorophenyl	H	phenyl
11	2-methylphenyl	H	phenyl
12	2-ethylphenyl	H	phenyl
13	3-fluorophenyl	H	phenyl
14	3-chlorophenyl	H	phenyl
15	3-methylthiophenyl	H	phenyl
16	4-fluorophenyl	H	phenyl
17	4-chlorophenyl	H	phenyl
18	4-methoxyphenyl	H	phenyl
19	3,4-methylene dioxypheyl	H	phenyl
20	3,4-(methylenexymethylene)phenyl	H	phenyl
21	methyl	methyl	2-hydroxyphenyl

(wherein H stands for hydrogen); and from the following combinations:—

No	Ra + Rb	Benzene Ring B
22	pentamethylene	phenyl
23	hexamethylene	phenyl
24	(3-methyl)pentamethylene	phenyl

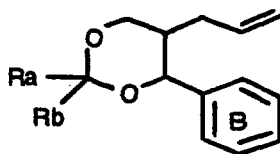
or a salt thereof with a base affording a physiologically acceptable cation.

11. A salt as claimed in any one preceding claim which is an alkali metal, alkaline earth metal, aluminium or ammonium salt, or a salt with an organic amine or quaternary base, forming a physiologically acceptable cation.

12. A methanesulphonamido derivative of an acid as claimed in claim 10 or of 5(Z)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid.



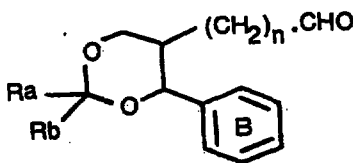
13. A 5-allyl-5-phenyl-1,3-dioxane derivative of the formula VII:—



VII

wherein Ra, Rb and benzene ring B have any of the meanings defined in claims 1—10, and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry.

14. A (4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde derivative of the formula II:—



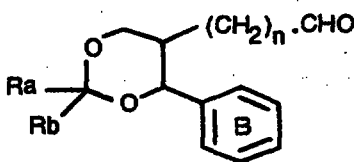
II

wherein n is the integer 1, and Ra, Rb and benzene ring B have any of the meanings defined in claims 1—10, and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry.

15. A pharmaceutical composition which comprises a compound of formula I, or a salt thereof, as claimed in any one of claims 1—12, together with a pharmaceutically acceptable diluent or carrier.

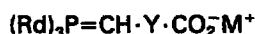
16. A process for the manufacture of a compound of the formula I, or a salt thereof, as claimed in claim 1, wherein Ra, Rb, Rc, benzene ring B, n, A and Y have any of the meanings defined in claims 1—10; characterised by:—

(a) for a compound wherein Rc is hydroxy and A is vinylene, reacting an aldehyde of the formula II:—



II

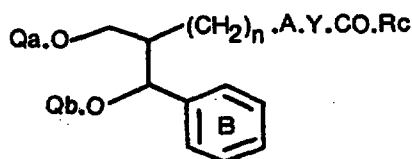
with a Wittig reagent of the formula:—



III

wherein Rd is (1—6C)alkyl or aryl and M⁺ is an alkali metal cation;

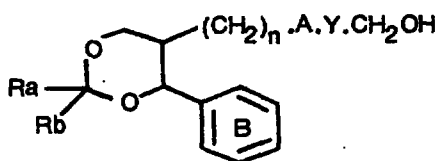
(b) reacting an *erythro*-diol derivative of the formula XIII:—



XIII

wherein one of Qa and Qb is hydrogen and the other is hydrogen, alkanesulphonyl, arenesulphonyl or a group of the formula —CRR¹.OH wherein R and R¹ are the same or different alkyl, with a carbonyl, compound of the formula RaRb-CO, or an acetal, hemiacetal or hydrate thereof;

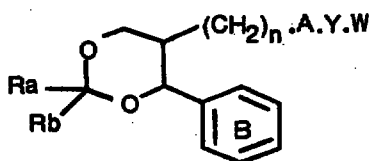
(c) for a compound of formula I wherein Rc is hydroxy, oxidising an alcohol of the formula XVI:—



XVI



(d) for a compound of formula I wherein Rc is hydroxy, hydrolysing a compound of the formula XVIII:—

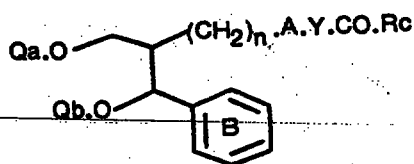


XVIII

wherein W is alkoxy, carbonyl, phenoxy, benzyloxy, cyano or carbamoyl;

(e) for a compound of formula I wherein Ra, Rb or benzene ring B bears a hydroxy substituent, deprotecting a corresponding derivative of said compound wherein the hydroxy substituent is protected by a trimethylsilyl, (1-6C)alkyl or acyl protecting group;

(f) for a compound of formula I wherein Ra and Rb are both hydrogen, reacting an *erythro*-diol of the formula XIII:—



XIII

wherein Qa and Qb are both hydrogen, with methylene bromide in the presence of a base;

whereafter: when a compound of formula I wherein Rc is (1-6C)alkoxy is required, the corresponding acid of formula I wherein Rc is hydroxy, or a reactive derivative thereof, is esterified using a conventional procedure;

when a compound of formula I wherein Rc is (1-6C)alkanesulphonamido is required, the corresponding acid of formula I wherein Rc is hydroxy is reacted with the appropriate (1-6C)alkanesulphonamide in the presence of a dehydrating agent, or a reactive derivative of said acid of formula I is reacted with the appropriate (1-6C)alkanesulphonamide or an alkali metal salt thereof;

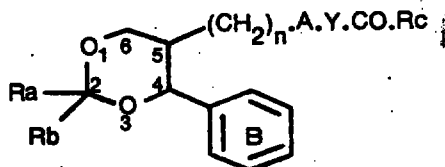
when a compound of formula I wherein A is ethylene is required, the corresponding compound of formula I wherein A is vinylene is hydrogenated in the presence of a catalyst;

when a salt of a compound of formula I wherein Rc is hydroxy is required, said compound is reacted with the appropriate base affording a physiologically acceptable cation; and

when an optionally active form of a compound of formula I is required, either one of the aforesaid procedures is carried out using an optically active starting material, or a racemic form of a compound of formula I wherein Rc is hydroxy is reacted with an optically active form of a suitable organic base, followed by separation of the diastereoisomeric mixture of salts thus obtained, and liberation of the required optically active form of said compound of formula I by treatment with acid followed, when Rc is other than hydroxy, by esterification or amidification as aforesaid.

Claims for the Contracting State: AT

1. A process for the manufacture of a 4-phenyl-1,3-dioxan-*cis*-5-ylalkenoic acid derivative of the formula I



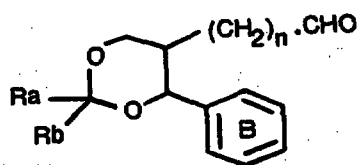
wherein Ra and Rb are independently hydrogen, (2-6C)alkenyl, (1-8C)alkyl optionally bearing up to three halogeno substituents, pentafluorophenyl, aryl or aryl(1-4C)alkyl, the latter two of which may optionally bear up to three substituents selected from halogeno, (1-6C)alkyl, (1-6C)alkoxy, (1-4C)alkylenedioxy, trifluoromethyl, cyano, nitro, hydroxy, (2-6C)alkanoyloxy, (1-6C)alkylthio, (1-6C)alkanesulphonyl, (1-6C)alkanoylamino, and oxapolyethylene of 2 to 4 carbon atoms, provided that when both Ra and Rb are alkyl or alkenyl, the total number of carbon atoms in Ra and Rb taken together is 8 or less; or Ra and Rb together form polymethylene of 2 to 7 carbon atoms, optionally bearing one or two (1-4C)alkyl substituents; Rc is hydroxy, (1-6C)alkoxy or (1-6C)alkanesulphonamido; n is the integer 1 or 2; A is





ethylene or vinylene; Y is polymethylene of 2 to 5 carbon atoms optionally bearing (1-4C)alkyl as a substituent; benzene ring B optionally bears one or two substituents selected from halogeno, (1-6C)alkyl, (1-6C)alkoxy, hydroxy, (2-6C)alkanoyloxy, (1-6C)alkanoylamino, trifluoromethyl and nitro; and the substituents at positions 4 and 5 of the dioxane ring have *cis*-relative stereochemistry; or for those compounds wherein R_c is hydroxy, a salt thereof with a base affording a physiologically acceptable cation; characterised by:—

(a) for a compound wherein R_c is hydroxy and A is vinylene, reacting an aldehyde of the formula II:—



II

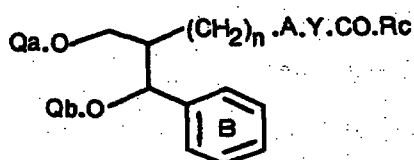
with a Wittig reagent of the formula:—



III

wherein Rd is (1-6C)alkyl or aryl and M⁺ is an alkali metal cation;

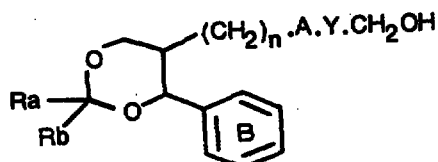
(b) reacting an *erythro*-diol derivative of the formula XIII:—



XIII

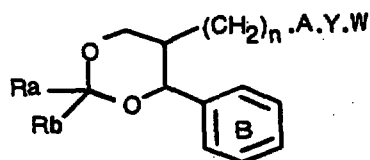
wherein one of Qa and Qb is hydrogen and the other is hydrogen, alkanesulphonyl, arenesulphonyl or a group of the formula —CRR¹·OH wherein R and R¹ are the same or different alkyl, with a carbonyl compound of the formula RaRb·CO, or an acetal, hemiacetal or hydrate thereof;

(c) for a compound of formula I wherein R_c is hydroxy, oxidising an alcohol of the formula XVI:—



XVI

(d) for a compound of formula I wherein R_c is hydroxy, hydrolysing a compound of the formula XVIII:—



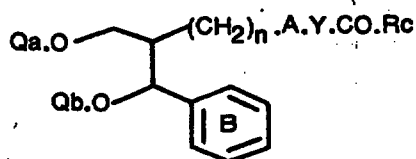
XVIII

wherein W is alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, cyano or carbamoyl;

