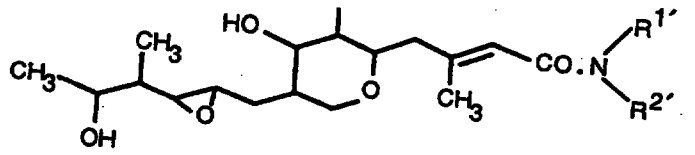
Description

The present invention relates to a class of compounds having antibacterial and/or antimycoplasmal activity, to processes for their production and to their use in human and veterinary medicine.

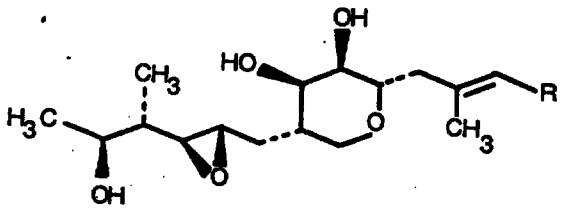
EP—A—0001914 discloses a carboxylic acid amide of formula (A):



(A)

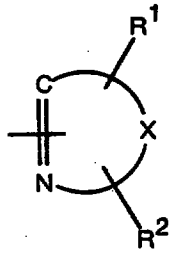
wherein $R^{1'}$ and $R^{2'}$ are the same or different and each represents (a) hydrogen or (b) C_{1-20} alkyl, C_{2-8} alkenyl, either of which may be optionally substituted with C_{3-7} cycloalkyl, halogen, carboxy, C_{1-8} alkoxycarbonyl, carbamyl, aryl, heterocyclyl, hydroxy, C_{1-6} alkanoyloxy, amino, mono- or di-(C_{1-6}) alkylamino; or (c) C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; or (d) aryl or (e) heterocyclyl; or (f) $R^{1'}$ and $R^{2'}$ together with the nitrogen atom to which they are attached represent C_{5-7} heterocyclic ring.

The present invention provides a compound of formula (I):



(I)

wherein R is a group



wherein

R is a group

R^1 and R^2 are the same or different and each is selected from:

a) hydrogen

b) phenyl or 5 or 6-membered heterocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur optionally substituted with a substituent selected from halogen, C_{1-6} alkoxy, hydroxy, carboxy, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6})alkyl carbamoyl, sulphamoyl, mono- or di(C_{1-6}) sulphamoyl, cyano, nitro, amino, mono- and di-(C_{1-6})alkylamino, C_{1-6} acylamino, ureido, C_{1-6} alkoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanesulphinyl, and C_{1-6} alkanesulphonyl,

c) C_{1-20}, C_{2-8} alkenyl or C_{2-8} alkynyl, optionally substituted with a substituent selected from halogen, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, mono- or di(C_{1-6})alkyl carbamoyl, sulphamoyl, mono- or di(C_{1-6})alkylsulphamoyl, amino, mono- and di-(C_{1-6})-alkylamino, C_{1-6} acylamino, ureido, C_{1-6} alkoxycarbonylamino, 2,2,2-trichloroethoxy carbonylamino, phenyl, a 5 or 6-membered heterocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, hydroxy, C_{1-6} alkoxy, oxo, 2-thenoyl, C_{1-6} alkylthio, C_{1-6} alkanesulphinyl, C_{1-6} alkanesulphonyl, hydroxyimino, hydrazono, benzohydroximoyl, and 2-thiophenecarbohydroximoyl, and

d) C_{3-7} cycloalkyl,

X is a divalent group —Y—C=C—, and

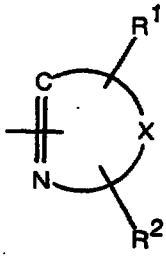
Y is oxygen or sulphur.

An exemplary heterocyclyl group is thienyl.

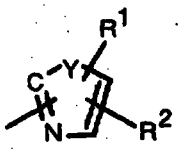
Compounds of formula (I) have a tri-substituted double bond and this may be in either the E or Z configuration giving rise to two geometrically isomeric forms. The present invention encompasses both such isomers individually and admixed in any proportions. In general, greater biological activity is associated with the E isomer and for this reason the E isomer is preferred.

Compounds of formula (I) having the E configuration have been named "1-normon-2-yl-heterocycles". The absolute stereochemistry of the 1-normon-2-yl radical is as shown in formula (I).

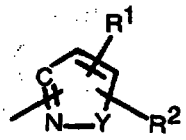
It will be appreciated that R, i.e. the group



represents the residues of four related heterocyclic systems, viz:



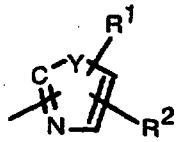
oxazoles and thiazoles and



isoxazoles and isothiazoles.

All these are encompassed by the invention.

Preferably R is a group



Preferably Y is oxygen.

Preferably R^1 and R^2 are different and more preferably R^2 is hydrogen.

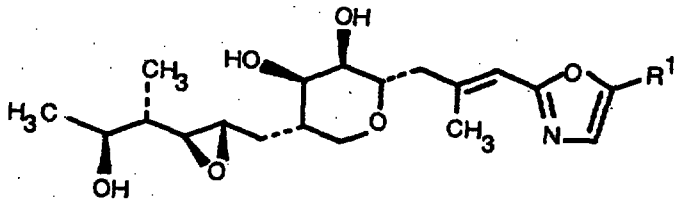
Most preferably R is substituted or unsubstituted oxazolyl.

The 1-normon-2-yl moiety may be bonded to any carbon atoms or R, but preferably it is bonded to a carbon atom adjacent the nitrogen atom.

Most preferably the group R is substituted or unsubstituted 2-oxazolyl.

Preferably R^1 is bonded to a carbon atom adjacent to the atom Y.

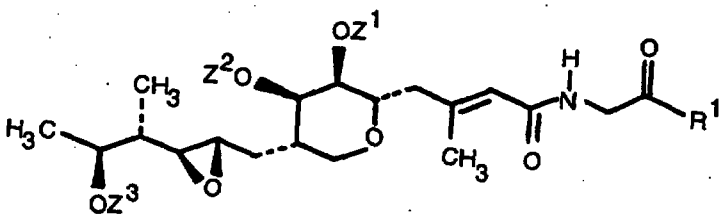
Most preferably the compound of formula (I) is a compound of formula (IA):



(IA)

wherein R^1 is as defined above.

The present invention also provides a process for producing a compound of formula (IA) which process comprises cyclising a compound of formula (II):



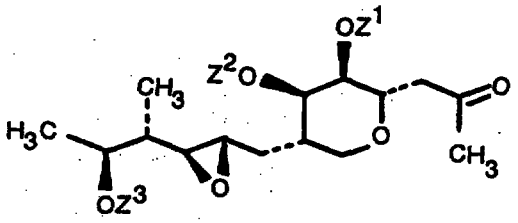
(II)

wherein

R^1 is as defined in relation to formula (I); and

Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group to form a compound of formula (IA) and, where necessary, removing any hydroxyl-protecting groups, and, if desired, converting one compound of formula (IA) into a further compound of formula (IA).

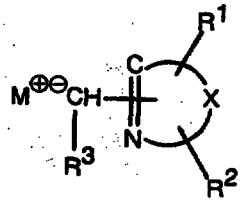
The present invention also provides a process for producing a compound of formula (I) which process comprises reacting a compound of formula (III):



(III)

wherein

Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group, with a compound of formula (IV):



(IV)

wherein

R^1 and R^2 are as defined in relation to formula (I) $M^{\oplus}$ is a metal cation, preferably an alkali metal cation, most preferably a lithium or sodium cation, and

R^3 is an anion-stabilising group which will spontaneously eliminate with a β-hydroxyl group to producde an olefin, preferably a trialkylsilyl or a dialkylphosphonate group, most preferably trimethylsilyl or diethylphosphate, and, where necessary removing any hydroxyl-protecting groups, and, if desired, converting one compound of formula (i) into a further compound of formula (I).

The cyclisation of a compound of formula (II) is suitably effected using a chlorinating agent such as phosphorus oxychloride, phosgene, thionyl chloride or phosphorus pentachloride in the presence of a tertiary amine, such as triethylamine or pyridine. Such reactions are conveniently effected in an organic solvent, for instance dichloromethane or tetrahydrofuran, at ambient or reduced temperature, for instance −80 to 100°C, over a period of several hours to a few days. Preferably phosgene or phosphorus oxychlorde are used, at temperatures of from 0 to 20°C.

Alternatively, cyclisation may be effected using triphenylphosphine and carbon tetrachloride as the chlorinating reagent, in the presence of a tertiary amine, for instance triethylamine, in an inert solvent such as acetonitrile or acetonitrile-pyridine. This type of process is described by H. Vorbruggen and K. Krolikiewicz in *Tet. Letts.*, 1981, 4471: it is particularly advantageous in that the production of compounds of formula (II) and cyclisation of these to compounds of formula (IA) may be conducted *in situ*.

Compounds of formula (II) may also be cyclised using a carboxylic anhydride or mixed anhydride, such as trifluoroacetic anhydride. In this reaction the hydroxy groups of the 1-normon-2-yl moiety become acylated and must subsequently be deprotected. When trifluoroacetic anhydride is used to effect the cyclisation the trifluoroacetyl groups may be removed using aqueous base such as potassium carbonate. Appropriate deprotecting conditions for removing other acyl residues will be readily apparent to the skilled person. Alternatively the hydroxy groups of the 1-normon-2-yl moiety may be protected, prior to cyclising with a carboxylic anhydride, and deprotected by conventional methods such as described below.

The reaction of a compound of formula (III) with a compound of formula (IV) may conveniently be effected in an organic solvent, such as tetrahydrofuran, diethyl ether and dimethyl sulphoxide, at reduced or elevated temperature, such as from −80 to 100°C.

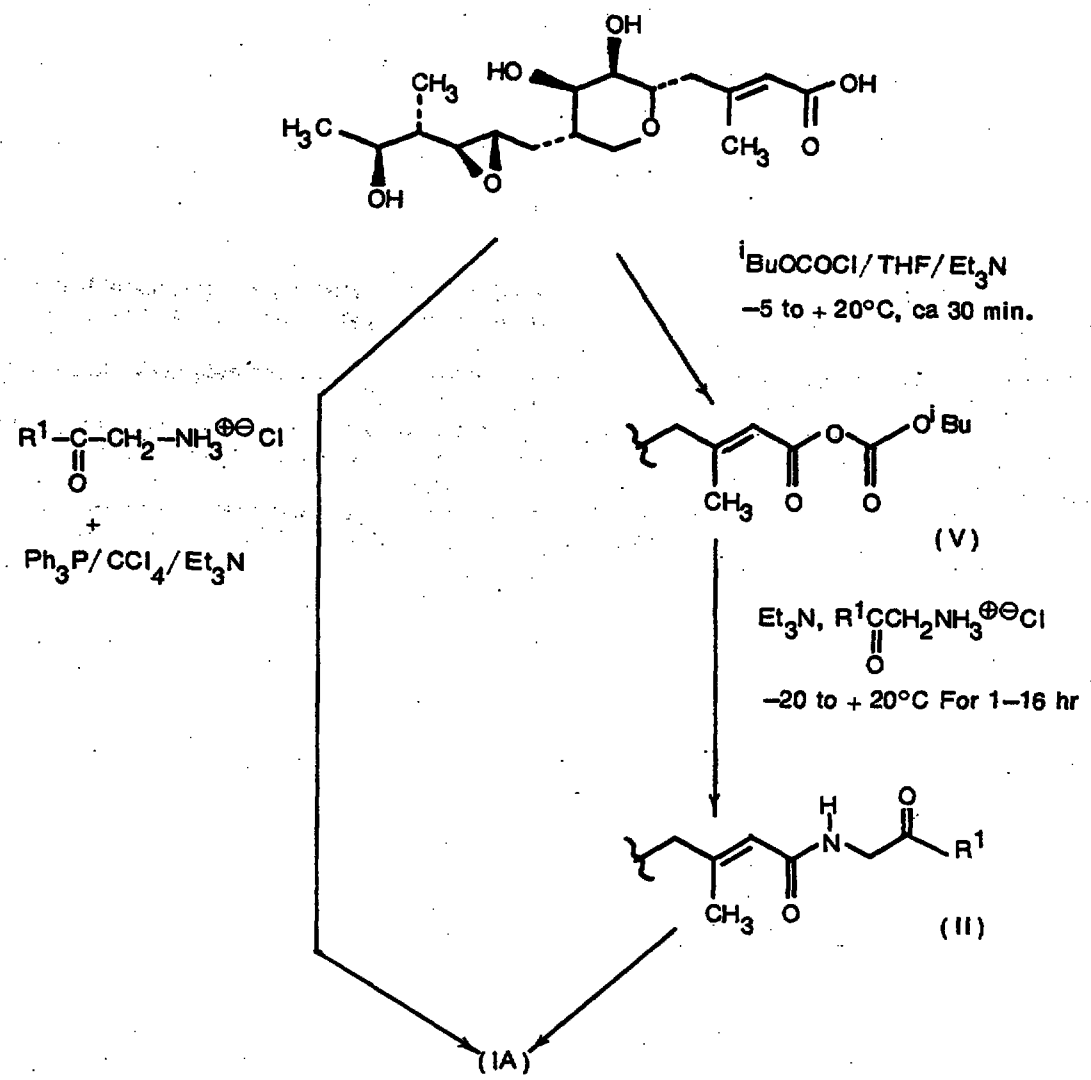
Conversion of one compound of formula (I) to another compound of formula (I) may be effected by conventional methods. Thus, for instance, substituents on the groups R^1 and R^2 may be modified or additional substituents may be inserted. Included within modification of the groups R^1 and R^2 are salification and esterification of a carboxy substituent, trans- and de-esterfication of an ester-containing substituent and formation of the free carboxy group from a carboxylate salt. Another example of such conversion is the formation of alkanesulphinyl and alkanesulphonyl compounds from the corresponding alkylthio compound of formula (I). This latter conversion may be achieved using conventional oxidising agents such as percarboxylic acids, for instance m-chloroperbenzoic acid, in a suitable solvent.

Compounds of formula (II) as defined above are novel and useful as chemical intermediates in the aforementioned process.

Accordingly, the present invention also provides a compound of formula (II), as hereinbefore defined.

Compounds of formula (II) may be produced according to the reaction sequence shown in Scheme I below.

Scheme I



The hydroxyl groups of monic acid, and compounds of formulae (II) and (V) may be protected at any stage in this scheme, using conventional processes.

Particularly suitable protecting groups are silyl groups since these are readily removed under mild conditions. Such groups are introducted using conventional silylating agents, including halosilanes and silazines, of the formulae below:

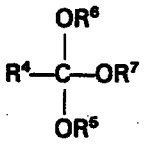
L_3SiX, L_2SiX_2, L_3SiNL_2, $L_3SiNHSiL_3$, $L_3SiNHCOL$, $L_3SiNHCONHSiL_3$, $LNHCONHSiL_3$



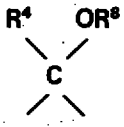
wherein

X is halogen and each group L is independently selected from hydrogen, alkyl, aryl or aralkyl. A preferred silyating agent is trimethylsilyl chloride. Particularly suitable protecting groups are trimethylsilyl, *t*-butyldimethylsilyl and *t*-butyldiphenylsilyl groups. Preferred protecting groups are trimethylsilyl groups because of their ease of removal.

The glycol function of monic acid and the compounds of formulae (II) and (III) may be protected by forming a cyclic derivative using a compound of formula (VI):



wherein R^4 is hydrogen or C_{1-6} alkyl and each of R^5, R^6 and R^7 is C_{1-6} alkyl. In the cyclic derivative Z^1 and Z^2 together are a moiety:



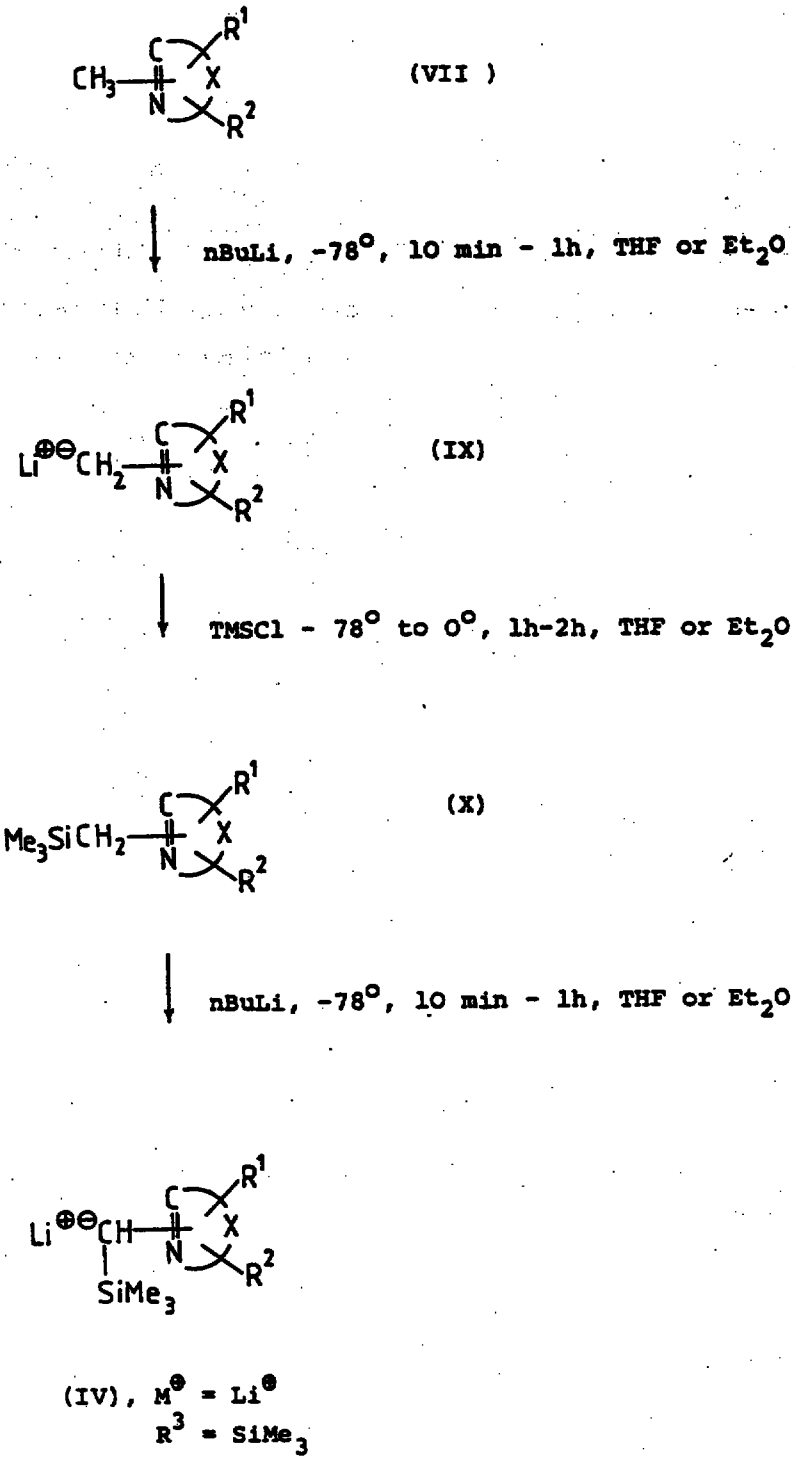
wherein R^8 C_{1-8} alkyl. Suitably R^4 is hydrogen, methyl, ethyl, n- or *iso*-propyl; most suitably it is hydrogen. The groups R^5, R^6 and R^7 are suitably methyl, ethyl, *n*- or *iso*-propyl, *n*-, *iso*-, *sec*- or *t*-butyl; most suitably methyl.

Similarly the hydroxyl groups of a compound of formula (I) may be protected prior to conversion to a further compound of formula (I) as described above.

In each case the protecting groups described above may be removed by mild acid hydrolysis followed by alkaline hydrolysis, for instance, as described by J. P. Clayton, K. Luk and N. H. Rogers, in 'Chemistry of Pseudomonic Acid, Part II", *J. C. S. Perkin Trans. I*, 1979, 308.

The compound of formula (III) wherein Z^1, Z^2 and Z^3 are hydrogen, and processes for its production, are described in U.K. Patent No. 1,587,060. Derivatives thereof wherein Z^1, Z^2 and Z^3 are hydroxyl protecting groups may be producted by conventional methods such as

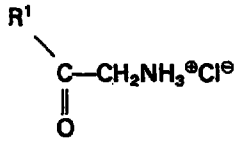
Scheme II



those mentioned above. When this compound is produced with hydroxyl protecting groups already in place it may be used directly or even *in situ* in the above reaction or it may be optionally deprotected and/or isolated.

Compounds of formula (IV) may be produced by conventional processes such as those shown in Scheme II.

When R is 2-oxazolyl, the corresponding compound of formula (IV) may be produced from the compound of formula (VIII) by conventional methods:

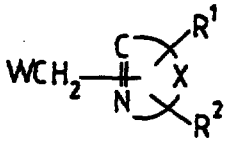


(VIII)

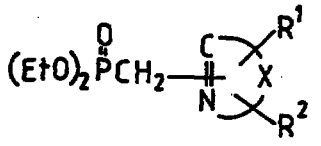
Preparation of the compounds of formula (VIII) is described in Organic Syntheses Coll. Vol. V, 909, and one method for converting these to compounds of formula (VII) is that described by J. L. La Mattina, [J. Org. Chem., (1980), 45, 2261]. Analogous processes to those of the reaction sequence from compounds of formula (VII) to compounds of formula (IV) are described by E. J. Corey and D. L. Boger [Tet. Letters, (1978), 5]; T. H. Chan [Acc. Chem. Res., (1977), 10, 442] and B. H. Lipshutz and R. W. Hungate [J. Org. Chem., (1981), 46, 1410].

An alternative procedure for producing compounds of formula (IV) is shown in Scheme III:

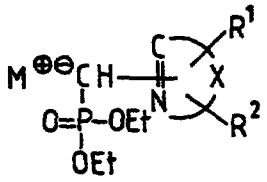
Scheme III



(XI) W = H, Halogen



(XII)



(IV), $R^3 = P(O)(OEt)_2$

The production of oxazoles (cf compounds of formula (VII) in Scheme II) are described by R. A. Jeffreys [*J. Chem. Soc.*, (1952), 4823] and J. W. and R. H. Cornforth [*J. Chem. Soc.*, (1947), 96] and suitable reaction conditions to produce compounds of formula (IV) wherein R^3 is



is described by W. S. Wadsworth Jr., [*Organic Reactions*, (1977), *25*, 73].

The infections against which compounds of this invention are particularly useful include venereal disease. They are also effective in the treatment of respiratory infections such as bacterial bronchitis; and bacterial meningitis, non-specific urethritis and pneumonia. In animals it may be employed for the treatment of mastitis in cattle, for swine dysentery, and for mycoplasma infections in animals such as turkeys, chickens, pigs and cattle.

Some of the human and veterinary diseases either cuased by mycoplasma species or in which they play a prominent role, and against which compounds of this invention are effective, are as follows:

Avian
M. gallisepticum — chronic respiratory diseases (airsacculitis) of chickens and turkeys

Bovine
M. bovis — mastitis, respiratory disease and arthritis of cattle
M. dispar — calf pneumonia

Porcine
M. suipneumoniae — enzootic pneumonia of pigs
M. hyorhinis — arthritis in pigs
M. hyosynoviae

Human
M. pneumoniae — primary atypical pneumonia

Compounds of the present invention are particularly useful in the treatment of enzootic pneumonia in animals such as pigs, cattle and sheep, because they also have activity against the bacteria *Bordetella bronchiseptica, Pasteurella multocida* and *Haemophilus spp*, which often cause respiratory complications in cases of this disease.

This invention also provides a pharmaceutical or veterinary composition which comprises a compound of formula (I) (hereinafter referred to as the "drug") together with a pharmaceutically or veterinarily acceptable carrier or excipient.

The compositions may be formulated for administration by any route, and would depend on the disease being treated. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, and the British Pharmacopoeia.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the drug and a sterile vehicle. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. In preparing solutions the drug can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local

anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability the composition can be frozen after filling into the vial and water removed under vacuum. The dry lypophilized powder is then sealed in the vial. Parenteral suspensions are prepared in substantially the same manner except that the drug is suspended on the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The drug can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the drug.

For topical application to the ear, the drug may be made up into a solution or suspension in a suitable liquid carrier, such as water, glycerol, diluted ethanol, propylene glycol, polyethylene glycol or fixed oils.

For topical application to the eye, the drug is formulated as a solution or suspension in a suitable, sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edetate; preservatives including bactericidal and fungicidal agents, such as phenylmercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage employed for compositions administered topically will, of course, depend on the size of the area being treated. For the ears and eyes each dose will typically be in the range from 10 to 100 mg of the drug.

Veterinary compositions for intramammary treatment of mammary disorders in animals, especially bovine mastitis, will generally contain a suspension of the drug in an oily vehicle.

The compositions may contain from 0.1% to 99% by weight, preferably from 10—60% by weight, of the drug, depending on the method of administration. Where the compositions are in unit dose form, each dosage unit will preferably contain from 50—500 mg, of the drug. The dosage as employed for adult human treatment will preferably range from 100 mg to 3 g, per day, for instance 250 mg to 2 g of the drug per day, depending on the route and frequency of administration.