(e) for a compound of formula I wherein Ra, Rb or benzene ring B bears a hydroxy substituent, deprotecting a corresponding derivative of said compound wherein the hydroxy substituent is protected by a trimethylsilyl, (1-6C)alkyl or acyl protecting group;

(f) for a compound of formula I wherein Ra and Rb are both hydrogen, reacting an *erythro*-diol of the formula XIII:—





XIII

wherein Qa and Qb are both hydrogen, with methylene bromide in the presence of a base;

wherein Ra, Rb, Rc, benzene ring B, n, A and Y have the meanings defined above;

whereafter: when a compound of formula I wherein Rc is (1-6C)alkoxy is required, the corresponding acid of formula I wherein Rc is hydroxy, or a reactive derivative thereof, is esterified using a conventional procedure;

when a compound of formula I wherein Rc is (1-6C)alkanesulphonamido is required, the corresponding acid of formula I wherein Rc is hydroxy is reacted with the appropriate (1-6C)alkanesulphonamide in the presence of a dehydrating agent, or a reactive derivative of said acid of formula I is reacted with the appropriate (1-6C)alkanesulphonamide or an alkali metal salt thereof;

when a compound of formula I wherein A is ethylene is required, the corresponding compound of formula I wherein A is vinylene is hydrogenated in the presence of a catalyst;

when a salt of a compound of formula I wherein Rc is hydroxy is required, said compound is reacted with the appropriate base affording a physiologically acceptable cation; and

when an optionally active form of a compound of formula I is required, either one of the aforesaid procedures is carried out using an optically active starting material, or a racemic form of a compound of formula I wherein Rc is hydroxy is reacted with an optically active form of a suitable organic base, followed by separation of the diastereoisomeric mixture of salts thus obtained, and liberation of the required optically active form of said compound of formula I by treatment with acid followed, when Rc is other than hydroxy, by esterification or amidification as aforesaid.

2. A process according to part (a) of claim 1 characterised in that the reaction is performed in a solvent or diluent such as an aromatic solvent, an ether or in a mixture of one or more such solvents or diluents, at a temperature in the range -80°C. to 40°C.

3. A process according to part (b) of claim 1 characterised in that Qa and Qb are both hydrogen, or one is a group of the formula -CRR¹.OH. and the other is hydrogen, and the reaction is carried out in the presence of an acid catalyst in a solvent or diluent such as an ether and at a temperature in the range 10°C to 120°C.

4. A process according to part (b) of claim 1 characterised in that the starting material of formula XIII wherein Qa and Qb are other than alkanesulphonyl or arenesulphonyl is produced *in situ* by reaction of a compound of formula I wherein Ra and Rb are both methyl or ethyl, in the presence of an acid catalyst.

5. A process according to part (c) of claim 1 characterised in that it is performed in a solvent or diluent at a temperature in the range 10°C to 50°C.

6. A process according to part (d) of claim 1 characterised in that it is carried out under the influence of base in an aqueous solvent such as a (1-4C)alkanol or a glycol and at a temperature in the range 15°C. to 150°C.

7. A process according to part (e) of claim 1 characterised in that the starting material is a compound of formula I wherein Ra, Rb or benzene ring B bears a (1-6C)alkoxy radical and the reaction is carried out using sodium thioethoxide in a solvent such as N,N-dimethylformamide at a temperature in the range 90°C. to 160°C.

8. A process according to part (f) of claim 1 characterised in that the base is an alkali metal hydroxide or hydride and the reaction is performed in a solvent or diluent such as dimethyl sulphoxide at a temperature in the range 10°C. to 40°C.

9. A process according to any preceding claim characterised in that in the starting materials:

(i) Ra and Rb are both hydrogen, methyl, ethyl, propyl, butyl, or trifluoromethyl;

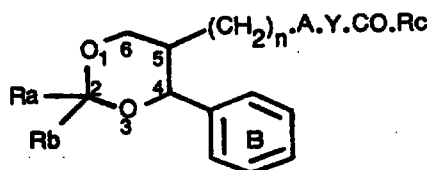
(ii) Ra and Rb together form trimethylene, tetramethylene, pentamethylene, hexamethylene or a group of the formula: -CH₂CH₂.CHCH₂.CH₂CH₂-; or

(iii) Ra is (3-8C)alkyl, trifluoromethyl, chloromethyl, 2-chloroethyl, pentafluorophenyl, or phenyl, benzyl or naphthyl, the last three of which may optionally bear 1 or 2 halogeno, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl, hydroxy, cyano, (1-4C)alkylthio or (1-4C)alkanoylamino substituents, or a methylenedioxy or methyleneoxymethylene substituent, and Rb is hydrogen; and

benzene ring B is unsubstituted or is 2-halogeno-, 2-(1-4C)alkyl-, 2-(1-4C)alkoxy-, 2-hydroxy- or 3-halogeno-phenyl; n is the integer 1; Y is trimethylene; and A is vinylene, the carbon atoms adjacent to which group have *cis*-relative stereochemistry.



1. 4-Phenyl-1,3-dioxan-cis-5-ylalkensäure-Derivat der Formel I



worin Ra und Rb unabhängig voneinander für Wasserstoff, (2-6C)Alkenyl, (1-8C)Alkyl, das gegebenenfalls bis zu drei Halogensubstituenten trägt, Pentafluorophenyl, Aryl oder Aryl(1-4C)alkyl stehen, wobei die beiden letztgenannten Reste gegebenenfalls bis zu drei Substituenten, ausgewählt aus Halogen, (1-6C)Alkyl, (1-6C)Alkoxy, (1-4C)Alkylendioxy, Trifluoromethyl, Cyano, Nitro, Hydroxy, (2-4C)Alkanoyloxy, (1-6C)Alkylthio, (1-6C)Alkansulfonyl, (1-6C)Alkanoylamino und Oxapolymethylen mit 2 bis 4 Kohlenstoffatomen, tragen können, wobei gilt, daß dann, wenn beide Reste Ra und Rb Alkyl oder Alkenyl bedeuten, die Gesamtzahl der Kohlenstoffatome in Ra und Rb zusammengekommen 8 oder weniger beträgt; oder Ra und Rb zusammen Polymethylen mit 2 bis 7 Kohlenstoffatomen bilden, das gegebenenfalls einen oder zwei (1-4C)Alkyl-Substituenten trägt; Rc für Hydroxy, (1-6C)Alkoxy oder (1-6C)-Alkansulfonamido steht; n für die ganze Zahl 1 oder 2 steht; A für Ethylen oder Vinylen steht; Y für Polymethylen mit 2 bis 5 Kohlenstoffatomen steht, das gegebenenfalls (1-4C)Alkyl als einen Substituenten trägt; der Benzolring B gegebenenfalls einen oder zwei Substituenten, ausgewählt aus Halogen, (1-6C)Alkyl, (1-6C)Alkoxy, Hydroxy, (2-6C)Alkanoyloxy, (1-6C)Alkanoylamino, Trifluoromethyl und Nitro, trägt; und die Substituenten in Stellung 4 und 5 des Dioxanringes relativ zueinander cis-Stereochemie aufweisen; oder im Falle derjenigen Verbindungen, in denen Rc für Hydroxy steht, ein Salz desselben mit einer Base, die ein physiologisch verträgliches Kation liefert.

2. Verbindung nach Anspruch 1, worin Ra und Rb unabhängig voneinander für Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, Butyl, Pentyl, Hexyl, Heptyl, Octyl, Vinyl, Allyl, 2-Methylallyl, Chloromethyl, Trifluoromethyl oder 2,2,2-Trifluoroethyl, Pentafluorophenyl, 1-Naphthyl, 2-Naphthyl, Benzyl, 1-Phenylethyl, 2-Phenylethyl oder Phenyl stehen, wobei die letztgenannten sechs Reste gegebenenfalls bis zu drei Substituenten, ausgewählt aus Fluor, Chlor, Brom, Jod, Methyl, Ethyl, Propyl, Isopropyl, Methoxy, Ethoxy, Propoxy, Methylendioxy, Ethylendioxy, Isopropylidendioxy, Trifluoromethyl, Cyano, Nitro, Methylthio, Ethylthio, Methansulfonyl, Ethansulfonyl, Formamido, Acetamido, Propionamido, Hydroxy, Acetoxy, Propionyloxy, Methylenoxymethylen und Ethylenoxymethylen, tragen können; wobei gilt, daß dann, wenn beide Reste Ra und Rb für Alkyl oder Alkenyl stehen, die Gesamtzahl der Kohlenstoffatome in Ra und Rb zusammengekommen acht oder weniger beträgt; oder Ra und Rb zusammen Ethylen, Trimethylen, Tetramethylen, Pentamethylen oder Hexamethylen bilden, wobei jeder dieser Reste gegebenenfalls einen Methylsubstituenten tragen kann; Rc für Hydroxy, Methoxy, Ethoxy, Methansulfonamido, Ethansulfonamido oder 1-Methylethansulfonamido steht; n für die ganze Zahl 1 oder 2 steht; A für Ethylen oder Vinylen steht; Y für Ethylen, Trimethylen oder Tetramethylen steht, wobei jeder dieser Reste gegebenenfalls einen Methylsubstituenten tragen kann; und der Benzolring B gegebenenfalls einen oder zwei Substituenten, ausgewählt aus Fluor, Chlor, Brom, Jod, Methyl, Ethyl, Isopropyl, Propyl, Methoxy, Ethoxy, Propoxy, Hydroxy, Acetoxy, Propionyloxy, Formamido, Acetamido, Propionamido, Trifluoromethyl und Nitro, trägt.