Alternatively, the drug may be administered as part of the total dietary intake. In this case the amount of drug employed may be less than 1% by weight of the diet and in preferably no more than 0.5% by weight. The diet for animals may consist of normal foodstuffs to which the drug may be added or the drug may be included in a premix for admixture with the foodstuff.

A suitable method of administration of the drug to animals is to add it to the animals' drinking water. In this case a concentration of the drug in the drinking water of about 5—500 µg/ml, for example 5—200 µg/ml, is suitable.

The following Examples illustrate the invention, but are not intended to limit the scope in any way.

The following abbreviations have been used in the Examples:

DMF — N,N-dimethylformamide

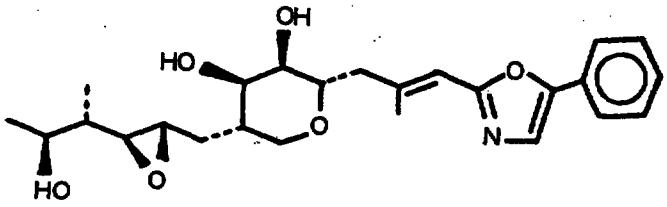
THF — Tetrahydrofuran

$MgSO_4$ — Anhydrous magnesium sulphate

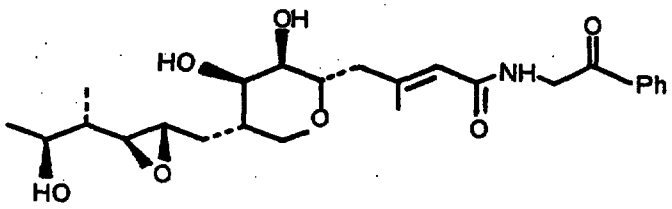
Celite — (Trade Mark) is a grade of diatomaceous earth

Example 1

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-phenyloxazole; 2-(1-normon-2-yl)-5-phenyloxazole A



(a) N-Phenacyl-4-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-3-methylbut-2-(E)-enamide; phenacyl monamide A



A solution of monic acid A (13.8 g, 40 mmol) in dry tetrahydrofuran (250 ml) was cooled to 0°C and then triethylamine (5.4 ml, 40 mmol) and isobutylchloroformate (5.1 ml, 40 mmol) were added. The cooling bath was removed and after 30 min, triethylamine (5.4 ml, 40 mmol) and phenacylammonium chloride (6.6 g, 40 mmol) were added. After 16 h at 20°C the reaction mixture was filtered, the filtrate evaporated to dryness

under reduced pressure and the resulting residue purified by chromatography (50 g silica gel, 0 to 6% methanol in dichloromethane) to give phenacyl monamide A as a white foam (5.5 —10.9 g, 30 to 60%);
i.r. spectrum: ν_{max} (film) 3400, 1690, 1660, 1630, 1600 cm^{-1};
U.V. spectrum: λ_{max} (EtOH) 240 nm (ε_m 22,400);
^{1}H nmr: δH ($CDCl_3$) 7.98 (2H, d, H2'', 6''), 7.63 (1H, t, H4''), 7.50 (2H, t, H3'', 5''), 6.88 (1H, t, NH), 5.86 (1H, s, H2), 4.82 (2H, d, H1'), 2.20 (3H, s, CH_3-15), 1.20 (3H, d, CH_3-14), 0.90 (3H, d, CH_3-17);
^{13}C nmr: δC ($CDCl_3$) 194.6 (C2'), 167.1 (C1), 151.9 (C3), 134.5 (C1''), 133.8 (C4''), 128.8 (C2'', C6''), 128.7 (C3'', C5''), 119.6 (C2), 74.9 (C5), 70.8 (C13), 70.3 (C7), 68.8 (C6), 65.2 (C16), 60.9 (C11), 55.4 (C10), 46.1 (C1'), 42.5 (C4), 42.5 (C12), 39.5 (C8), 31.6 (C9), 20.5 (C14), 18.8 (C15), 12.3 (C17);
mass spectrum: m/e (relative intensity) 461 ($M^{\oplus}$, 11%), 327 (18), 217 (96), 136 (100)

Found: 461.2415. $C_{25}H_{35}NO_7$
requires: 461.2414

Analysis:
Found: C, 65.0; H, 7.5; N, 3.1%
$C_{25}H_{35}NO_7$ requires: C, 65.1; H, 7.6; N, 3.0%

(b) 2-(1-Normon-2-yl)-5-phenyloxazole A

Phenacyl monamide A (0.92 g, 2 mmol) was treated with chlorotrimethylsilane (0.76 ml, 6 mmol) and triethylamine (0.84 ml, 6 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine in tetrahydrofuran (20 ml) until protection was complete (6 h by t.l.c.). The resulting solution was filtered and evaporated to dryness under reduced pressure. The residual oil was dissolved in dichloromethane (20 ml) and reacted with phosgene in toluene (2.3 mmol) in the presence of triethylamine (0.6 ml, 4.6 mmol) at 5°C for 16 h. The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure. The residue was dissolved in dioxan (40 ml) and water (10 ml) and concentrated aqueous hydrochloric acid (12 drops) added. After 12 min the solution was neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography (50 g silica, 0 to 10% methanol in dichloromethane). 2-(1-Normon-2-yl)-5-phenyloxazole A, the second component to be eluted from the column, was obtained as a white foam (0.11 g, 14%);
i.r. spectrum: ν_{max} (film) 3400, 1655, 1120, 1050 cm^{-1};
U.V. spectrum: λ_{max} (EtOH) 301 nm (ε_m 20,800);
^{1}H nmr: δH (CD_3OD) 7.3—7.8 (6H, m, aryl + Het-H), 6.26 (1H, s, H2), 2.20 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.90 (3H, d, CH_3-17);
^{13}C nmr: δC ($CDCl_3$) 161.2 (C1), 150.1 (C3), 146.8, 128.9, 128.1, 124.1, 122.5 (aryl + heteroacyl), 113.2 (C2), 75.4 (C5), 71.2 (C13) 70.5 (C7), 69.0 (C6), 65.5 (C16), 61.2 (C11), 55.6 (C10), 42.8 (C4, C12), 39.6 (C8), 31.8 (C9), 20.8 (C14), 19.6 (C15), 12.6 (C17);
mass spectrum: m/e (relative intensity) 443 ($M^{\oplus}$, 11%), 199 (100)

Found: 443.2270. $C_{25}H_{33}NO_6$
requires: 443.2305

(c) 2-(1-Normon-2-yl)-5-phenyloxazole A (alternative cyclisation)

t-Trifluoroacetic anhydride (0.5 ml) was added to phenacyl monamide A (92 mgs, 0.20 mmol) in a flask cooled to 0°C. The cooling bath was removed and the homogeneous solution stirred for 1 h at room temperature. The excess anhydride was removed under reduced pressure then the residue was stirred with aqueous potassium carbonate/THF (1:4) for 2 days. This solution was extracted with ethyl acetate (2 × 30 ml), dried ($MgSO_4$) and solvent removed under reduced pressure to leave the crude product (89 mgs). Column chromatography (0 to 5% methanol in dichloromethane on silica gel:2 g) gave the title compound (43.5 mgs, 0.10 mmol, 50%) which was identical to sample obtained in Example 1(b).

Example 2

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-phenyloxazole; 2-(1-normon-2-yl)-5-phenyloxazole A

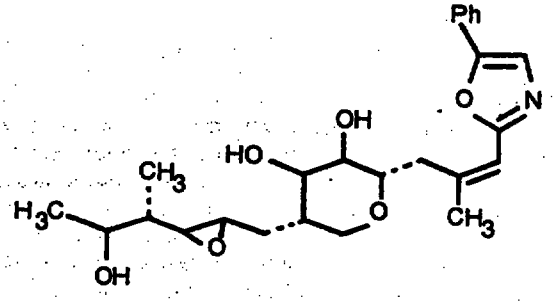
(a) A solution of 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]propan-2-one (300 mg, 1 mmol) in tetrahydrofuran (10 ml) was treated with chlorotrimethylsilane (0.42 ml, 3.3 mmol), triethylamine (0.46 ml, 3.3 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine. After 2 h at 20°C the resulting "TMS-protected ketone" was isolated, by filtration and evaporation to dryness under reduced pressure, as an oil which was dissolved in tetrahydrofuran (5 ml). This solution was set aside for addition to the lithium anion, the production of which is described in part (b) below.

(b) A solution of 2-methyl-5-phenyloxazole (175 mg, 1.1 mmol) in dry tetrahydrofuran (10 ml) was cooled to −78°C under an atmosphere of argon. A solution of *n*-butyl lithium in hexane (0.9 ml, 1.2M, 1.1 mmol) was added, followed after 10 min by chlorotrimethylsilane (0.15 ml, 1.1 mmol). After 40 min at

−78°C the solution was warmed to 0°C for 45 min and then recooled to −78°C. A further quantity of *n*-butyl lithium (0.9 ml, 1.1 mmol) was added and the solution stirred at −78°C for 40 min.

(c) The solution of "TMS-protected ketone" described in part (a) above was added to the reaction mixture obtained in part (b) above and the mixture was stirred for 2 h at 20°C and then poured into aqueous ammonium chloride. The resultant mixture was extracted with ethyl acetate and the organic extracts were combined, dried (magesium sulphate) and evaporated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran/water (4:1, 25 ml) and concentrated hydrochloric acid (6 drops). After stirring for 12 min excess sodium bicarbonate was added and the mixture extracted with ethyl acetate. The organic extracts were combined, dried (magnesium sulphate), and evaporated under reduced pressure to an oil, which was purified by chromatography on silica gel (10 g) eluting with a gradient of 0 to 4% methanol in dichloromethane. 2-(1-Normon-2-yl)-5-phenyloxazole A was obtained as a white foam (156 mg, 35%) and found to be identical to the sample obtained in Example 1.

In addition, the less polar Z-isomer, 2-{3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(Z)-enyl}-5-phenyloxazole (15 mg, 3%);



was also obtained.

i.r. spectrum: ν_{max} (film) 3600—3100, 2970, 2930, 1650, 1450, 1110, 1050, 950, 910, 760, 690 cm^{-1};

U.V. spectrum: λ_{max} (EtOH) 302 nm (ε_m 17,100);

'H nmr: δH ($CDCl_3$) 0.95 (3H, d, J=7Hz, CH_3-17), 1.20 (3H, d, J=7Hz, CH_3-14), 1.29 (1H, m, CH-12), 1.60 (1H, dt, J=15, 5HZ, $CH_2$9), 2.04 (1H, m, CH-8), 2.13 (3H, d, J=0.5Hz, CH_3-15), 2.68 (1H, dd, J=10, 2Hz, CH-11), 2.75—3.00 (2H, m, CH-10, CH_2-4), 3.06 (1H, dd, J=15, 5Hz, CH_2-4), 3.5—4.0 (6H, m), 6.30 (1H, s, CH-2), 7.32 (1H, s, CH-1'), 7.33—7.70 (5H, m, Ph);

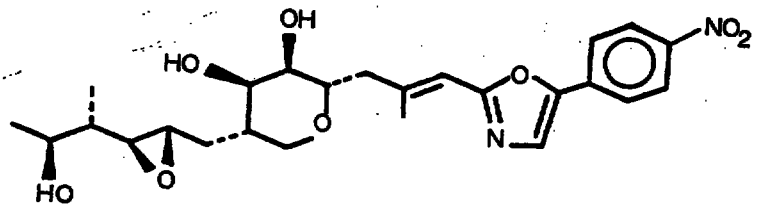
^{13}C nmr: δC ($CDCl_3$) 12.7 (C17), 20.7 (C14), 27.4 (C15), 31.9 (C9), 36.3 (C4), 38.9 (C8), 43.0 (C12), 56.1 (C10), 61.5 (C11), 65.6 (C16), 66.9 (C6), 70.3 (C7), 71.3 (C13), 76.6 (C5), 112.5 (C2), 121.6, 124.3, 127.7, 128.6, 129.0 (aromatic + heteroaromatic), 150.4 (C3), 166.8 (C1);

mass spectrum: m/e (relative intensity) 443 ($M^{\oplus}$, 10%), 211 (32), 199 (100), 77 (32), 69 (30), 55 (39), 45 (64), 43 (63), 41 (62)

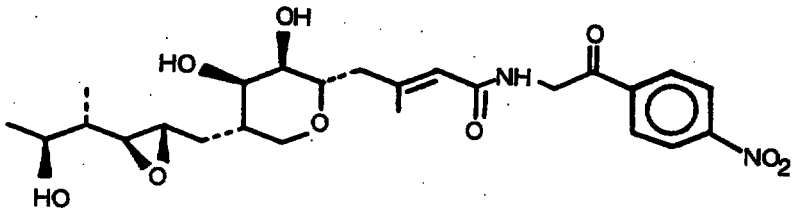
Found 443.2334. $C_{25}H_{33}NO_6$ requires: 443.2308.

Example 3

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-p-nitrophenyloxazole; 5-p-nitro-phenyl-2-(1-normon-2-yl)-oxazole A



(a) N-p-Nitrophenacyl-4-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-3-methylbut-2(E)-enamide; p-nitrophenacyl monamide A



To a solution of monic acid A (3.1 g, 9 mmol) in dry tetrahydrofuran (50 ml) were added triethylamine (1.2 ml, 9 mmol) and isobutylchloroformate (1.1 ml, 9 mmol). After 30 min *p*-nitrophenacylammonium

chloride (2.2 g, 9 mmol) and additional triethylamine (1.2 ml, 9 mmol) were added. The reaction mixture was stirred for 2 h at 20°C, poured into brine and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate, dried (magnesium sulphate) and evaporated to dryness under reduced pressure. Chromatography on silica gel (20 g) eluting with a gradient of 0 to 10% methanol in dichloromethane afforded the *p*-nitrophenacyl monamide A as a yellow foam (1.4 g, 31%);

i.r. spectrum: ν_{max} (film) 3380, 1710, 1660, 1630, 1605, 1525, 1350 cm^{-1};

U.V. spectrum: λ_{max} (EtOH) 223 nm (ε_m 16,200), 262 nm (ε_m 13,200);

'H nmr: δH (CD_3OD) 8.28 (4H, ABq, aryl), 5.91 (1H, s, H2), 4.73 (2H, s, H1'), 2.13 (3H, s, CH_3-15), 1.15 (3H, d, CH_3-14), 0.90 (3H, d, CH_3-17).

(b) 5-p-Nitrophenyl-2-(1-normon-2-yl)-oxazole A

p-Nitrophenacyl monamide A (1.01 g, 2 mmol) was treated with chlorotrimethylsilane (0.76 ml, 6 mmol), triethylamine (0.84 ml, 6 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine in tetrahydrofuran (20 ml) until protection was complete (16 h as indicated by t.l.c.). The resulting solution was filtered and evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 ml) and reacted with phosphoryl chloride (0.3 ml, 3.5 mmol) and pyridine (0.5, 6 mmol) for 16 h at 20°C. The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to give an oil, which was dissolved in dioxan (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give 5-p-nitrophenyl-2-(1-normon-2-yl)-oxazole A as a yellow foam (0.08 g, 8%);

i.r. spectrum: ν_{max} (film) 3410, 1650, 1605, 1520, cm^{-1};

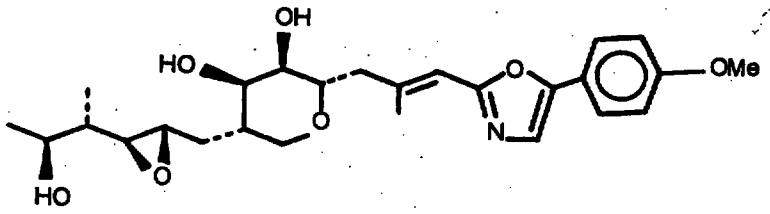
U.V. spectrum: λ_{max} (EtOH) 267 nm (ε_m 11,900), 356 nm (ε_m 18,200);

'H nmr: δH ($CDCl_3$) 8.28 and 7.79 (4H, ABq, aryl), 7.56 (1H, s, heterocyclyl), 6.32 (1H, s, H2), 2.34 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17);

^{13}C nmr: δC ($CDCl_3$) 162.7 (C1), 149.0 (C3), 147.7 (aryl C4), 147.0 (oxazole C4), 134.0 (aryl C1), 126.3 (oxazole C5), 124.5 (aryl C2, C6), 124.3 (aryl C3, C5), 112.8 (C2), 75.3 (C5), 71.3 (C13), 70.5 (C7), 69.0 (C6), 65.5 (C16), 61.2 (C11, 55.5 (C10), 43.0 (C12), 42.8 (C4), 39.7 (C8), 31.7 (C9), 20.8 (C14), 19.8 (C15), 12.7 (C17).

Example 4

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-p-methoxyphenyloxazole; 5-p-methoxyphenyl-2-(1-normon-2-yl)-oxazole A



A solution of 2-methyl-5-p-methoxyphenyloxazole (190 mg, 1.0 mmol) in dry tetrahydrofuran (10 ml) was cooled to −78°C under an argon atmosphere. A solution of n-butyl lithium in hexane (0.9 ml, 1.2M, 1.1 mmol) was added, and after 10 min chlorotrimethylsilane (0.15 ml, 1.1 mmol). After 40 min at −78°C, the solution was warmed to 0°C for 45 min and then recooled to −78°C. More n-butyl lithium (0.9 ml, 1.1 mmol) was then added, and the solution stirred at −78°C for 40 min. A solution of the "TMS-protected ketone" derived from 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-propan-2-one, by the method described in Example 2, (1 mmol) in tetrahydrofuran (10 ml) was added and the reaction mixture stirred at 20°C for 2 h, poured into aqueous ammonium chloride and extracted with ethyl acetate. The combined organic fractions were dried (magnesium sulphate) and evaporated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran/water (4:1, 25 ml). Concentrated hydrochloric acid (6 drops) was added, followed 12 min later by excess aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate and the combined extracts dried (magnesium sulphate), evaporated under reduced pressure and the residue by chromatography on silica gel (10 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to give 5-p-methoxyphenyl-2-(1-normon-2-yl)-oxazole A as a white foam (0.07 g, 15%).

i.r. spectrum: ν_{max} (film) 3400, 1655, 1615, 1500, cm^{-1};

U.V. spectrum: λ_{max} (EtOH) 307 nm (ε_m 22.700);

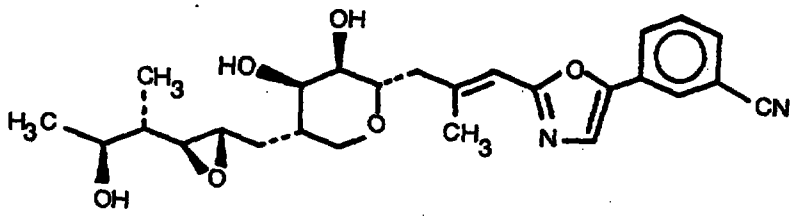
'H nmr: δH ($CDCl_3$) 7.55 and 6.93 (4H, ABq, aryl), 7.22 (1H, s, heteraryl), 6.29 (1H, s, H2), 3.81 (3H, s, 0Me), 2.21 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17);

^{13}C nmr: δC ($CDCl_3$) 160.6 (C1), 159.8 (aryl C4), 150.1 (C3), 145.9 (oxazole C4), 125.6 (aryl C2, C6), 121.1

(aryl C1), 119.9 (oxazole C5), 114.5 (aryl C3, C5), 113.3 (C2), 75.4 (C5), 71.3 (C13), 70.5 (C7), 69.0 (C6), 65.5 (C16), 61.3 (C11), 55.5 (C10), 55.4 (OMe), 42.8 (C4, C12), 39.5 (C8), 31.8 (C9), 20.8 (C14), 19.6 (C15), 12.6 (C17).

Example 5

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-m-cyanophenyloxazole; 5-m-cyanophenyl-2-(1-normon-2-yl)-oxazole A



A solution of 2-methyl-5-*m*-cyanophenyloxazole (200 mg, 1.1 mmol) in dry tetrahydrofuran (10 ml) was cooled to −78°C under an argon atmosphere. A solution of n-butyl lithium in hexane (0.9 ml, 1.2M, 1.1 mmol) was added, and after 10 min chlorotrimethylsilane (0.15 ml, 1.1 mmol). After 40 min at −78°C, the solution was warmed to 0°C for 45 min and then recooled to −78°C. More n-butyl lithium (0.9 ml, 1.1 mmol) was then added, and the solution stirred at −78°C for 40 min. A solution of the "TMS-protected derivative" of 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-propan-2-one (1 mmol) in tetrahydrofuran (10 ml) (prepared by the method described in Example 2), was added and the reaction mixture stirred at 20°C for 2 h, poured into aqueous ammonium chloride and extracted with ethyl acetate. The combined organic fractions were dried (magnesium sulphate) and evaporated under reduced pressure. The resulting residue was dissolved in 4:1 tetrahydrofuran/water (25 ml). Concentrated hydrochloric acid (6 drops) was added, followed, after 12 min by excess aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate and the combined extracts, dried (magnesium sulphate), evaporated under reduced pressure and the residue purified by chromatography on silica gel (10 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to give 5-m-cyanophenyl-2-(1-normon-2-yl)-oxazole A as a yellow foam (0.035 g, 7%).

i.r. spectrum: ν_{max} (film) 3400, 2225, 1680, 1655, 1610, cm^{-1};

U.V. spectrum: λ_{max} (EtOH) 305 nm (ε_m 28,600);

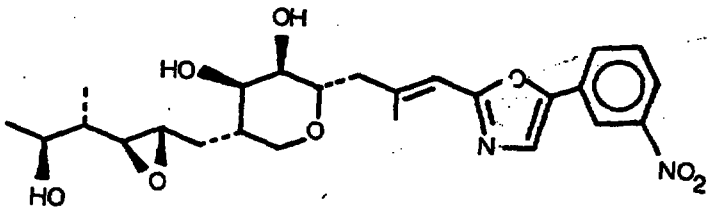
'H nmr: δH ($CDCl_3$) 7.5—7.9 (4H, m, aryl), 7.44 (1H, s, H4'), 6.31 (1H, s, H2), 2.33 (3H, s, CH_3-15), 1.24 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17);

^{13}C nmr: δC ($CDCl_3$) 165.5 (C1), 148.2 (C3), 147.5 (C4'), 131.2, 129.8, 127.8, 127.3, 123.5 (aryl), 124.5 (C5'), 112.9 (C2), 75.2 (C5), 71.3 (C13), 70.5 (C7), 69.0 (C6), 65.4 (C16), 61.2 (C11), 55.5 (C10), 42.8 (C4, C12), 39.6 (C8), 31.7 (C9), 20.8 (C14), 19.7 (C15), 12.7 (C17);

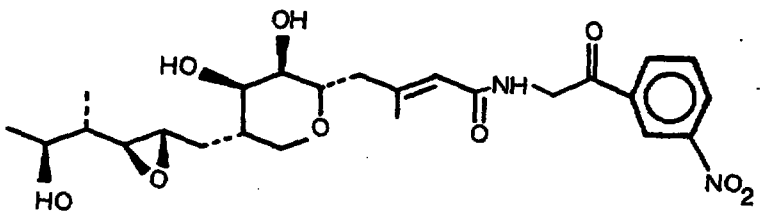
mass spectrum m/e (relative intesity) 468 ($M^{\oplus}$, 6%), 283 (34), 224 (100) (found 468.2273, $C_{26}H_{32}N_2O_6$ requires 468.2289).

Example 6

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-p-nitrophenyloxazole; 5-m-nitrophenyl-2-(1-normon-2-yl)-oxazole A



(a) N-m-Nitrophenacyl-4-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-3-methylbut-2(E)enamide; m-nitrophenacyl monamide A



To a solution of monic acid (3.1 g, 9 mmol) in dry tetrahydrofuran (50 ml) were added triethylamine (1.2 ml, 9 mmol) and isobutylchloroformate (1.1 ml, 9 mmol). After 30 min *m*-nitrophenacylammonium chloride (2.2 g, 9 mmol) and additional triethylamine (1.2 ml, 9 mmol) were added. The reaction mixture was stirred for 2 h at 20°C, poured into brine and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate, dried (magnesium sulphate) and evaporated to dryness under reduced pressure. Chromatography on silica gel (20 g) eluting with a gradient of 0 to 10% methanol in dichloromethane afforded the *m*-nitrophenacyl monoamide A as a yellow crystals, mp 132—135°C (dec., CH_2Cl_2), (2.7 g, 60%);

ν_{max} (KBr) 3470, 3340, 1705, 1660, 1635, 1625, 1350 cm^{-1};

λ_{max} (EtOH) 227 nm (ε_m 30,600);

δH (CD_3OD) 8.80 (1H, s, H2''), 8.49 (1H, dd, H4''), 8.38 (1H, dd, H6''), 7.80 (1H, t, H5''), 5.91 (1H, s, H2), 4.88 (2H, s, H1'), 2.19 (3H, s, CH_3-15), 1.23 (3H, d, CH_3-14), 0.96 (3H, d, CH_3-17);

δ (CD_3OD) 194.5 (C2'), 169.3 (C1), 153.0 (C3), 149.5 (C3''), 137.4 (C1''), 134.4 (C6''), 131.0 (C5''), 128.4 (C4''), 66.0 (C16), 61.1 (C11), 56.5 (C10), 47.0 (C1'), 43.3 (C4), 43.3 (C12), 41.0 (C8), 32.6 (C9), 20.3 (C14), 19.0 (C15), 12.2 (C17).