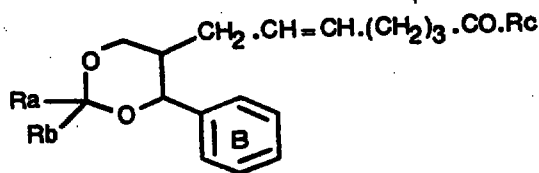
3. Verbindung nach Ansprüchen 1 oder 2, worin Ra und Rb unabhängig voneinander für Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, Butyl, Pentyl, Hexyl, Octyl, Vinyl, Allyl, 2-Methylallyl, Trifluoromethyl, Chloromethyl, 2-Chloroethyl, Phenyl, das gegebenenfalls einen Fluor-, Chlor-, Brom-, Methyl-, Methoxy-, Trifluoromethyl-, Methylthio-, Methansulfonyl-, Nitro-, Hydroxy-, Cyano-, Acetamido-, Methylendioxy- oder einen Methylenoxymethylen(-CH₂OCH₂)-Substituent trägt, Dichlorophenyl, Dimethylphenyl, Pentafluorophenyl, 1-Naphthyl, 2-Naphthyl oder Benzyl stehen, oder zusammen Trimethylen, Pentamethylen oder Hexamethylen, die gegebenenfalls einen Methylsubstituenten tragen, bilden; wobei gilt, daß dann, wenn beide Reste Ra und Rb für Alkyl oder Alkenyl stehen, die Gesamtzahl der Kohlenstoffatome in Ra und Rb zusammengekommen 8 oder weniger beträgt; und der Benzolring B für Phenyl, 2-Methylphenyl, 2-Ethylphenyl, 2-Isopropylphenyl, 2-Methoxyphenyl, 2-Fluorophenyl, 2-Chlorophenyl, 2-Bromophenyl, 2-Hydroxyphenyl, 2-Trifluoromethylphenyl, 3-Trifluoromethylphenyl, 3-Fluorophenyl, 3-Chlorophenyl, 4-Fluorophenyl, 4-Methylphenyl oder 2,6-Difluorophenyl steht.

4. Verbindung nach Ansprüchen 1, 2 oder 3, worin der Benzolring B unsubstituiert ist; durch Fluor, Chlor, Methyl, Hydroxy, Methoxy, Ethyl oder Isopropyl orthosubstituiert ist, oder durch Fluor oder Chlor metasubstituiert ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, worin Rc für Hydroxy, Methoxy, Ethoxy, Methansulfonamido oder Ethansulfonamido steht.

6. 7-(4-Phenyl-1,3-dioxan-cis-5-yl)heptensäure-Derivat der Formel Ia





1a

worin Ra und Rb

(i) unabhängig voneinander für Wasserstoff oder (1—4C)Alkyl, das gegebenenfalls 1 bis 3 Halogensubstituenten trägt, stehen;

(ii) einer der beiden Reste für Wasserstoff oder (1—4C)Alkyl steht und der andere für Phenyl, Naphthyl oder Phenyl-(1—4C)alkyl steht, die gegebenenfalls 1 oder 2 Substituenten, ausgewählt aus Halogen, (1—4C)Alkyl, (1—4C)Alkoxy, (1—4C)Alkylendioxy, Trifluoromethyl, Cyano, Nitro, Hydroxy, (2—4C)Alkanoyloxy, (1—4C)Alkylthio, (1—4C)Alkansulfonyl, (1—4C)Alkanoylamino und Oxapolymethylen mit 2 bis 4 Kohlenstoffatomen, tragen, oder für Pentafluorophenyl steht;

(iii) einer der beiden Reste für Wasserstoff steht und der andere für (5—8C)Alkyl oder (2—6C)Alkenyl steht; oder

(iv) beide Reste zusammen Polymethylen mit 2 bis 7 Kohlenstoffatomen bilden, das gegebenenfalls einen (1—4C)Alkyl-Substituenten trägt;

Rc für Hydroxy, (1—4C)Alkoxy oder (1—4C)Alkansulfonamido steht; und der Benzolring B gegebenenfalls einen einzelnen, in der 2-Stellung befindlichen Substituenten, ausgewählt aus Halogen, (1—4C)Alkyl, (1—4C)Alkoxy, Hydroxy, (2—4C)Alkanoyloxy, (1—4C)Alkanoylamino und Trifluoromethyl, trägt, oder einen 3-Halogen-Substituenten trägt; und die Substituenten in den Stellungen 4 und 5 des Dioxanringes relativ zueinander cis-Stereochemie aufweisen; oder im Falle derjenigen Verbindungen, in denen Rc für Hydroxy steht, ein Salz desselben mit einer Base, die ein physiologisch verträgliches Kation liefert.

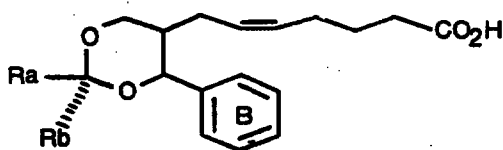
7. Verbindung nach Anspruch 6, worin

(i) Ra und Rb beide für Wasserstoff, Methyl, Ethyl, Propyl, Butyl oder Trifluoromethyl stehen;

(ii) einer der Reste Ra und Rb für Wasserstoff und der andere für Trifluoromethyl, Chloromethyl, Benzyl, Isopropyl, Hexyl, Octyl, Phenyl (das gegebenenfalls 1 oder 2 Fluor-, Chlor-, Brom-, Methyl-, Methoxy, Trifluoromethyl-, Hydroxy-, Cyano-, Methylthio- oder Acetamido-Substituenten trägt), Phenyl, das Methylendioxy oder Methylenoxymethylen ($-\text{CH}_2\text{OCH}_2-$) trägt, Pentafluorophenyl, 1-Naphthyl oder 2-Naphthyl steht; oder

(iii) Ra und Rb zusammen Trimethylen, Tetramethylen, Pentamethylen, Hexamethylen oder eine Gruppe der Formel $-\text{CH}_2\text{CH}_2\text{CHCH}_3\text{CH}_2\text{CH}_2-$ bilden; und der Benzolring B für Phenyl, 2-Fluorophenyl, 2-Chlorophenyl, 2-Bromophenyl, 2-Methylphenyl, 2-Ethylphenyl, 2-Isopropylphenyl, 2-Methoxyphenyl, 2-Hydroxyphenyl, 3-Fluorophenyl oder 3-Chlorophenyl steht; und Rc für Hydroxy, Methansulfonamido oder Ethansulfonamido steht.

8. 5(Z)-7-(4-Phenyl-1,3-dioxan-cis-5-yl)heptensäure der Formel 1b



1b

worin

(i) Ra und Rb beide für Wasserstoff, Methyl, Ethyl, Propyl, Butyl oder Trifluoromethyl stehen;

(ii) Ra und Rb zusammen Trimethylen, Tetramethylen, Pentamethylen, Hexamethylen oder eine Gruppe der Formel $-\text{CH}_2\text{CH}_2\text{CHCH}_3\text{CH}_2\text{CH}_2-$ bilden; oder

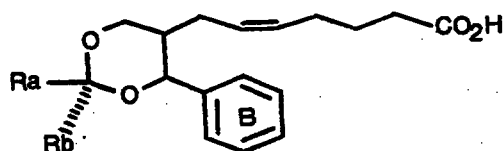
(iii) Ra für (3—8C)Alkyl, Trifluoromethyl, Chloromethyl, 2-Chloroethyl, Pentafluorophenyl oder für Phenyl, Benzyl oder Naphthyl steht, wobei die letztgenannten drei Reste gegebenenfalls 1 oder 2 Halogen-, (1—4C)Alkyl-, (1—4C)Alkoxy-, Trifluoromethyl-, Hydroxy-, Cyano-, (1—4C)Alkylthio- oder (1—4C)Alkanoylamino-Substituenten, oder einen Methylendioxy- oder Methylenoxymethylen-Substituenten tragen können, und Rb für Wasserstoff steht;

der Benzolring B unsubstituiert ist oder für 2-Halogen-, 2-(1—6C)Alkyl-, 2-(1—6C)Alkoxy-, 2-Hydroxy- oder 3-Halogenphenyl steht;

Ra und die Substituenten in der 4- und 5-Stellung des Dioxanringes relative cis-Stereochemie aufweisen und die benachbart zu der Vinylengruppe befindlichen Kohlenstoffatome die angezeigte relative cis-Stereochemie aufweisen; oder ein Salz derselben mit einer Base, die ein physiologisch verträgliches Kation liefert, oder ein Methyl- oder Ethylester derselben, oder ein Methansulfonamido-, Ethansulfonamido- oder 1-Methylethansulfonamido-Derivat derselben.



9. Verbindung nach Anspruch 8, worin Ra und Rb die in (i) und (ii) des Anspruchs 8 angegebene Bedeutung haben, oder Ra für Isopropyl, Butyl, Hexyl, Octyl, Trifluoromethyl, Chloromethyl, 2-Chloroethyl, Pentafluorophenyl, Benzyl, Naphthyl oder Phenyl (das gegebenenfalls 1 oder 2 Fluor-, Chlor-, Brom-, Methyl-, Methoxy-, Trifluoromethyl-, Hydroxy-, Cyano-, Methylthio- oder Acetamido-Substituenten oder einen Methylendioxy- oder Methylenoxymethylen-Substituenten trägt) steht und Rb für Wasserstoff steht; und der Benzolring B unsubstituiert ist oder einen 2-Fluor-, 2-Chlor-, 2-Brom-, 3-Fluor-, 3-Chlor-, 2-Methyl-, 2-Ethyl-, 2-Isopropyl-, 2-Methoxy- oder 2-Hydroxy-Substituenten trägt.
10. 5(Z)-7-(4-Phenyl-1,3-dioxan-cis-5-yl)heptensäure der Formel Ib



Ib

worin Ra, Rb und der Benzolring B aus folgenden Kombinationen ausgewählt sind:





Nr.	Ra	Rb	Benzolring B
1	Methyl	Methyl	3-Fluorophenyl
2	Methyl	Methyl	3-Chlorophenyl
3	Methyl	Methyl	2-Methoxyphenyl
4	Methyl	Methyl	2-Methylphenyl
5	Methyl	H	Phenyl
6	Trifluoromethyl	H	Phenyl
7	Isopropyl	H	Phenyl
8	Ethyl	Ethyl	Phenyl
9	Ethyl	Ethyl	2-Fluorophenyl
10	2-Chlorophenyl	H	Phenyl
11	2-Methylphenyl	H	Phenyl
12	2-Ethylphenyl	H	Phenyl
13	3-Fluorophenyl	H	Phenyl
14	3-Chlorophenyl	H	Phenyl
15	3-Methylthiophenyl	H	Phenyl
16	4-Fluorophenyl	H	Phenyl
17	4-Chlorophenyl	H	Phenyl
18	4-Methoxyphenyl	H	Phenyl
19	3,4-Methylenedioxyphenyl	H	Phenyl
20	3,4-(Methylenoxy-methylen)phenyl	H	Phenyl
21	Methyl	Methyl	2-Hydroxyphenyl

(worin H für Wasserstoff steht); und aus den folgenden Kombinationen ausgewählt ist:

Nr	Ra + Rb	Benzolring B
22	Pentamethylen	Phenyl
23	Hexamethylen	Phenyl
24	(3-Methyl)pentamethylen	Phenyl

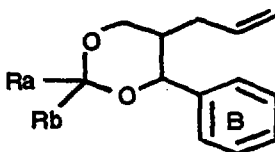
oder ein Salz derselben mit einer Base, die ein physiologisch verträgliches Kation liefert.