(b) 5-m-Nitrophenyl-2-(1-normon-2-yl)-oxazole A

m-Nitrophenacyl monamide A (1.45 g, 3 mmol) in acetonitrile (20 ml) was treated with chlorotrimethylsilane (1.3 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol) and 4-N,N-dimethylaminopyridine (50 mg) for 2 h at 20°C. The mixture was then filtered and evaporated under reduced pressure, and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (15 ml), pyridine (15 ml), triethylamine (0.8 ml, 6 mmol) and tetrachloromethane (1.2 ml, 12 mmol). Triphenylphosphine (1.6 g, 6 mmol) was then added and the mixture was allowed to stand at 20°C for 2 h and then at 5°C for 16 h. The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulfate) and evaporated under reduced pressure to give an oil, which was dissolved in dioxan (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give 5-m-nitrophenyl-2-(1-normon-2-yl)-oxazole A as a yellow foam (0.18 g, 12%);

i.r. spectrum: ν_{max} (film) 3400, 1655, 1530, 1350, cm^{-1};

U.V. spectrum: λ_{max} (EtOH) 307 nm (ε_m 16,700);

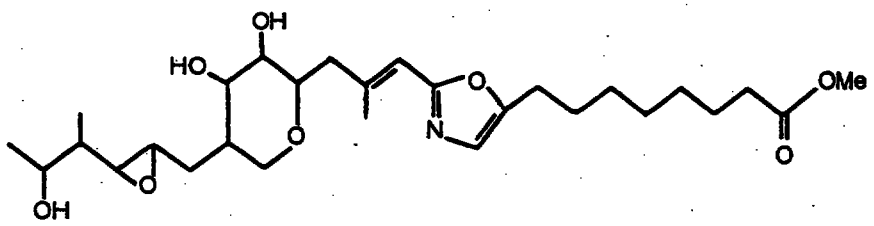
^{1}H nmr: δH ($CDCl_3$) 8.45 (1H, s, H2''), 8.14 (1H, d, H4''), 7.92 (1H, d, H6''), 7.60 (1H, t, H5''), 7.51 (1H, s, H4'), 6.31 (1H, s, H2), 2.34 (3H, s, CH_3-15), 1.22 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17);

^{13}C nmr: δC ($CDCl_3$) 162.7 (C1), 148.9 (C3), 148.6 (C4), 147.5 (C3''), 130.0 (C6''), 129.7 (C1''), 129.4 (C5'), 124.8 (C5''), 122.5 (C4''), 118.7 (C2''), 112.7 (C2), 75.3 (C5), 71.2 (C13), 70.5 (C7), 69.0 (C6), 65.5 (C16), 61.2 (C11), 55.6 (C10), 42.9 (C12), 42.8 (C4), 39.6 (C8), 31.7 (C9), 20.8 (C14), 19.7 (C15), 12.6 (C17);

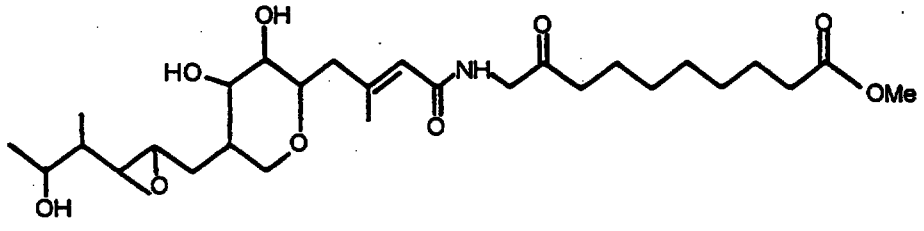
mass spectrum m/e (relative intensity) 488 ($M^{\oplus}$, 7%), 244 (100), 214 (48) (Found 488.2168, $C_{25}H_{32}N_2O_8$ requires 488.2181.

Example 7

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-(7-methoxycarbonylheptyl)oxazole; 5-(7-Methoxy-carbonylheptyl)-2-(1-normon-2-yl)oxazine A



(a) N-(9-Methoxycarbonyl-2-oxononyl)-4-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl-3,4-dihydroxytetrahydropyran-2-yl]-3-methylbut-2(E)-enamide; 9-Methoxycarbonyl-2-oxononyl monamide A



To a solution of monic acid A (2.38 g, 7 mmol) in dry tetrahydrofuran (50 ml) were added triethylamine (0.98 ml, 7 mmol) and isobutylchloroformate (0.91 ml, 7 mmol). After 30 min, methyl 10-amino-9-oxodecanoate hydrochloride (2.1 g, 7 mmol) and more triethylamine (0.98 ml, 7 mmol) were added. The reaction mixture was stirred for 2h at 20°C, poured into brine and the resulting mixture extracted with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate, dried (magnesium sulphate) and evaporated to dryness under reduced pressure. Chromatography on silica gel (20 g) eluting with a gradient of 0 to 10% methanol in dichloromethane afforded the amide as a colourless oil (0.50 g, 14%);

ν_{max} (film) 3400, 1725, 1660, 1635 cm^{-1};
δ_H ($CDCl_3$) 6.50 (1H, bs, NH), 5.76 (1H, s, H2), 4.14 (2H, d, H1'), 3.65 (3H, s, OMe), 2.16 (3H, s, CH_3-15), 1.19 (3H, d, CH_3-14), 0.90 (3H, d, CH_3-17).

(b) 5-(7-Methoxycarbonylheptyl)-2-(1-normon-2-yl)oxazole A

9-Methoxycarbonyl-2-oxononyl monamide A (0.50 g, 1 mmol) in tetrahydrofuran (20 ml) was treated with chlorotrimethylsilane (0.8 ml, 6 mmol), triethylamine (0.9 ml, 6 mmol) and 4-N,N-dimethylaminopyridine (50 mg) for 16h at 20°C. The mixture was then filtered and evaporated under reduced pressure, and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (6 ml), pyridine (6 ml), triethylamine (0.28 ml, 2 mmol) and tetrachloromethane (0.4 ml, 4 mmol). Triphenylphosphine (0.53 g, 2 mmol) was then added and the mixture stirred for 3h at 20°C and then poured into aqeuous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to give an oil, which was dissolved in dioxan (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (10 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give the oxazole as a yellow oil (0.16 g, 29%);

ν_{max} (film) 3600, 1740, 1725 sh, 1635 cm^{-1};
λ_{max} (EtOH) 266 nm (m 11,200);
δ_H ($CDCl_3$) 6.72 (1H, s, H4'), 6.16 (1H, s, H2), 3.65 (3H, s, OCH_3), 2.64 (2H, t, H1''), 2.32 (2H, t, H7''), 2.21 (3H, s, CH_3-15), 1.23 (3H, d, CH_3-17);
δ_C ($CDCl_3$) 174.5 (ester C0), 160.8 (C1), 151.8 (C4'), 145.5 (C3), 122.4 (C5'), 113.3 (C2), 75.4 (C5), 70.9 (C13), 68.9 (C6), 65.6 (C16), 61.21 (C11), 55.6 (C10), 51.4 (OMe), 42.7 (C4, C12), 39.6 (C8), 34.1 (C7''), 31.9 (C9), 29.0, 28.9, 28.9, 27.5, 25.5, 24.9 (C1''-C6''), 20.6 (C14), 19.3 (C15), 12.4 (C17);
m/e (relative intensity) 523 ($M^{\oplus}$, 6%), 420 (10), 308 (17), 279 (100) (Found: 523.3154, $C_{28}H_{45}NO_6$ requires 523.3164).

Example 8

2-{3-[5-(2,3-Eoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-phenyloxazole; 2-(1-normon-2-yl)-5-phenyloxazole A

To a solution of monic acid A (1.03 g, 3 mmol) in dry tetrahydrofuran (50 ml) were aded 4-N,N-dimethylaminopyridine (50 mg), triethylamine (1.82 ml. 13 mmol) and chlorotrimethylsilane (1.65 ml, 13 mmol). After 3h the solution was filtered and the filtrate evaporated umder reduced pressure. The resulting residue was partitioned between aqeuous ammonium chloride and ethyl acetate, and the organic part then washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to give 6,7,13-tris(trimethylsilyl)monic acid.

The latter was dissolved in a mixture of acetonitrile (10 ml), pyridine (10 ml), tetrachloromethane (1.5 ml, 15 mmol), and triethylamine (1.6 ml, 12 mmol). Phenacylammonium chloride (0.51 g, 3 mmol) and triphenylphosphine (0.8 g, 3 mmol) were added and, after an hour, more triphenylphosphine (1.6 g, 6 mmol) was added. After a further 16h the reaction mixture was poured into a mixture of brine and aqeuous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to give an oil, which was dissolved in a mixture of tetrahydrofuran (60 ml) and water (15 ml). Concentrated hydrochloric acid (20 drops) was added and after 12 min the solution poured into aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate, and the extracts washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g), eluting with 0 to 8% methanol in dichloromethane, from which 2-(1-normon-2-yl)-5-phenyloxazole A was obtained as a white foam (0.28 g, 21%), identical to that obtained in Examples 1 and 2.

Example 9

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-p-methylthiophenyloxazole; (5-p-methylthiophenyl-2-(1-normon-2-yl)oxazole A)

(a) p-(Methylthio)phenacyl monamide A

To a solution of monic acid A (2.1 g, 6 mmol) in dry tetrahydrofuran (35 ml) were added triethylamine (0.8 ml, 6 mmol) and isobutyl chloroformate (0.7 ml, 6 mmol). After 30 minutes p-(methylthio)phenacyl-ammonium chloride (1.3 g, 6 mmol) and more triethylamine (0.8 ml, 6 mmol) were added. The reaction mixture was stirred for 4h at 20°C, poured into brine and the resulting mixture extracted with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate, dried (magnesium sulphate) and evaporated under reduced pressure. Chromatography on silicagel (20 g) eluting with 0 to 10% methanol in dichloromethane then gave the title amide as white crystals, mp 84—87°C (ether) (1.7 g, 56%);

ν_{max} (film) 3400, 1685, 1660, 1620, 1590 cm^{-1},
λ_{max} (EtOH) 223 nm (ε_m 18,100);
δ_H (CD_3OD) 7.94 and 7.36 (4H, ABq, aryl), 5.91 (1H, s, H2), 4.69 (2H, s, H1'), 2.54 (3H, s, cMe), 2.19 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.97 (3H, d, CH_3-17);
δ_C (CD_3OD) 195.4 (C2'), 169.7 (C1), 153.0 (C3), 148.4 (C4''), 132.5 (C3'', C5''), 129.3 (C2'', C6''), 120.7 (C2), 126.1 (C1''), 120.7 (C2), 76.2 (C5), 71.6 (C13), 70.7 (C7), 70.0 (C6), 66.3 (C16), 61.3 (C11), 56.8 (C10), 46.7 (C1'), 43.6 (C4, C12), 41.5 (C8), 32.9 (C9), 40.3 (C14), 19.0 (C15), 14.6 (SMe), 12.2 (C17);
m/e (relative intensity) 507 ($M^{\cdot}$, 0.7%), 489 (0.8), 151 (100) (Found: $M^{\cdot}$, 507.2251, $C_{26}H_{37}NO_7S$ requires 507.2290).

(b) 5-p-Methylthiophenyl-2-(1-normon-2-yl) oxazole A

p-(Methylthio)phenacyl monamide A (0.50 g, 1 mmol) in tetrahydrofuran (20 ml) was treated with chlorotrimethylsilane (0.8 ml, 6 mmol), triethylamine (0.9 ml, 6 mmol) and 4-N,N-dimethylaminopyridine (50 mg) for 16h at 20°C. The mixture was then filtered and evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (6 ml), pyridine (6 ml), triethylamine (0.28 ml, 2 mmol), and tetrachloromethane (0.4 ml, 4 mmol). Triphenylphosphine (0.53 g, 2 mmol) was then added and the mixture stirred for 3h at 20°C and then poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to give an oil, which was dissolved in dioxan (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (12 drops) was added and after 12 minutes the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried (magnesium sulphate) and evaporated under reduced pressure to leave a brown oil which was purified by chromatogrpahy on silica gel (10 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give the oxazole as a yellow oil (314 mg, 64%):

ν_{max} (film) 3400, 1685, 1485 cm^{-1},
λ_{max} (EtOH) 223 nm (ε_m 15,300), 267 nm (ε_m 9,200), 326 nm (ε_m 34,100);
δ_H ($CDCl_3$) 7.52 and 7.23 (4H, ABq, aryl), 7.25 (1H, s, oxazole H), 6.26 (1H, s, H2), 3.50 (3H, s, SMe), 2.30 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17);
δ_C ($CDCl_3$) 160.9 (C1), 149.7 (C3), 146.7 (C4'), 139.0 (C4''), 126.8 (C3'', C5''), 124.8 (C5'), 124.4 (C2'', C'), 122.1 (C1''), 113.1 (C2), 75.4 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6), 65.5 (C16), 61.2 (C11), 55.6 (C10), 42.8 (C12), 42.8 (C4), 39.6 (C8), 31.7 (C9), 20.8 (C14), 19.6 (C15), 15.6 (SMe), 12.6 (C17);
m/e (relative intensity) 489 ($M^{\oplus}$, 17%), 245 (100) (Found: $M^{\oplus}$, 489.2218, $C_{26}H_{35}NO_6S$ requires 489.2266).

Example 10

2-{3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl-3,4-dihydroxytetrahydropyran-2-yl]-2-methylprop-1(E)-enyl}-5-p-methylsulphonylphenyloxazole; (5-p-methyl-sulphonyl-2-(1-normon-2-yl)oxazole A)

A mixture of 5-*p*-methylthiophenyl-2-(1-normon-2-yl) oxazole A (0.20 g, 0.4 mmol), sodium bicarbonate (0.13 g, 1.6 nnol) and m-chloroperbenzoic acid (0.16 g, 0.8 mmol) in dichloromethane (10 ml) was stirred for 2h at 0°C and 1h at 20°C, and then diluted with ethyl acetate. The solution was washed with aqueous sodium bicarbonate, dried (Magnesium sulphate) and evaporated under reduced presure. The residue was purified by chromatography (silicagel, 0 to 10% methanol in dichloromethane) to give the title compound as a yellow foam (0.11 g, 53%);

ν_{max} (film) 3450, 1655, 1605, 1305, 1150 cm^{-1},
λ_{max} (EtOH) 323 nm (ε_m 23,500);
δ_H ($CDCl_3$) 7.92 (4H, ABq, aryl), 7.57 (1H, s, oxazole H), 6.35 (1H, s, H2), 3.09 (3H, s, SO_2Me), 2.34 (3H, s, CH_3-15), 1.20 (3H, d, CH_3-14), 0.89 (3H, d, CH_3-17);

δ_C (CD_3OD: $CDCl_3$) 163.5 (C1), 150.4 (C3), 149.3 (C4'), 140.6 (C4''), 133.9 (C1''), 129.0 (C3'', C5''), 126.3 (C5'), 125.3 (C2'', C6''), 113.2 (C2), 76.1 (C5), 71.3 (C13), 70.5 (C7), 69.7 (C6), 66.2 (C16), 61.2 (C11), 56.6 (C10), 44,4 (SO_2Me), 43.8 (C4), 43.4 (C12), 41.2 (C8), 32.8 (C9), 20.3 (C14), 19.9 (C15), 12.2 (C17);

m/e (relative intensity) 521 (M·, 9%), 306 (12), 277 (100) (Found: M·, 521.2050, $C_{28}H_{35}NO_6S$ requires 521.2081).

Example 11

5-p-Methylsulphinylphenyl-2-(1-normon-2-yl)oxazole A

A solution containing 5-*p*-methylthiophenyl-2-(1-normon-2-yl)oxazole A (0.20 g, 0.4 mmol), sodium bicarbonate (0.13 g, 1.6 mmol), and *m*-chloroperbenzoic acid (0.16 g, 0.8 mmol) in dichloromethane (5 ml) was stirred at 0°C for 2.6h and then diluted with ethyl acetate. The solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was puried by chromatography (silicagel, 0 to 10% methanol in dichloromethane) to give the title compound as a yellow oil (0.08 g, 40%); ν_{max} 3400, 1655, 1045 cm^{-1}; λ_{max} (EtOH) 321 nm (ε_m 30,000); δ_C ($CDCl_3$) 7.84 (4H, AA't, aryl), 7.56 (1H, s, oxazole-H), 6.38 (1H, s, H2), 2.80 (3H, s, SOMe), 2.34 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17); m/e (relative intensity) 505 (M·, 17%), 261 (96), 244 (100) (Found: M·, 505.2148, $C_{28}H_{35}NO_7S$ requires 505.2132).

Example 12

Sodium 8-[2-(1-normon-2-yl)-5-oxazolyl]-octanoate A

A mixture of 5-(7-methoxycarbonylheptyl)-2-(1-normon-2-yl) oxazole A (64 mg, 0.12 mmol), DMF (1.8 ml), bakers' yeast (2.5 g) and 0.2M pH 7 phosphate buffer (30 ml) was vigorously stirred for 18 h at 20°C and then filtered through celite and evaporated under reduced pressure. The resulting residue was resuspended in water and the pH adjusted to 4. The resulting residue was extracted with ethyl acetate, which was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative hplc (75% 0.05M aqueous ammonium acetate: 25% THF, C-8 reverse phase 250 × 10 mm column) to give the title sodium salt as a colourless oil (9 mg, 14%); δ_H (CD_3OD) 6.79 (1H, s, oxazole-H4), 6.13 (1H, s, H2), 2.68 (2H, t, oxazole-CH_2), 2.14 (2H, t, $CH_2CO_2^-$), 2.19 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17).

Example 13

5-p-Hydroxymethylphenyl-2-(1-normon-2-yl)oxazole A

A solution of *p*-hydroxymethylphenacyl monamide A (0.30 g, 0.6 mmol) in THF (20 ml) was treated with chlorotrimethylsilane (0.39 ml, 3 mmol), triethylamine (0.42 ml, 3 mmol) and 4-N,N-dimethylaminopyridine (5 mg) for 2h at 20°C. The mixture was then filtered, the filtrate was evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered, the filtrate was evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (3 ml), pyridine (3 ml), triethylamine (0.18 ml, 1.2 mmol) and tetrachloromethane (0.24 ml, 2.4 mmol). Triphenylphosphine (0.33 g, 1.2 mmol) was then added and the mixture allowed to stand at 60°C for 1h.

The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil, which was dissolved in dioxan (20 ml) and water (5 ml). Concentrated aqueous hydrochloric acid (6 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and evaporated under duced pressure to leave a brown oil which was purified by chromatography on silica gel (10 g) eluting ith a gradient of 4 to 10% methanol in dichloromethane to give the title oxazole as pale yellow needles, mp 128—130° (CH_2Cl_2) (0.16 g, 56%); ν_{max} 3400, 1655, 1530 cm^{-1}; λ_{max} (EtOH) 306 nm (ε_m 33,200); δ_C ($CDCl_3$) 7.67 and 7.43 (4H, ABq, aryl), 7.35 (1H, s, oxazole-H), 6.29 (1H, s, H2), 4.71 (2H, d, $ArCH_2$), 2.33 (3H, s, CH_3-15), 1.24 (3H, d, CH_3-17); δ_C ($CDCl_3$) 161.9 (C1), 150.9 (C5'), 148.2 (C3), 142.5 (C4''), 128.0 (C3'', C5''), 127.1 (C1''), 124.6 (C2'', C6''), 122.4 (C4'), 113.3 (C2), 75.9 (C5), 71.0 (C13), 70.4 (C7), 69.4 (C9), 66.0 (C16), 64.5 (CH_2Ar), 61.1 (C11), 56.4 (C10), 43.5 (C12), 43.1 (C4), 40.7 (C8), 32.5 (C9), 20.2 (C14), 19.7 (C15), 12.2 (C17); *m/e* (relative intensity) 473 ($M^{\oplus}$, 8%), 229 (100) (Found: $M^{\oplus}$, 473.2379, $C_{28}H_{35}NO_7$ requires 473.2411).

Example 14

5-Methyl-2-(1-normon-2-yl)oxazole A

A solution containing glycine (7.5 g, 0.10 mol), pyridine (50 ml, 0.60 mol) and acetic anhydride (110 ml, 1.17 mol) was boiled under reflux for 6h and then evaporated under reduced pressure. Distillation of the residue gave diacetylaminoacetone as a yellow oil (10.0 g, 64%); b.p. 100—120°C/1 mm; δ_H ($CDCl_3$) 4.5 (2H, s, CH_2), 2.3 (6H, s, Ac-N), 2.2 (3H, s, Ac-C).

Diacetylaminoacetone (5 g) and phosphoryl chloride (10 ml) were heated together at reflux for 1h. The mixture was cooled and decomposed with aqueous sodium bicarbonate. This was extracted with ether and the combined extracts carefully concentrated under reduced pressure. Distillation of the residue gave 2,5-dimethyloxazole as a mobile colourless liquid (1.0 g, 32%); b.p. ~120°C/760 mm; δ_H (CDCl3) 6.6 (1H, s, H-4), 2.4, 2.25 (6H, 2s, Me_2).

To a solution of 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]propan-2-one, (2.0 mmol) and triethylamine (0.86 ml, 6.20 mmol) in dry THF (25 ml) was added trimethylsilyl

chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethylamino)-pyridine. After stirring at room temperature for 2h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in ether then filtered and concentrated under reduced pressure again. This oil (the "protected ketone") was taken up in dry THF (15 ml) ready for the next stage of the reaction.

A solution of 2,5-dimethyloxazole (0.21 g, 2.20 mmol) and butyl lithium (2.20 mmol) in dry THF at −78°C was stirred for 10—15 minutes. To the metalated species produced was added trimethylsilyl chloride (0.28 ml, 2.20 mmol) and this mixture stirred at −78°C for 45 minutes, followed by a further 45 minutes at −20°C to −25°C. The resultant solution was cooled to −78°C and a further equivalent of butyl lithium (2.04 mmol) added. Stirring was continued for 45 minutes before adding the protected ketone, *vide supra*, and allowing to warm to room temperature. The mixture was quenched with ammonium chloride solution, extracted with ethyl acetate (3 × 50 ml) and the extract dried ($MgSO_4$). Solvent removal under reduced pressure gave the protected oxazole which was taken up in THF/water (4:1, 50 ml) and treated with concentrated hydrochloric acid (10 drops) for 5 min, then finally quenched with sodium bicarbonate solution. Extraction with ethyl acetate, drying ($MgSO_4$) and solvent removal under reduced pressure gave the triol which was further purified by column chromatography on silicagel (20 g) using dichloromethane/methanol (0 to 6%) as eluant. This gave the title oxazole as a colourless oil (0.20 g, 26%); ν_{max} (film) 3400, 1655, 1610 cm^{-1}; λ_{max} (EtOH) 264 nm (ε_m 15,000); δ_H ($CDCl_3$) 6.73 (1H, s, H4'), 6.16 (1H, s, H2), 2.33 (3H, s, Het-CH_3-15), 1.23 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17); δ_C ($CDCl_3$) 160.7 (C1), 147.4 (Het-C5), 145.3 (C3), 123.1 (Het-C4), 113.2 (C2), 75.4 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6), 65.4 (C16), 61.2 (C11), 55.6 (C10), 42.8 (C4), 42.6 (C12), 39.5 (C8), 31.8 (C9), 20.7 (C14), 19.3 (C15), 12.6 (C17), 10.8 (Het-Me); *m/e* (relative intensity) 381 ($M^{\oplus}$, 6%), 176 (12), 137 (100) (Found: $M^{\oplus}$ = 381.2133, $C_{20}H_{31}NO_6$ requires 381.2116).

Example 15

5-p-Formylphenyl-2-(1-normon-2-yl)oxazole A

A mixture of 5-*p*-hdyroxymethylphenyl-2-(1-normon-2-yl)oxazole A (100 mg), activated manganese dioxide (500 mg) and acetonitrile (40 ml) was stirred vigorously for 1.5h and then filtered. The filtrate was evaporated under reduced pressure and the resulting residue chromatographed quickly (10 g silica, 0 to 10% methanol in dichloromethane) to give the title aldehyde as a yellow oil (21 mg, 21%); ν_{max} (film) 3400, 1695, 1665, 1605 cm^{-1}; λ_{max} (EtOH) 337 nm; δ_H ($CDCl_3$) 10.01 (1H, s, CHO), 7.94, 7.79 (4H, ABq, aryl), 7.53 (1H, s, Het-H), 6.32 (1H, s, H2), 2.36 (3H, s, CH_3-15), 1.25 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17); δ_C ($CDCl_3$) 191.2 (CHO), 162.3 (C1), 148.5 (C3), 148.3 (Het-C4), 135.6 (C'4), 133.5 (C1'), 130.4 (C3', C5'), 125.6 (Het-C5), 124.1 (C2', C6'), 113.0 (C2), 75.3 (C5), 71.3 (C13), 70.5 (C7), 69.0 (C6), 65.5 (C16), 61.2 (C11), 55.5 (C10), 43.0 (C4), 42.8 (C12), 39.7 (C8), 31.8 (C9), 20.8 (C14), 19.7 (C15), 12.7 (C17); *m/e* (relative intensity) 471 ($M^{\oplus}$, 9%), 227 (100) (Found: $M^{\oplus}$ = 471.2249, $C_{26}H_{33}NO_7$ requires 471.2243).