11. Salz von Verbindungen nach einem der vorstehenden Ansprüche, welches ein Alkalimetall-, Erdalkalimetall-, Aluminium- oder Ammoniumsalz oder ein Salz mit einem organischen Amin oder einer quaternären Base, die ein physiologisch verträgliches Kation bildet, ist.



12. Methansulfonamido-Derivat einer Säure nach Anspruch 10 oder von 5(Z)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-cis-5-yl)heptensäure.

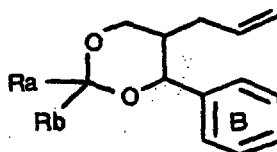
13. 5-Allyl-5-phenyl-1,3-dioxan-Derivat der Formel VII



VII

worin Ra, Rb und der Benzolring B eine der in Ansprüchen 1 bis 10 angegebenen Bedeutungen haben und die Substituenten in den Stellungen 4 und 5 des Dioxanringes relative cis-Stereochemie aufweisen.

14. (4-Phenyl-1,3-dioxan-cis-5-yl)acetaldehyd-Derivat der Formel II



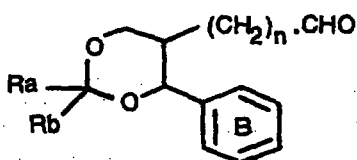
VII

worin n für die ganze Zahl 1 steht und Ra, Rb und der Benzolring B eine der in Ansprüchen 1 bis 10 angegebenen Bedeutungen haben und die Substituenten in den Stellungen 4 und 5 des Dioxanringes relative cis-Stereochemie aufweisen.

15. Pharmazeutische Zusammensetzung, welche eine Verbindung der Formel I oder ein Salz derselben nach einem der Ansprüche 1 bis 12 aufweist zusammen mit einem pharmazeutisch verträglichen Verdünnungs- oder Trägermittel.

16. Verfahren zur Herstellung einer Verbindung der Formel I oder eines Salzes derselben nach Anspruch 1, worin Ra, Rb, Rc, der Benzolring B, n, A und Y eine der in Ansprüchen 1 bis 10 angegebenen Bedeutungen aufweisen, dadurch gekennzeichnet, daß man

(a) für eine Verbindung, worin Rc für Hydroxy und A für Vinylen stehen, einen Aldehyd der Formel II



II

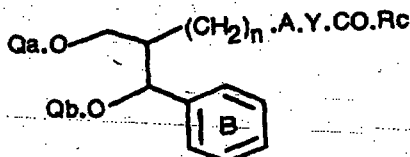
mit einem Wittig-Reagenz der Formel III



III

worin Rd für (1-6C)Alkyl oder Aryl steht und M⁺ für ein Alkalimetall-Kation steht, umsetzt;

(b) ein erythro-Diolderivat der Formel XIII

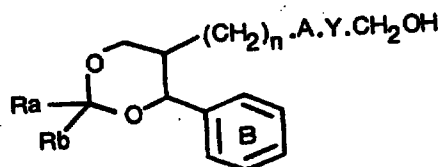


XIII

worin einer der Reste Qa und Qb für Wasserstoff steht und der andere für Wasserstoff, Alkansulfonyl, Arensulfonyl oder eine Gruppe der Formel -CRR'.OH steht, worin R und R' das gleiche oder ein unterschiedliches Alkyl bedeuten, mit einer Carbonylverbindung der Formel RaRb.CO oder einem Acetal, Hemiacetal oder Hydrat derselben umsetzt;



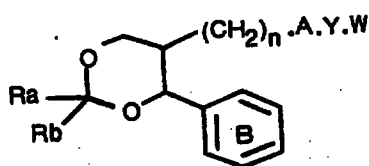
(c) für eine Verbindung der Formel I, worin Rc für Hydroxy steht, einen Alkohol der Formel XVI



XVI

oxidiert;

(d) für eine Verbindung der Formel I, worin Rc für Hydroxy steht, eine Verbindung der Formel XVIII

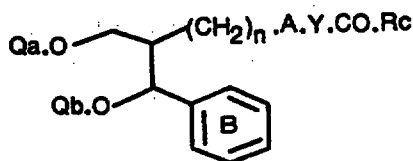


XVIII

worin W für Alkoxycarbonyl, Phoxycarbonyl, Benzyloxycarbonyl, Cyano oder Carbamoyl steht, hydrolysiert;

(e) für eine Verbindung der Formel I, worin Ra, Rb oder der Benzolring B einen Hydroxy-Substituenten tragen, ein entsprechendes Derivat dieser Verbindung, worin der Hydroxy-Substituent durch eine Trimethylsilyl-, (1-6C)Alkyl- oder Acyl-Schutzgruppe geschützt ist, von der Schutzgruppe befreit;

(f) für eine Verbindung der Formel I, worin Ra und Rb beide für Wasserstoff stehen, ein erythro-Diol der Formel XIII



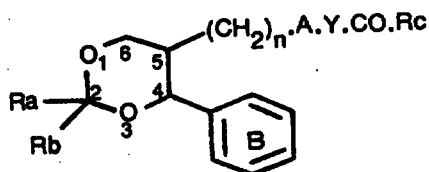
XIII

worin Qa und Qb beide für Wasserstoff stehen, mit Methylenbromid in Gegenwart einer Base umgesetzt, woraufman, wenn eine Verbindung der Formel I, worin Rc für (1-6C)-Alkoxy steht, angestrebt wird, die entsprechende Säure der Formel I, worin Rc für Hydroxy steht, oder ein reaktives Derivat derselben, verestert unter Verwendung einer üblichen Verfahrensweise; wenn eine Verbindung der Formel I, worin Rc für (1-6C)Alkansulfonamido steht, angestrebt wird, die entsprechende Säure der Formel I, worin Rc für Hydroxy steht, mit dem geeigneten (1-6C)Alkansulfonamid in Gegenwart eines Dehydratisierungsmittels umgesetzt oder ein reaktives Derivat der Säure der Formel I mit dem geeigneten (1-6C)Alkansulfonamid oder einem Alkalimetallsalz desselben umgesetzt; wenn eine Verbindung der Formel I, worin A für Ethylen steht, angestrebt wird, die entsprechende Verbindung der Formel I, worin A für Vinylen steht, in Gegenwart eines Katalysators hydriert; wenn ein Salz einer Verbindung der Formel I, worin Rc für Hydroxy steht, angestrebt wird, diese Verbindung mit der geeigneten Base, welche ein physiologisch verträgliches Kation liefert, umgesetzt; und wenn eine optisch aktive Form einer Verbindung der Formel I angestrebt wird, eine der angegebenen Verfahrensweisen unter Verwendung eines optisch aktiven Ausgangsmaterials durchführt oder eine racemische Form eine Verbindung der Formel I, worin Rc für Hydroxy steht, mit einer optisch aktiven Form einer geeigneten organischen Base umgesetzt, mit nachfolgender Trennung des auf diese Weise erhaltenen diastereoisomeren Gemisches von Salzen und Freisetzung der gewünschten optisch aktiven Form der Verbindung der Formel I durch Behandlung mit Säure, gefolgt von einer Veresterung oder Amidierung wie oben angegeben, wenn Rc für einen anderen Rest als Hydroxy steht.



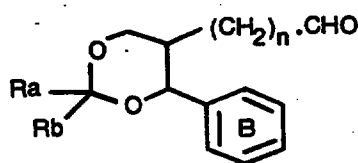
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines 4-Phenyl-1,3-dioxan-cis-5-ylalkensäure-Derivats der Formel I



worin Ra und Rb unabhängig voneinander für Wasserstoff, (2-6C)Alkenyl, (1-8C)Alkyl, das gegebenenfalls bis zu drei Halogensubstituenten trägt, Pentafluorophenyl, Aryl oder Aryl(1-4C)alkyl stehen, wobei die beiden letztgenannten Reste gegebenenfalls bis zu drei Substituenten, ausgewählt aus Halogen, (1-6C)Alkyl, (1-6C)Alkoxy, (1-4C)Alkylendioxy, Trifluoromethyl, Cyano, Nitro, Hydroxy, (2-4C)Alkanoyloxy, (1-6C)Alkylthio, (1-6C)Alkansulfonyl, (1-6C)Alkanoylamino und Oxapolymermethylen mit 2 bis 4 Kohlenstoffatomen, tragen können, wobei gilt, daß dann, wenn beide Reste Ra und Rb Alkyl oder Alkenyl bedeuten, die Gesamtzahl der Kohlenstoffatome in Ra und Rb zusammengekommen 8 oder weniger beträgt; oder Ra und Rb zusammen Polymethylen mit 2 bis 7 Kohlenstoffatomen bilden, das gegebenenfalls einen oder zwei (1-4C)Alkyl-Substituenten trägt; Rc für Hydroxy, (1-6C)Alkoxy oder (1-6C)Alkansulfonamido steht; n für die ganze Zahl 1 oder 2 steht; A für Ethylen oder Vinylen steht; Y für Polymethylen mit 2 bis 5 Kohlenstoffatomen steht, das gegebenenfalls (1-4C)Alkyl als einen Substituenten trägt; der Benzolring B gegebenenfalls einen oder zwei Substituenten, ausgewählt aus Halogen, (1-6C)Alkyl, (1-6C)Alkoxy, Hydroxy, (2-6C)Alkanoyloxy, (1-6C)Alkanoylamino, Trifluoromethyl und Nitro, trägt; und die Substituenten in Stellung 4 und 5 des Dioxanringes relativ zueinander cis-Stereochemie aufweisen; oder im Falle derjenigen Verbindungen, in denen Rc für Hydroxy steht, ein Salz desselben mit einer Base, die ein physiologisch verträgliches Kation liefert, dadurch gekennzeichnet, daß man

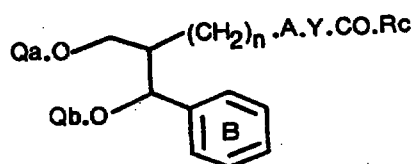
(a) für eine Verbindung, worin Rc für Hydroxy und A für Vinylen stehen, einen Aldehyd der Formel II



mit einem Wittig-Reagenz der Formel III

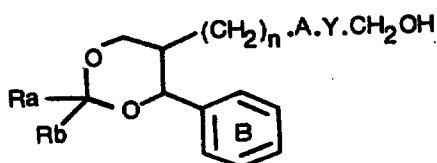


worin Rd für (1-6C)Alkyl oder Aryl steht und M⁺ für ein Alkalimetall-Kation steht, umsetzt;
(b) ein erythro-Diolderivat der Formel XIII



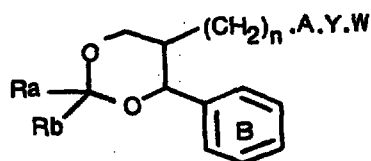
worin einer der Reste Qa und Qb für Wasserstoff steht und der andere für Wasserstoff, Alkansulfonyl, Arensulfonyl oder eine Gruppe der Formel -CRR'.OH steht, worin R und R' das gleiche oder ein unterschiedliches Alkyl bedeuten, mit einer Carbonylverbindung der Formel RaRb.CO oder einem Acetal, Hemiacetal oder Hydrat derselben umsetzt;

(c) für eine Verbindung der Formel I, worin Rc für Hydroxy steht, einen Alkohol der Formel XVI



oxidiert;

(d) für eine Verbindung der Formel I, worin Rc für Hydroxy steht, eine Verbindung der Formel XVIII

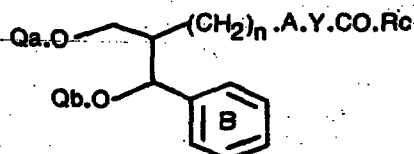


XVIII

worin W für Alkoxycarbonyl, Phenoxycarbonyl, Benzyloxycarbonyl, Cyano oder Carbamoyl steht, hydrolysiert;

(e) für eine Verbindung der Formel I, worin Ra, Rb oder der Benzolring B einen Hydroxy-Substituenten tragen, ein entsprechendes Derivat dieser Verbindung, worin der Hydroxy-Substituent durch eine Trimethylsilyl-, (1-6C)Alkyl- oder Acyl-Schutzgruppe geschützt ist, von der Schutzgruppe befreit;

(f) für eine Verbindung der Formel I, worin Ra und Rb beide für Wasserstoff stehen, ein erythro-Diol der Formel XIII



XIII

worin Qa und Qb beide für Wasserstoff stehen, mit Methylenbromid in Gegenwart einer Base umsetzt; wobei Ra, Rb, Rc, der Benzolring B, n, A und Y die oben angegebene Bedeutung haben; worauf man, wenn eine Verbindung der Formel I, worin Rc für (1-6C)-Alkoxy steht, angestrebt wird, die entsprechende Säure der Formel I, worin Rc für Hydroxy steht, oder ein reaktives Derivat derselben, verestert unter Verwendung einer üblichen Verfahrensweise; wenn eine Verbindung der Formel I, worin Rc für (1-6C)Alkansulfonamido steht, angestrebt wird, die entsprechende Säure der Formel I, worin Rc für Hydroxy steht, mit dem geeigneten (1-6C)Alkansulfonamid in Gegenwart eines Dehydratisierungsmittels umsetzt oder ein reaktives Derivat der Säure der Formel I mit dem geeigneten (1-6C)Alkansulfonamid oder einem Alkalimetallsalz desselben umsetzt; wenn eine Verbindung der Formel I, worin A für Ethylen steht, angestrebt wird, die entsprechende Verbindung der Formel I, worin A für Vinylen steht, in Gegenwart eines Katalysators hydriert; wenn ein Salz einer Verbindung der Formel I, worin Rc für Hydroxy steht, angestrebt wird, diese Verbindung mit der geeigneten Base, welche ein physiologisch verträgliches Kation liefert, umsetzt; und wenn eine optisch aktive Form einer Verbindung der Formel I angestrebt wird, eine der angegebenen Verfahrensweisen unter Verwendung eines optisch aktiven Ausgangsmaterials durchführt oder eine racemische Form einer Verbindung der Formel I, worin Rc für Hydroxy steht, mit einer optisch aktiven Form einer geeigneten organischen Base umsetzt, mit nachfolgender Trennung des auf diese Weise erhaltenen diastereoisomeren Gemisches von Salzen und Freisetzung der gewünschten optisch aktiven Form der Verbindung der Formel I durch Behandlung mit Säure, gefolgt von einer Veresterung oder Amidierung wie oben angegeben, wenn Rc für einen anderen Rest als Hydroxy steht.

2. Verfahren nach Teil (a) des Anspruchs 1, dadurch gekennzeichnet, daß die Umsetzung in einem Lösungs- oder Verdünnungsmittel, wie einem aromatischen Lösungsmittel, einem Ether oder einem Gemisch aus einem oder mehreren derartiger Lösungs- oder Verdünnungsmittel bei einer Temperatur im Bereich von -80 bis 40°C durchgeführt wird.

3. Verfahren nach Teil (b) des Anspruchs 1, dadurch gekennzeichnet, daß Qa und Qb beide für Wasserstoff stehen oder einer der Reste für eine Gruppe der Formel $-CRR^1.OH$ und der andere für Wasserstoff steht und die Umsetzung in Gegenwart eines Säure-Katalysators in einem Lösungs- oder Verdünnungsmittel wie einem Ether und bei einer Temperatur im Bereich von 10 bis 120°C durchgeführt wird.

4. Verfahren nach Teil (b) des Anspruchs 1, dadurch gekennzeichnet, daß das Ausgangsmaterial der Formel XIII, worin Qa und Qb für einen anderen Rest als Alkansulfonyl oder Arensulfonyl stehen, in situ erzeugt wird durch Umsetzung einer Verbindung der Formel I, worin Ra und Rb beide für Methyl oder Ethyl stehen, in Gegenwart eines Säure-Katalysators.

5. Verfahren nach Teil (c) des Anspruchs 1, dadurch gekennzeichnet, daß in einem Lösungs- oder Verdünnungsmittel bei einer Temperatur im Bereich von 10 bis 50°C gearbeitet wird.

6. Verfahren nach Teil (d) des Anspruchs 1, dadurch gekennzeichnet, daß unter dem Einfluß von Base in einem wäßrigen Lösungsmittel wie einem (1-4C)Alkanol oder einem Glycol und bei einer Temperatur im Bereich von 15 bis 150°C gearbeitet wird.

7. Verfahren nach Teil (e) des Anspruchs 1, dadurch gekennzeichnet, daß das Ausgangsmaterial eine



Verbindung der Formel I, worin Ra, Rb oder der Benzolring B einen (1-6C)Alkoxyrest trägt, ist und die Umsetzung unter Verwendung von Natriumthioethoxid in einem Lösungsmittel wie N,N-Dimethylformamid bei einer Temperatur im Bereich von 90 bis 160°C durchgeführt wird.

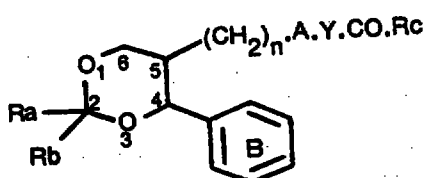
8. Verfahren nach Teil (f) des Anspruchs 1, dadurch gekennzeichnet, daß die Base ein Alkalimetallhydroxid oder -hydrid ist und die Umsetzung in einem Lösungs- oder Verdünnungsmittel wie Dimethylsulfoxid bei einer Temperatur im Bereich von 10 bis 40°C durchgeführt wird.

9. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß in den Ausgangsmaterialien:

- (i) Ra und Rb beide für Wasserstoff, Methyl, Ethyl, Propyl, Butyl oder Trifluoromethyl stehen;
 - (ii) Ra und Rb zusammen Trimethylen, Tetramethylen, Pentamethylen, Hexamethylen oder eine Gruppe der Formel $-\text{CH}_2\text{CH}_2\text{CHCH}_3\text{CH}_2\text{CH}_2-$ bilden; oder
 - (iii) Ra für (3-8C)Alkyl, Trifluoromethyl, Chloromethyl, 2-Chloroethyl, Pentafluorophenyl oder für Phenyl, Benzyl oder Naphthyl steht, wobei die letztgenannten drei Reste gegebenenfalls 1 oder 2 Halogen-, (1-4C)Alkyl-, (1-4C)Alkoxy-, Trifluoromethyl-, Hydroxy-, Cyano-, (1-4C)Alkylthio- oder (1-4C)Alkanoylamino-Substituenten, oder einen Methylendioxy- oder Methylenoxymethylen-Substituenten tragen können, und Rb für Wasserstoff steht;
- der Benzolring B unsubstituiert ist oder für 2-Halogen-, 2-(1-4C)Alkyl-, 2-(1-4C)Alkoxy-, 2-Hydroxy- oder 3-Halogenphenyl steht; n für die ganze Zahl 1 steht; Y für Trimethylen steht; und A für Vinylen steht, wobei die zu dieser Gruppe benachbarten Kohlenstoffatome relativ cis-Stereochemie aufweisen.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Dérivé d'acide 4-phényl-1,3-dioxanne-*cis*-5-ylalcénoïque de formule I:



dans laquelle Ra et Rb représentent, indépendamment, l'hydrogène, un groupe alcényle en C₂ à C₆, alkyle en C₁ à C₆ portant éventuellement jusqu'à trois substituants halogéno, un groupe pentafluorophényle, aryle ou aryl(alkyle en C₁ à C₄), ces deux derniers groupes pouvant porter facultativement jusqu'à trois substituants choisis entre des radicaux halogéno, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, alkylènedioxy en C₁ à C₄, trifluorométhyle, cyano, nitro, hydroxy, alcanoyloxy en C₂ à C₆, alkylthio en C₁ à C₆, alcanesulfonyle en C₁ à C₆, alcanoylamino en C₁ à C₆ et oxapoly-méthylène de 2 à 4 atomes de carbone, sous réserve que lorsque Ra et Rb sont tous deux un groupe alkyle ou alcényle, le nombre total d'atomes de carbone dans Ra et Rb pris ensemble soit égal ou inférieur à 8; ou bien Ra et Rb forment conjointement un groupe polyméthylène de 2 à 7 atomes de carbone, portant facultativement un ou deux substituants alkyle en C₁ à C₄; Rc est un groupe hydroxy, alkoxy en C₁ à C₆ ou alcanesulfamido en C₁ à C₆, n est le nombre entier 1 ou 2; A est un groupe éthylène ou vinylène; Y est un groupe polyméthylène de 2 à 5 atomes de carbone portant facultativement un groupe alkyle en C₁ à C₄ comme substituant; le noyau benzénique B porte facultativement un ou deux substituants choisis entre des radicaux halogéno, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, hydroxy, alcanoyloxy en C₂ à C₆, alcanoylamino en C₁ à C₆, trifluorométhyle et nitro; et les substituants en positions 4 et 5 du noyau de dioxanne ont la stéréochimie relative *cis*; ou pour les composés dans lesquels Rc est un groupe hydroxy, un sel de ce groupe avec une base apportant un cation physiologiquement acceptable.