Example 16

5-p-Methoxycarbonylphenyl-2-(1-normon-2-yl)oxazole A

A mixture of 5-*p*-hydroxymethylphenyl-2-(1-normon-2-yl)oxazole A (50 mg, 0.1 mmol), sodium cyanide (25 mg, 0.5 mmol), acetic acid (18 µl, 0.3 mmol), activated manganese dioxide (500 mg), and methanol (10 ml) was stirred for 6h at 20°C. More manganese dioxide (500 g) was then added and the mixture stirred for another 2h at 20°C and then filtered. The filtrate was evaporated under reduced pressure and the resulting residue purified by chromatography to give the title methyl ester as a yellow oil (12—15 mg, 23—30%); ν_{max} (film) 3400, 1715, 1655, 1610 cm^{-1}; λ_{max} (EtOH) 328 nm; δ_H ($CDCl_3$) 8.07 and 7.69 (4H, 2d, aryl), 7.47 (1H, s, Het-H), 6.30 (1H, s, H2), 2.33 (3H, s, CH_3-15), 1.24 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-14); δ_C ($CDCl_3$) 166.6 ($\underline{C}O_2Me$), 162.0 (C1), 149.0 (C3), 147.9 (Het-C4), 132.2 (C1'), 130.4 (C3'), 129.5 (C4'), 124.8 (Het-C5), 123.8 (C2'), 113.1 (C2), 75.4 (C5), 71.4 (C13), 70.6 (C7), 69.1 (C6), 65.6 (C16), 61.3 (C11), 55.6 (C10), 55.2 ($CO_2\underline{Me}$), 43.0 (C12), 42.9 (C4), 39.7 (C8), 31.8 (C9), 20.9 (C14), 19.8 (C15), 12.7 (C17); *m/e* (relative intensity) 501 ($M^{\oplus}$, 8%), 257 (100) (Found: $M^{\oplus}$ = 501.2362. $C_{27}H_{35}NO_8$ requires 501.2363).

Example 17

Sodium 4-[2-(1-normon-2-yl)-5-oxazolyl]benzoate A

5-*p*-Methoxycarbonylphenyl-2-1-normon-2-yloxazole A (50 mg, 0.1 mmol) was dissolved in excess trimethylorthoformate (2 ml). *p*-Toluenesulphonic acid (*ca.* 5 mg) was added, and the mixture stirred 25 min at 20°C and then evaporated under reduced pressure. The residue was treated with sodium hydroxide (40 mg, 1.0 mmol), water (10 ml) and methanol (10 ml) at 20°C for 18h. The mixture was then acidified to pH2 for 15 min, and then adjusted to pH9.5 for 3h, and then to pH4.

Extraction with ethyl acetate and evaporation of the extracts under reduced pressure then gave the free acid, which was immediately converted to the sodium salt with sodium bicarbonate in aqueous methanol. The sodium salt was obtained as a gummy solid (23 mg, 45%); ν_{max} (film) 3400, 1660, 1595, 1540 cm^{-1}; δ_H (CD_3OD) 8.03 and 7.68 (4H, ABq, aryl), 7.52 (1H, s, Het-H), 6.25 (1H, s, H2), 2.30 (3H, s, CH_3-15), 1.19 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17).

Example 18

5-p-Bromophenyl-2-(1-normon-2-yl)oxazole A

To 1,4'-dibromoacetophenone (27.8 g, 100 mmol) in dichloromethane (200 ml) was added hexamine (14.0 g, 100 mmol). The precipitated salt was collected and dissolved in a mixture of concentrated hydrochloric acid (33 ml) and ethanol (67 ml). After 16h at 20°C the precipitate was collected and recrystallised from dilute hydrochloric acid to give p-bromophenacylammonium chloride as white platelets (9.0 g, 36%); m.p. 287°C (dec.); δ_H (dmso-d_6) 8.6 (3H, bs, $-NH_3^{\oplus}$), 7.8 (4H, ABq, aryl).

To a solution of monic acid A (1.72 g, 5 mmol) in dry THF (50 ml) were added triethylamine (0.69, 5 mmol) and isobutyl chloroformate (0.65 ml, 5 mmol) and after 10 min, p-bromophenacylammonium chloride (1.26 g, 5 mmol) and more triethylamine (0.69 ml, 5 mmol). After 3h at 20°C the solution was poured into water and extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation of the extract under reduced pressure then gave crude p-bromophenacyl monamide A as a gummy white solid (1.51 g, 59%); ν_{max} 3400, 2985, 1695, 1660, 1635, 1590 cm^{-1}; δ_H (CD_3OD) 7.72 (4H, ABq, aryl), 5.88 (1H, s, H2), 4.70 (2H, s, H1'), 2:12 (3H, s, CH_3-15), 1.14 (3H, d, CH_3-14), 0.90 (3H, d, CH_3-17).

p-Bromophenacyl monomide A (1.35 g, 2.5 mmol) in THF (50 ml) was treated with chlorotrimethylsilane (1.0 ml, 8 mmol), triethylamine (1.1 ml, 8 mmol) and 4-N,N-dimethylaminopyridine (50 mg) for 2h at 20°C. The mixture was then filtered and evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under educed pressure and the resulting residue dissolved in a mixture of acetonitrile (10 ml), pyridine (10 ml), triethylamine (0.7 ml, 5 mmol) and tetrachloromethane (1.0 ml, 10 mmol). Triphenylphosphine (1.3 g, 5 mmol) was then added and the mixture allowed to stand at 20°C for 3h.

The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil, which was dissolved in THF (80 ml) and water (20 ml). Concentrated aqueous hydrochloric acid (25 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to leave a brown oil which was purified by chromatography on silica gel (50 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give the title oxazole as a yellow foam (0.30 g, 23%); ν_{max} (film) 3400, 1655, 1480, 730 cm^{-1}; λ_{max} (EtOH) 306 nm (ε_m 26,300); δ_H 7.49 (4H, ABq, aryl), 7.34 (1H, s, het-H), 6.28 (1H, s, H2), 2.31 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17); δ_C ($CDCl_3$) 161.3 (C1), 148.9 (C3), 147.4 (C4'), 132.1 (C2''), 126.9 (C5'), 125.4 (C5'), 125.4 (C3''), 123.0 (C4''), 122.0 (C1''), 112.9 (C2), 75.2 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6), 65.4 (C16), 61.2 (C11), 55.5 (C10), 42.8 (C12), 42.7 (C4), 39.5 (C8), 31.7 (C9), 20.8 (C14), 19.6 (C15), 12.6 (C17); *m/e* (relative intensity) 521, 523 (4%, 1:1, $M^{\oplus}$), 277, 279 (72, 58), 41 (100) (Found: $M^{\oplus}$ = 521.1428. $C_{25}H_{32}NO_6{}^{79}Br$ requires 521.1410).

Example 19

5-(8-Hydroxyoctyl)-2-(1-normon-2-yl)oxazole A

9-Hydroxynonanoic acid (8.7 g, 50 mmol) in pyridine (8.1 ml, 100 mmol) was treated with acetic anhydride (4.7 ml, 50 mmol) at below 20°C for 2h. The mixture was poured onto ice and acidified. Two ether extractions gave 9-acetoxynonanoic acid as a colourless oil (10.8 g, 100%)) δ_H ($CDCl_3$) 10.0 (1H, s, CO_2H), 4.0 (2H, t, H9), 2.3 (2H, m, H2), 2.0 (3H, s, OAC), 1.1—1.8 (12H, m, H3-H8).

9-Acetoxynonanoic acid (10.8 g, 50 mmol) was added to thionyl chloride (7.2 ml, 100 mmol) at reflux. After 30 min at reflux distillation at reduced pressure gave first excess thionyl chloride and then 9-acetoxyonanoyl chloride as a yellow oil (4.0 g, 32%); δ_H ($CDCl_3$) 4.0 (2H, t, H9), 2.9 (2H, t, H2), 2.0 (3H, s, OAc), 1.1—1.8 (12H, m, H3-H8).

9-Acetoxynonanoyl chloride (4.0 g, 17 mmol) was slowly added to a solution of diazomethane (40 mmol) in ether (100 ml) at 0°C. After 1h at 0°C concentrated hydrobromic acid (20 ml) was added. After 1h at 20°C the ether was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give 10-bromo-9-oxodecyl acetate as a yellow oil (4.4 g, 88%); δ_H ($CDCl_3$) 4.0 (2H, t, 0), 3.8 (2H, s, CH_2Br), 2.6 (2H, t, CH_2CO), 2.0 (3H, s, 0AC), 1.1—1.8 (12H, m, $(CH_2)_6$).

10-Bromo-9-oxodecyl acetate (2.2 g, 7.5 mmol) and hexamine (1.4 g, 10 mmol) in chloroform (50 ml) were stirred for 16h at 20°C; and then the solution was evaporated under reduced pressure. The residue was dissolved in a mixture of concentrated hydrochloric acid (10 ml) and ethanol (30 ml). After 16h at 20°C the solution was evaporated under reduced pressure and the residue extracted with ethanol. Evaporation of the ethanol under reduced pressure then gave 10-hdyroxy-2-oxodecylammonium chloride as a brown powder which also contained ammonium chloride (2.8 g); δ_H (D_2O), 3.5 (2H, t, H10), 2.6 (2H, t, H3), 1.1—1.8 (12H, m, H4-H9).

10-Hydroxy-2-oxodecylammonium chloride (2.8 g, crude) in methanol (20 ml) was added to isobutyloxycarbonyl monate A (10 mmol, prepared from monic acid (10 mmol), isobutyl chloroformate (10 mmol) and triethylamine (10 mmol)) in THF (50 ml). After 2h at 20°C the solution was partitioned between aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting residue purified by chromatography (20 g silicagel, 0 to 15% methanol in dichloromethane) to give 10-hydroxy-2-oxodecyl monamide A as a colourless oil (0.8 g, 21%); ν_{max} (film) 3400, 2960, 1720, 1660, 1630 cm^{-1}; δ_H (CD_30D) 5.75 (1H, s, H2), 4.71 (2H, s, H1'), 2.08 (3H, s, CH_3-15), 1.3 (12H, m, H4'-H9'), 1.20 (3H, d, CH_3-14), 0.89 (3H, d, CH_3-17).

10-Hydroxy-2-oxodecyl monamide A (0.51 g, 1 mmol) in THF (20 ml) was treated with chlorotrimethylsilane (0.63 ml, 5 mmol), triethylamine (0.70 ml, 5 mmol) and 4-N,N-dimethylaminopyridine (5 mg) for 2h at 20°C. The mixture was then filtered and evaporated under reduced pressure, and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue dissolved in a mixture of acetonitrile (3 ml), pyridine (3 ml), triethylamine (0.28 ml, 2 mmol) and tetrachloromethane (0.39 ml, 4 mmol). Triphenylphosphine (0.52 g, 2 mmol) was then added and the mixture allowed to stand at 20°C for 3h.

The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil, which was dissolved in THF (20 ml) and water (5 ml). Concentrated aqueous hydrochloric acid (6 drops) was added and after 12 min the solution neutralised with aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and evaporated on silica gel (10 g) eluting with a gradient of 4 to 10% methanol in dichloromethane to give the title oxazole as a colourless oil (0.15 g, 27%); ν_{max} (film) 3400, 2960, 1655, 1605 cm^{-1}; δ_H ($CDCl_3$) 6.81 (1H, s, het-H), 6.16 (1H, s, H2), 3.62 (2H, t, H8'), 2.64 (2H, t, H1'), 2.21 (3H, s, CH_3-15), 1.3 (12H, m, H2'-H7'), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17); δ_C ($CDCl_3$) 160.6 (C1), 151.7 (C4'), 145.3 (C3), 122.6 (C5'), 113.3 (C2), 75.3 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6), 65.5 (C16), 62.8 (C8''), 61.2 (C11), 55.6 (C10), 42.7 (C4, C12), 39.5 (C8), 32.7 (C1''), 31.8 (C9), 29.2, 29.1, 28.9, 27.5, 25.7, 25.5 (C2''-C7''), 20.8 (C14), 19.3 (C15), 12.6 (C17); *m/e* (relative intensity) 495 ($M^{\oplus}$, 9%), 251 (100) (Found: $M^{\oplus}$ 495.3200, $C_{27}H_{46}NO_7$ requires 495.3196).

Example 20

5-(3-Thienyl)-2-(1-normon-2-yl)oxazole A

3-Acetylthiophene (6.3 g, 50 mmol) was dissolved in anhydrous ether (100 ml) and aluminium chloride (catalytic amount) added, Bromine (2.55 ml, 50 mmol) was added dropwise and then stirred for 10 min. The ether was removed under reduced pressure and the residue washed with water. The crude product was recrystallised from petroleum-ether (60—80°C) to yield 3-bromoacetylthiophene m.p. 54—56°C (8.76 g, 85%), δ_H ($CDCl_3$) 8.15 (1H, dd, H2), 7.55 (1H, dd, H4'), 7.35 (1H, dd, H5').