2. Composé suivant la revendication 1, dans lequel Ra et Rb représentent, indépendamment, l'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle, pentyle, hexyle, heptyle, octyle, vinyle, allyle, 2-méthylallyle, chlorométhyle, trifluorométhyle ou 2,2,2-trifluoréthyle, pentafluorophényle, 1-naphtyle, 2-naphtyle, benzyle, 1-phényléthyle, 2-phényléthyle ou phényle, les six derniers de ces groupes pouvant facultativement porter jusqu'à trois substituants choisis entre des radicaux fluoro, chloro, bromo, iodo, méthyle, éthyle, propyle, isopropyle, méthoxy, éthoxy, propoxy, méthylènedioxy, éthylènedioxy, isopropylidènedioxy, trifluorométhyle, cyano, nitro, méthylthio, éthylthio, méthanesulfonyle, éthanesulfonyle, formamido, acétamido, propionamido, hydroxy, acétoxy, propionyloxy, méthylèneoxyméthylène et éthylèneoxyméthylène; sous réserve que lorsque Ra et Rb sont chacun un groupe alkyle ou alcényle, le nombre total d'atomes de carbone de Ra et Rb pris ensemble soit égal ou inférieur à 8; ou bien Ra et Rb constituent conjointement un groupe éthylène, triméthylène, tétraméthylène, pentaméthylène ou hexaméthylène, chacun d'eux pouvant porter un substituant méthyle facultatif; Rc est un groupe hydroxy, méthoxy, éthoxy, méthanesulfamido, éthanesulfamido ou 1-méthyléthanesulfamido; n est le nombre entier 1 ou 2; A est un groupe éthylène ou vinylène; Y est un groupe éthylène, triméthylène ou tétraméthylène, l'un quelconque de ces groupes pouvant facultativement



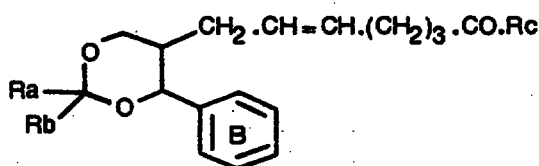
porter un substituant méthyle; et le noyau benzénique B porte facultativement un ou deux substituants choisis entre des radicaux fluoro, chloro, bromo, iodo, méthyle, éthyle, isopropyle, propyle, méthoxy, éthoxy, propoxy, hydroxy, acétoxy, propionyloxy, formamido, acétamido, propionamido, trifluorométhyle et nitro.

3. Composé suivant la revendication 1 ou 2, dans lequel Ra et Rb représentent, indépendamment, l'hydrogène, un groupe méthyle, éthyle, propyle, isopropyle, butyle, pentyle, hexyle, octyle, vinyle, allyle, 2-méthylallyle, trifluorométhyle, chlorométhyle, 2-chloréthyle, phényle portant facultativement un substituant fluoro, chloro, bromo, méthyle, méthoxy, trifluorométhyle, méthylthio, méthanesulfonyl, nitro, hydroxy, cyano, acétamido, méthylènedioxy ou un substituant méthylèneoxyméthylène ($-\text{CH}_2\text{OCH}_2-$), dichlorophényle, diméthylphényle, pentafluorophényle, 1-naphtyle, 2-naphtyle ou benzyle; ou forment conjointement un groupe triméthylène, pentaméthylène ou hexaméthylène portant facultativement un substituant méthyle; sous réserve que lorsque Ra et Rb représentent chacun un groupe alkyle ou alcényle, le nombre total d'atomes de carbone dans Ra et Rb pris conjointement soit égal ou inférieur à 8; et le noyau benzénique B est un groupe phényle, 2-méthylphényle, 2-éthylphényle, 2-isopropylphényle, 2-méthoxyphényle, 2-fluorophényle, 2-chlorophényle, 2-bromophényle, 2-hydroxyphényle, 2-trifluorométhylphényle, 3-trifluorométhylphényle, 3-fluorophényle, 3-chlorophényle, 4-fluorophényle, 4-méthylphényle ou 2,6-difluorophényle.

4. Composé suivant la revendication 1, 2 ou 3, dans lequel le noyau benzénique B n'est pas substitué; il est substitué en *ortho* par un radical fluoro, chloro, méthyle, hydroxy, méthoxy, éthyle ou isopropyle, ou substitué en *méta* par un radical fluoro ou chloro.

5. Composé suivant l'une quelconque des revendications 1 à 4, dans lequel Rc est un groupe hydroxy, méthoxy, éthoxy, méthanesulfamido ou éthanesulfamido.

6. Dérivé d'acide 7-(4-phényl-1,3-dioxanne-*cis*-5-yl)hepténoïque de formule Ia:



Ia

dans laquelle Ra et Rb représentent:

(i) indépendamment, l'hydrogène ou un groupe alkyle en C₁ à C₄ portant facultativement 1 à 3 substituants halogéno;

(ii) l'un des deux est un atome d'hydrogène ou un groupe alkyle en C₁ à C₄ et l'autre est un groupe phényle, naphtyle ou phényl-(alkyle en C₁ à C₄) portant facultativement 1 ou 2 substituants choisis entre des radicaux halogéno, alkyle en C₁ à C₄, alkoxy en C₁ à C₄, alkylènedioxy en C₁ à C₄, trifluorométhyle, cyano, nitro, hydroxy, alcanoyloxy en C₂ à C₄, alkylthio en C₁ à C₄, alcanesulfonyl en C₁ à C₄, alcanoylamino en C₁ à C₄ et oxapolyméthylène ayant 2 à 4 atomes de carbone, ou pentafluorophényle;

(iii) l'un des deux est un atome d'hydrogène et l'autre est un groupe alkyle en C₅ à C₈ ou alcényle en C₂ à C₆; ou bien

(iv) tous deux forment un groupe polyméthylène de 2 à 7 atomes de carbone portant facultativement un substituant alkyle en C₁ à C₄;

Rc est un groupe hydroxy, alkoxy en C₁ à C₄ ou alcanesulfamido en C₁ à C₄; et le noyau benzénique B porte facultativement un unique substituant se trouvant en position 2, choisi entre des substituants halogéno, alkyle en C₁ à C₄, alkoxy en C₁ à C₄, hydroxy, alcanoyloxy en C₂ à C₄, alcanoylamino en C₁ à C₄ et trifluorométhyle, ou porte un substituant 3-halogéno; et les substituants en positions 4 et 5 du noyau de dioxanne ont une stéréochimie relative *cis*; ou bien pour les composés dans lesquels Rc est un groupe hydroxy, leur sel avec une base apportant un cation physiologiquement acceptable.

7. Composé suivant la revendication 6, dans lequel:

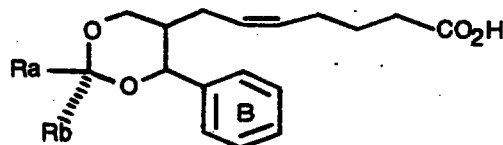
(i) Ra et Rb représentent chacun l'hydrogène ou un groupe méthyle, éthyle, propyle, butyle ou trifluorométhyle;

(ii) l'un de Ra et Rb est l'hydrogène et l'autre est un groupe trifluorométhyle, chlorométhyle, benzyle, isopropyle, hexyle, octyle, phényle (portant facultativement 1 ou 2 radicaux fluoro, chloro, bromo, méthyle, méthoxy, trifluorométhyle, hydroxy, cyano, méthylthio ou acétamido), phényle portant un groupe méthylènedioxy ou méthylèneoxyméthylène ($-\text{CH}_2\text{OCH}_2-$), pentafluorophényle, 1-naphtyle ou 2-naphtyle; ou bien

(iii) Ra et Rb forment ensemble un groupe triméthylène, tétraméthylène, pentaméthylène, hexaméthylène ou un groupe de formule $-\text{CH}_2\text{CH}_2\text{CHCH}_3\text{CH}_2\text{CH}_2-$; et le noyau benzénique B est un groupe phényle, 2-fluorophényle, 2-chlorophényle, 2-bromophényle, 2-méthylphényle, 2-éthylphényle, 2-isopropylphényle, 2-méthoxyphényle, 2-hydroxyphényle, 3-fluorophényle ou 3-chlorophényle; et Rc est un groupe hydroxy, méthanesulfamido ou éthanesulfamido.

8. Acide 5(Z)-7-(4-phényl-1,3-dioxanne-*cis*-5-yl)hepténoïque de formule Ib:





Ib

dans laquelle:

(i) Ra et Rb représentent chacun l'hydrogène ou un groupe méthyle, éthyle, propyle, butyle, ou trifluorométhyle;

(ii) Ra et Rb forment ensemble un groupe triméthylène, tétraméthylène, pentaméthylène, hexaméthylène ou un groupe de formule:



ou bien

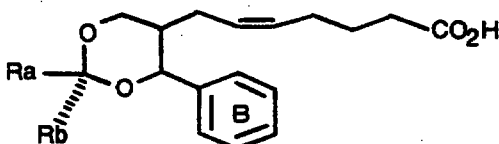
(iii) Ra est un groupe alkyle en C₃ à C₈, trifluorométhyle, chlorométhyle, 2-chloréthyle, pentafluorophényle, ou phényle, benzyle ou naphthyle, ces trois derniers groupes pouvant facultativement porter un ou deux radicaux halogéno, alkyle en C₁ à C₄, alkoxy en C₁ à C₄, trifluorométhyle, hydroxy, cyano, alkylthio en C₁ à C₄ ou alcanoylamino en C₁ à C₄, ou un substituant méthylènedioxy ou méthylèneoxyméthylène, et Rb est l'hydrogène;

le noyau benzénique B n'est pas substitué ou est un groupe 2-halogéno-, 2-(alkyle en C₁ à C₄)-, 2-(alkoxy en C₁ à C₄)-, 2-hydroxy ou 3-halogéno-phényle;

Ra et les substituants en positions 4 et 5 du noyau de dioxanne ont une stéréochimie relative *cis*; et les atomes de carbone adjacents au groupe vinyliène ont la stéréochimie relative *cis* indiquée; ou un sel de ce composé avec une base apportant un cation physiologiquement acceptable; ou un ester de méthyle ou d'éthyle de ce composé; ou un dérivé méthanesulfamido, éthanesulfamido ou 1-méthyléthanesulfamido de ce composé.

9. Composé suivant la revendication 8, dans lequel Ra et Rb ont les définitions données en (i) et (ii) dans la revendication 8; ou bien Ra est un groupe isopropyle, butyle, hexyle, octyle, trifluorométhyle, chlorométhyle, 2-chloréthyle, pentafluorophényle, benzyle naphthyle ou phényle (portant éventuellement 1 ou 2 substituants fluoro, chloro, bromo, méthyle, méthoxy, trifluorométhyle, hydroxy, cyano, méthylthio ou acétamido ou portant un substituant méthylènedioxy ou méthylèneoxyméthylène), et Rb est l'hydrogène; et le noyau benzénique B n'est pas substitué ou porte un substituant 2-fluoro, 2-chloro, 2-bromo, 3-fluoro, 3-chloro, 2-méthyle, 2-éthyle, 2-isopropyle, 2-méthoxy ou 2-hydroxy.

10. Acide 5(Z)-7-(4)-phényle-1,3-dioxanne-*cis*-5-yl)hepténoïque de formule Ib:



Ib

dans laquelle Ra, Rb et le noyau benzénique B sont choisis parmi les combinaisons suivantes:





N°	Ra	Rb	Noyau benzénique B
1	méthyle	méthyle	3-fluorophényle
2	méthyle	méthyle	3-chlorophényle
3	méthyle	méthyle	2-méthoxyphényle
4	méthyle	méthyle	2-méthylphényle
5	méthyle	H	phényle
6	trifluorométhyle	H	phényle
7	isopropyle	H	phényle
8	éthyle	éthyle	phényl
9	éthyle	éthyle	2-fluorophényle
10	2-chlorophényle	H	phényle
11	2-méthylphényle	H	phényle
12	2-éthylphényle	H	phényle
13	3-fluorophényle	H	phényle
14	3-chlorophényle	H	phényle
15	3-méthylthiophényle	H	phényle
16	4-fluorophényle	H	phényle
17	4-chlorophényle	H	phényle
18	4-méthoxyphényle	H	phényle
19	3,4-méthylène-dioxyphényle	H	phényle
20	3,4-(méthylène-oxyméthylène)-phényle	H	phényle
21	méthyle	méthyle	2-hydroxyphényle

(H représentant l'hydrogène); et parmi les combinaisons suivantes:

N°	Ra + Rb	Noyau benzénique B
22	pentaméthylène	phényle
23	hexaméthylène	phényle
24	(3-méthyl)pentaméthylène	phényle

ou un sel de ce composé avec une base apportant un cation physiologiquement acceptable.

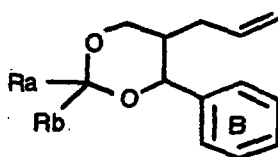
11. Sel suivant l'une quelconque des revendications précédentes, qui est un sel de métal alcalin, de



métal alcalino-terreux, d'aluminium ou d'ammonium ou un sel avec une amine organique ou une base quaternaire formant un cation physiologiquement acceptable.

12. Dérivé méthanesulfamido d'un acide suivant la revendication 10 ou de l'acide 5(Z)-7-(2,2-diméthyl-4-phényl-1,3-dioxanne-*cis*-5-yl)hepténoïque.

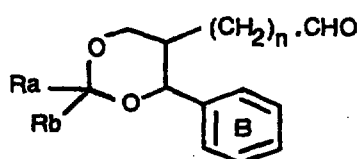
13. Dérivé de 5-allyl-5-phényl-1,3-dioxanne de formule VII:



VII

dans laquelle Ra, Rb et le noyau benzénique B ont l'une quelconque des définitions données dans les revendications 1 à 10, et les substituants en positions 4 et 5 du noyau de dioxanne ont la stéréochimie relative *cis*.

14. Dérivé (4-phényl-1,3-dioxanne-*cis*-5-yl)acétaldéhydique de formule (II):



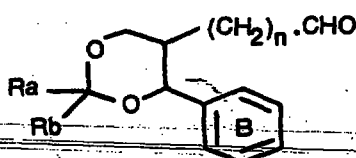
II

dans laquelle *n* est le nombre entier 1, et Ra, Rb et le noyau benzénique B ont l'une quelconque des définitions données dans les revendications 1 à 10, et les substituants en positions 4 et 5 du noyau de dioxanne ont la stéréochimie relative *cis*.

15. Composition pharmaceutique qui comprend un composé de formule I, ou un sel de ce composé suivant l'une quelconque des revendications 1 à 12, conjointement avec un diluant ou support acceptable du point de vue pharmaceutique.

16. Procédé de production d'un composé de formule I ou d'un sel de ce composé, suivant la revendication 1, formé dans laquelle Ra, Rb, Rc, le noyau benzénique B, *n*, A et Y ont l'une quelconque des définitions données dans les revendications 1 à 10, caractérisé par:

(a) pour un composé dans lequel Rc est un groupe hydroxy et A est un groupe vinyène, la réaction d'un aldéhyde de formule II:



II

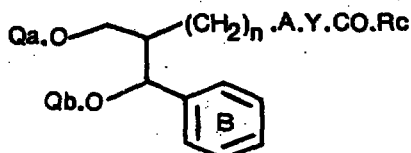
avec un réactif de Wittig de formule:



III

dans laquelle Rd est un groupe alkyle en C₁ à C₆ ou aryle et M⁺ est un cation de métal alcalin;

(b) la réaction d'un dérivé *erythro*-diol de formule XIII:



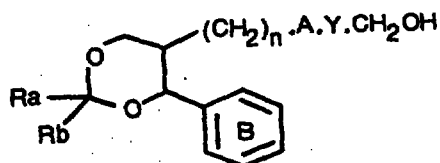
XIII

dans laquelle l'un de Qa et Qb est l'hydrogène et l'autre est l'hydrogène, un groupe alcanesulfonyle, arènesulfonyle ou un groupe de formule —CRR¹.OH dans laquelle R et R¹ sont des groupes alkyle identiques ou différents, avec un composé carbonyle de formule RaRb.CO ou son acétal, son hémicétal ou son hydrate;



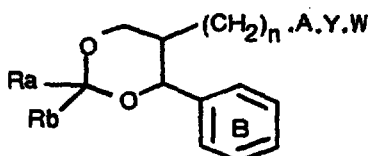


(c) pour un composé de formule I dans laquelle Rc est un groupe hydroxy, l'oxydation d'un alcool de formule XVI:



XVI

(d) pour un composé de formule I dans laquelle Rc est un groupe hydroxy, l'hydrolyse d'un composé de formule XVIII:

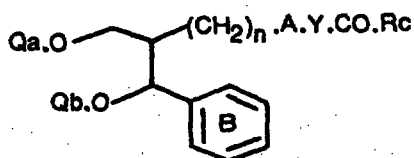


XVIII

dans laquelle W est un groupe alkoxycarbonyle, phénoxycarbonyle, benzyloxycarbonyle, cyano ou carbamoyle;

(e) pour un composé de formule I dans laquelle Ra, Rb ou le noyau benzénique B porte un substituant hydroxy, l'élimination de la protection d'un dérivé correspondant dudit composé dans lequel le substituant hydroxy est protégé par un groupe triméthylsilyle, alkyle en C₁ à C₆ ou acyle;

(f) pour un composé de formule I dans laquelle Ra et Rb sont tous deux de l'hydrogène, la réaction d'un érythro-diol de formule XIII:



XIII

dans laquelle Qa et Qb sont tous deux de l'hydrogène, avec le bromure de méthylène en présence d'une base;

après quoi: lorsqu'on désire un composé de formule I dans laquelle Rc est un groupe alkoxy en C₁ à C₆, l'acide correspondant de formule I dans laquelle Rc est un groupe hydroxy ou un dérivé réactif de cet acide, est estérifié en utilisant un procédé classique;

lorsqu'un composé de formule I dans laquelle Rc est un groupe alcanesulfamido en C₁ à C₆ est désiré, on fait réagir l'acide correspondant de formule I dans laquelle Rc est un groupe hydroxy avec l'alcanesulfamide en C₁ à C₆ approprié en présence d'un agent déshydratant, ou bien on fait réagir un dérivé réactif dudit acide de formule I avec l'alcanesulfamide en C₁ à C₆ approprié ou un sel de métal alcalin de ce composé;

lorsqu'on désire un composé de formule I dans laquelle A est un groupe éthylène, on hydrogène le composé correspondant de formule I dans laquelle A est un groupe vinyène en présence d'un catalyseur;

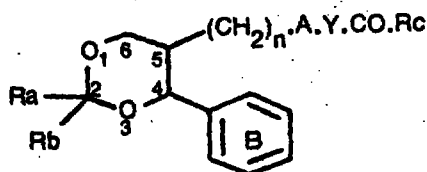
lorsqu'on désire un sel d'un composé de formule I dans laquelle Rc est un groupe hydroxy, on fait réagir ledit composé avec la base appropriée apportant un cation physiologiquement acceptable; et

lorsqu'on désire une forme optiquement active d'un composé de formule I, on conduit l'un des modes opératoires ci-dessus en utilisant une matière de départ optiquement active, ou bien on fait réagir une forme racémique d'un composé de formule I dans laquelle Rc est un groupe hydroxy avec une forme optiquement active d'une base organique convenable, la réaction étant suivie de la séparation du mélange diastéréoisomérique de sels ainsi obtenus et de la libération de la forme optiquement active dérivée dudit composé de formule I par traitement avec un acide, suivi, lorsque Rc est autre chose qu'un groupe hydroxy, d'une estérification ou d'une amidation comme ci-dessus.



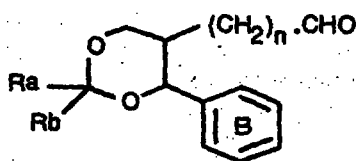
Revendications pour l'Etat contractant: AT

1. Procédé de production d'un dérivé d'acide 4-phényl-1,3-dioxanne-*cis*-5-ylalcénoïque de formule I

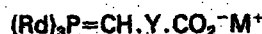


dans laquelle Ra et Rb représentent, indépendamment, l'hydrogène, un groupe alcényle en C₂ à C₆, alkyle en C₁ à C₆ portant éventuellement jusqu'à trois substituants halogéno, un groupe pentafluorophényle, aryle ou aryl(alkyle en C₁ à C₄), ces deux derniers groupes pouvant porter facultativement jusqu'à trois substituants choisis entre des radicaux halogéno, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, alkylènedioxy en C₁ à C₄, trifluorométhyle, cyano, nitro, hydroxy, alcanoyloxy en C₂ à C₆, alkylthio en C₁ à C₆, alcanesulfonyle en C₁ à C₆, alcanoylamino en en C₁ à C₆ et oxapolyméthylène de 2 à 4 atomes de carbone, sous réserve que lorsque Ra et Rb sont tous deux un groupe alkyle ou alcényle, le nombre total d'atomes de carbone dans Ra et Rb pris ensemble soit égal ou inférieur à 8; ou bien Ra et Rb forment conjointement un groupe polyméthylène de 2 à 7 atomes de carbone, portant facultativement un ou deux substituants alkyle en en C₁ à C₄; Rc est un groupe hydroxy, alkoxy en C₁ à C₆ ou alcanesulfamido en C₁ à C₆, n est le nombre entier 1 ou 2; A est un groupe éthylène ou vinyène; Y est un groupe polyméthylène de 2 à 5 atomes de carbone portant facultativement un groupe alkyle en C₁ à C₄ comme substituant; le noyau benzénique B porte facultativement un ou deux substituants choisis entre des radicaux halogéno, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, hydroxy, alcanoyloxy en C₂ à C₆, alcanoylamino en C₁ à C₆, trifluorométhyle et nitro; et les substituants en positions 4 et 5 du noyau de dioxanne ont la stéréochimie relative *cis*; ou pour les composés dans lesquels Rc est un groupe hydroxy, un sel de ce groupe avec une base apportant un cation physiologiquement acceptable; caractérisé par:

(a) pour un composé dans lequel Rc est un groupe hydroxy et A est un groupe vinyène, la réaction d'un aldéhyde de formule II:

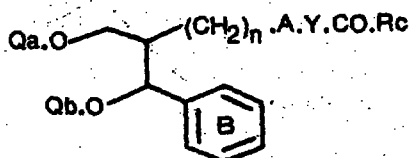


avec un réactif de Wittig de formule:



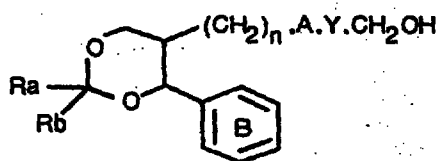
dans laquelle Rd est un groupe alkyle en C₁ à C₆ ou aryle et M⁺ est un cation de métal alcalin;

(b) la réaction d'un dérivé *érythro*-diol de formule XIII:

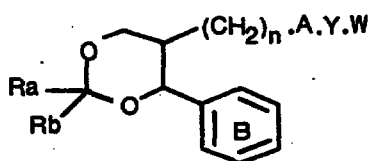


dans laquelle l'un de Qa et Qb est l'hydrogène et l'autre est l'hydrogène, un groupe alcanesulfonyle, arènesulfonyle ou un groupe de formule -CRR'.OH dans laquelle R et R' sont des groupes alkyle identiques ou différents, avec un composé carbonyle de formule RaRb.CO ou son acétal, son hémiacétal ou son hydrate;

(c) pour un composé de formule I dans laquelle Rc est un groupe hydroxy, l'oxydation d'un alcool de formule XVI:



(d) pour un composé de formule I dans laquelle Rc est un groupe hydroxy, l'hydrolyse d'un composé de formule XVIII:

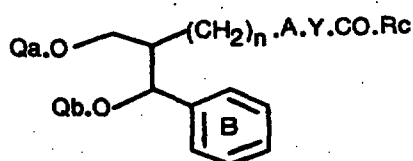


XVIII

dans laquelle W est un groupe alkoxycarbonyle, phénoxycarbonyle, benzyloxycarbonyle, cyano ou carbamoyle;

(e) pour un composé de formule I dans laquelle Ra, Rb ou le noyau benzénique B porte un substituant hydroxy, l'élimination de la protection d'un dérivé correspondant dudit composé dans lequel le substituant hydroxy est protégé par un groupe triméthylsilyle, alkyle en C₁ à C₆ ou acyle;

(f) pour un composé de formule I dans laquelle Ra et Rb sont tous deux de l'hydrogène, la réaction d'un érythro-diol de formule XIII:



XIII

dans laquelle Qa et Qb sont tous deux de l'hydrogène, avec le bromure de méthylène en présence d'une base;

dans laquelle Ra, Rb, Rc, le noyau benzénique B, n, A et Y ont les définitions données ci-dessus;

après quoi: lorsqu'on désire un composé de formule I dans laquelle Rc est un groupe alkoxy en C₁ à C₆, l'acide correspondant de formule I dans laquelle Rc est un groupe hydroxy ou un dérivé réactif de cet acide, est estérifié en utilisant un procédé classique;

lorsqu'un composé de formule I dans laquelle Rc est un groupe alcanesulfamido en C₁ à C₆ est dérisé, on fait réagir l'acide correspondant de formule I dans laquelle Rc est un groupe hydroxy avec l'alcanesulfamide en C₁ à C₆ approprié en présence d'un agent déshydratant, ou bien on fait réagir un dérivé réactif dudit acide de formule I avec l'alcanesulfamide en C₁ à C₆ approprié ou un sel de métal alcalin de ce composé;

lorsqu'on désire un composé de formule I dans laquelle A est un groupe éthylène, on hydrogène le composé correspondant de formule I dans laquelle A est un groupe vinyène en présence d'un catalyseur;

lorsqu'on désire un sel d'un composé de formule I dans laquelle Rc est un groupe hydroxy, on fait réagir ledit composé avec la base appropriée apportant un cation physiologiquement acceptable; et

lorsqu'on désire une forme optiquement active d'un composé de formule I, on conduit l'un des modes opératoires ci-dessus en utilisant une matière de départ optiquement active, ou bien on fait réagir une forme racémique d'un composé de formule I dans laquelle Rc est un groupe hydroxy avec une forme optiquement active d'une base organique convenable, la réaction étant suivie de la séparation du mélange diastéréoisomérique de sels ainsi obtenus et de la libération de la forme optiquement active désirée dudit composé de formule I par traitement avec un acide, suivi, lorsque Rc est autre chose qu'un groupe hydroxy, d'une estérification ou d'une amidation comme ci-dessus.

2. Procédé suivant la partie (a) de la revendication 1, caractérisé en ce que la réaction est conduite dans un solvant ou diluant tel qu'un solvant aromatique, un éther ou un mélange d'un ou plusieurs de ces solvants ou diluants, à une température comprise dans l'intervalle de -80 à 40°.

3. Procédé suivant la partie (b) de la revendication 1, caractérisé en ce que Qa et Qb sont tous deux de l'hydrogène ou bien l'un d'eux est un groupe de formule -CRR'.OH et l'autre est l'hydrogène, et la réaction est conduite en présence d'un catalyseur acide dans un solvant ou diluant tel qu'un éther et à une température comprise dans l'intervalle de 10 à 120°C.

4. Procédé suivant la partie (b) de la revendication 1, caractérisé en ce que la matière de départ de formule XIII dans laquelle Qa et Qb représentent autre chose qu'un groupe alcanesulfonyle ou arènesulfonyle est produite in situ par réaction d'un composé de formule I dans laquelle Ra et Rb sont tous deux un groupe méthyle ou éthyle, en présence d'un catalyseur acide.

5. Procédé suivant la partie (c) de la revendication 1, caractérisé en ce qu'il est mis en oeuvre dans un solvant ou diluant à une température comprise dans l'intervalle de 10 à 50°C.

6. Procédé suivant la partie (c) de la revendication 1, caractérisé en ce qu'il est mis en oeuvre sous l'influence d'une base dans un solvant aqueux tel qu'un alcool en C₁ à C₄ ou un glycol et à une température comprise dans l'intervalle de 15 à 150°C.

7. Procédé suivant la partie (e) de la revendication 1, caractérisé en ce que la matière de départ est un



composé de formule I dans laquelle Ra, Rb ou le noyau benzénique B porte un radical alkoxy en C₁ à C₆ et la réaction est conduite en utilisant le thio-éthylate de sodium dans un solvant tel que le N,N-diméthylformamide à une température comprise dans l'intervalle de 90 à 160°C.

8. Procédé suivant la partie (f) de la revendication 1, caractérisé en ce que la base est un hydroxyde ou un hydruide de métal alcalin et la réaction est conduite dans un solvant ou diluant tel que le diméthylsulfoxyde à une température comprise dans l'intervalle de 10 à 40°C.

9. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que dans les matières de départ:

(i) Ra et Rb sont tous deux de l'hydrogène ou un groupe méthyle, éthyle, propyle, butyle ou trifluorométhyle;

(ii) Ra et Rb forment conjointement un groupe triméthylène, tétraméthylène, pentaméthylène, hexaméthylène ou un groupe de formule:



ou bien

(iii) Ra est un groupe alkyle en C₃ à C₈, trifluorométhyle, chlorométhyle, 2-chloréthyle, pentafluorophényle, ou phényle, benzyle ou naphthyle, ces trois derniers groupes pouvant porter facultativement un ou deux substituants halogéno, alkyle en C₁ à C₄, alkoxy en C₁ à C₄, trifluorométhyle, hydroxy, cyano, alkylthio en C₁ à C₄ ou alcanoylamino en C₁ à C₄ ou un substituant méthylènedioxy ou méthylèneoxyméthylène et Rb est l'hydrogène; et

le noyau benzénique B n'est pas substitué ou est un groupe 2-halogéno-, 2-(alkyle en C₁ à C₄)-, 2-(alkoxy en C₁ à C₄)-, 2-hydroxy- ou 3-halogénophényle; n est le nombre entier 1; Y est le groupe triméthylène; et A est un groupe vinylène, les atomes de carbone adjacents à ce groupe ayant la stéréochimie relative *cis*.