3-Bromoacetylthiophene (6.15 g, 30 mmol) was dissolved in dichloromethane (200 ml) and hexamethylenetetramine (4.2 g, 30 mmol) added and stirred for 1h. The reaction was filtered and washed with dichloromethane to yield the hexamine salt as a pale pink solid m.p. 122—125°C (8.06 g, 78%). The hexamine salt (7.6 g, 22 mmol) was stirred in ethanol (30 ml) and hydrochloric acid (10 ml) for 1h and after standing overnight the mixture was filtered and the filtrate evaporated under reduced pressure. The resulting residue was taken up in methanol, filtered, and the filtrate evaporated under reduced pressure. The residue was recrystallized from isopropanol containing a few drops of dilute hydrochloric acid to yield 3-(2-amino-1-oxoethyl) thiophene hydrochloride (2.92 g, 75%) δ_H (CD_3OD) 8.55 (1H, s, H2'), 7.60 (2H, s, H4', 5'), 4.52 (2H, s, CH_2).

The isobutoxyformic mixed anhydride of monic acid A was prepared on a 10 mmol scale by mixing monic acid A (3.44 g, 10 mmol), triethylamine (1.5 ml, 11 mmol), and isobutylchloroformate (1.44 ml, 11 mmol) for 1h at 0°C. 3-(2-amino-1-oxoethyl)thiophene hydrochlorine (1.77 g, 10 mmol) and triethylamine (4.5 ml) added and stirred for 4h. The reaction mixture was then poured into brine, extracted with ethyl acetate, the extract was dried ($MgSO_4$), and evaporated under reduced pressure. The residual orange oil was purified by chromatography on silica gel (15 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to yield N-[2-oxo-2-(3-thienyl)ethyl] monamide A as a pale yellow oil (691 mg, 15%); ν_{max} (film) 3400, 1680, 1660, 1630, 1510 cm^{-1}; λ_{max} (EtOH) 216 nm (Em 23,622), 248 nm (Em 15,878); δ_H (CD_3OD) 8.42 (1H, dd, H2''), 7.59 (1H, dd, H4''), 7.51 (1H, dd, H5''), 5.89 (1H, s, H2), 4.63 (2H, s, $CH_2$1'), 2.18 (3H, 5, CH_3-15), 1.20 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17); δ_C (CD_3OD) 191.2 (C2'), 169.8 (C1), 153.1 (C3), 141.1 (C3''), 134.1, 127.9, 127.5 (C2'', 4'', 5''), 120.8 (C2), 76.3 (C5), 71.6 (C13), 70.8 (C7), 70.1 (C6), 66.3 (C16), 61.3 (C11), 56.9 (C10), 47.6 (C1'), 43.7, 43.2 (C4, 12), 41.6 (C8), 33.0 (C9), 20.4 (C14), 19.0 (C15), 12.2 (C17).

N-[2-Oxo-2-(3-thienyl)ethyl] monamide A (0.46 g, 1 mmol) in dry THF (25 ml) was treated with chlorotrimethylsilane (0.55 ml, 4.3 mmol), triethylamine (0.6 ml, 4.3 mmol) and 4-N,N-dimethylaminopyridine (catalytic amount) for 2½ h at 20°C. The mixture was then filtered and evaporated under reduced pressure. The residue was dissolved in a mixture of acetonitrile (5 ml) and pyridine (5 ml). Triethylamine (0.3 ml, 2 mmol), carbon tetrachloride (0.4 ml, 4 mmol), and triphenylphosphine (0.52 g, 2 mmol) were then added and the mixture heated at 60°C for 2h. The black solution was then evaporated under reduced pressure. The resulting residue was taken up in ethyl acetate, washed with aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure.

The residual oil was dissolved in THF (40 ml) and water (10 ml). Concentrated hydrochloric acid (15 drops) was added and after 6 min the solution was neutralised with aqueous sodium bicarbonate. The solution was extracted with ethyl acetate, washed with brine, the extract was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (7 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to give the title oxazole as a yellow oil (0.178 g, 40%); ν_{max} (film) 3400, 1650, 1610, 1540, 1520, 1490 cm^{-1}; λ_{max} (EtOH) 224 nm (Em 11,999), 300 nm (Em 19,837); δ_H ($CDCl_3$) 7.60 (1H, dd, H2''), 7.37 (1H, dd, H5''), 7.29 (1H, dd, H4''), 7.18 (1H, s, H4'), 6.26 (1H, s, H2), 2.30 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17); δ_C ($CDCl_3$) 160.6 (C1), 146.9, 146.7 (C3, 5'), 129.4 (C4'), 126.8, 124.5, 122.2, 120.4 (C2'', 3'', 4'', 5''), 113.2, (C2), 75.5 (C5), 71.3 (C13), 70.6 (C7), 69.1 (C6),

65.6 (C16), 61.3 (C11), 55.6 (C10), 42.9 (C4, 12), 39.7 (C8), 31.9 (C9), 20.9 (C14), 19.7 (C15), 12.7 (C17); *m/e* (relative intensity) 449, ($M^{\oplus}$, 5%), 227 (12), 205 (66), 69 (75), 43 (100) (Found: 449.1869, $C_{23}H_{31}NO_6S$ requires 449.1872).

Example 21

5-p-Cyanophenyl-2-(1-normon-2-yl)oxazole A

4-Acetylbenzonitrile (14.5 g, 100 mmol) was dissolved in anhydrous ether (150 ml). Aluminium chloride (catalytic amount) was added to the solution. Bromine (5.1 ml, 100 mmol) was added dropwise at room temperature and the solution stirred for ½h. A precipitate formed and was collected and dried to yield p-cyanophenacyl bromide, m.p. 85—86°C (19.34 g, 86%); δ_H ($CDCl_3$) 7.80 and 8.10 (4H, ABq, aryl), 4.45 (2H, s, CH_2).

p-Cyanophenacyl bromide (13.44 g, 60 mmol) was dissolved in methylene chloride (400 ml) and hexamethylenetetramine (8.4 g, 60 mmol) added and the reaction stirred for 3h. The precipitated solid was collected and dried to yield the hexamine salt, m.p. 146—148°C (21 g, 96%). The hexamine salt (14 g) was added to a mixture of methanol (42 ml) and concentrated hydrochloric acid (14 ml) and left standing for 3 days. Isopropanol was added to the residue, and the solid collected and dried to yield impure p-cyanophenacyl ammonium chloride.

Monic acid A (3.44 g, 10 mmol) was dissolved in dry THF (100 ml) and cooled to 0°C. Triethylamine (1.5 ml, 11 mmol) and isobutylchloroformate (1.44 ml, 11 mmol) were added and stirred ½h. Impure p-cyanophenacyl ammonium chloride (1.96 g, 10 mmol) and triethylamine (1.5 ml, 11 mmol) were added and the mixture stirred for 2h. Further p-cyanophenacyl ammonium chloride (1 g, 5 mmol) and triethylamine (0.8 ml, 5 mmol) were then added and stirred for ½h. The reaction was then poured into brine and extracted with ethyl acetate and the organic layer was separated, washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel (25 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to give N-(p-cyanophenacyl) monamide A as a pale yellow foam (1.35 g, 28%); ν_{max} (film) 3400, 2230, 1700, 1660, 1640 cm^{-1}; λ_{max} (EtOH) 204 nm (Em 26,197), 246 nm (Em 25,414); δ_H (CD_3OD) 8.15 and 7.90 (4H, ABq, aryl), 5.90 (1H, s, H2), 4.72 (2H, s, CH_2-1'), 2.17 (3H, s, CH_3-15), 1.20 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17); δ_C (CD_3OD) 195.7 (C2'), 169.8 (C1), 153.4 (C3), 139.7 (C1''), 133.8, 129.6 (C2'', 3'', 5'', 6''), 120.6 (C2), 118.9 (CN), 117.6 (C4''), 76.3 (C5), 71.6 (C13), 70.7 (C7), 70.1 (C6), 66.3 (C16), 61.3 (C11), 56.9 (C10), 47.3 (C1'), 43.7 (C4, 12), 41.6 (C8), 33.0 (C9), 20.4 (C14), 19.0 (C15), 12.2 (C17); *m/e* (relative intensity) 486, ($M^{\oplus}$, 2%), 327 (11), 242 (46), 227 (48), 111 (100) (Found: 486.2334, $C_{26}H_{34}NO_2O_7$ requires 486.2336).

N-(p-Cyanophenacyl) monamide A (0.49 g, 1 mmol) in dry THF (30 ml) was treated with chlorotrimethylsilane (0.55 ml, 4.3 mmol), triethylamine (0.6 ml, 4.3 mmol) and 4-N,N-dimethylaminopyridine (catalytic amount) for 1½h and 20°C. The mixture was then filtered and evaporated under reduced pressure. The residue was dissolved in a mixture of acetonitrile (2.5 ml), pyridine (2.5 ml), triethylamine (0.3 ml, 2 mmol) and carbon tetrachloride (2.5 ml), triethylamine (0.3 ml, 2 mmol) and carbon tetrachloride (0.4 ml, 4 mmol) was treated with triphenylphosphine (0.52 g, 2 mmol) and heated at 60°C for 1½h. The black solution was then evaporated under reduced pressure and the residue taken up in ethyl acetate. The extracts were washed with aqueous sodium bicarbonate and brine, dried ($MgSO_4$), evaporated under reduced pressure and the resulting residue dissolved in THF (40 ml) and water (10 ml). Concentrated aqueous hydrochloric acid (15 drops) was added and after 5 min the solution was neutralised with aqueous sodium bicarbonate. The solution was extracted with ethyl acetate and the extracts washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure and the residual oil purified by chromatography (7 g silica gel, 0 to 4% methanol in dichloromethane) to yield the title oxazole as a pale yellow oil (0.122 g, 26%); ν_{max} (film) 3440, 2230, 1650, 1610, 1530 cm^{-1}; λ_{max} (EtOH) 231 nm (Em 14,409), 326 nm (Em 22,655); δ_H ($CDCL_3$) 7.71 (4H, s aryl), 7.50 (1H, s, H4'), 6.30 (1H, s, H2), 2.35 (3H, s, CH_35), 1.23 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17); δ_C ($CDCl_3$) 162.4 (C1), 148.6, 148.0 (C3, 5'), 132.8 (C3'', 5''), 132.2 (C1''), 125.7 (C4'), 124.3 (C2'', 6''), 118.5 (C7''), 13.0 (C2), 111.4 (C4''), 75.4 (C5), 71.3 (C13), 70.6 (C7), 69.2 (C6), 65.5 (C16), 61.3 (C11), 55.6 (C10), 43.0, 42.9 (C4, 12), 39.8 (C8), 31.8 (C9), 20.9 (C14), 19.8 (C15), 12.7 (C17); *m/e* (relative intensity) 468, ($M^{\oplus}$, 8%), 277 (9), 224 (100) (Found: 468.2249, $C_{26}H_{32}N_2O_6$ requires 468.2260).

Example 22

5-m-Methylthiophenyl-2-(1-normon-2-yl)oxazole A

m-Acetylthiophenol (76 g, 50 mmol), sodium hydroxide (2.0 g, 50 mmol) and ethanol (50 ml) were stirred at room temperature for 1h. Iodomethane (3.2 ml, 50 mmol) was added and stirred for 2h then the solution was evaporated under reduced pressure and the residue taken up in ethyl acetate. This solution was washed with aqueous sodium bicarbonate, brine, then dried ($MgSO_4$), and evaporated under reduced pressure to yield m-Methylthioacetophenone (7.21 g, 87%); δH ($CDCL_3$) 705—785 (4H, m, aryl), 2.55 (3H, S, $COCH_3$), 2.45 (3H, S, SCH_3).

m-Methylthioacetophenone (7.14 g, 43 mmol) was dissolved in chloroform (100 ml). Aluminium chloride (catalytic amount) and bromine (2.2 ml, 43 mmol) were added and stirred for 1h. The reaction was quenched with aqueous sodium chloride — sodium bicarbonate and the organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was taken up in ethyl acetate, wshed with aqueous sodium bicarbonate, then brine, dried ($MgSO_4$) and evaporated under reduced pressure to yield

m-Methylthiophenacyl bromide (7.64 g, 73%); δH ($CDCL_3$) 7.1—7.9 (4H, m, aryl), 4.40 (2H, S, CH_2), 2.45 (3H, S, SCH_3).

m-Methylthiophenacyl bromide (7.6 g, 30 mmol) and hexamethylenetetramine (4.2 g, 30 mmol) were stirred in methylene chloride (160 ml) for 1½h at room temperature. The reaction was then filtered to yield the hexamine salt as a pale yellow solid (10.08 g, 85%) m.p. 140—142°C. The hexamine salt was added to a mixture of ethanol (40 ml) and concentrated hydrochloric acid (10 ml) and left standing overnight. A solution of dilute hydrochloric acid was added and the reaction filtered to yield the hydrochloride salt (4.22 g, 75%); δH ($(CD_3)_2SO$) 8.50 (S, NH), 7.8—7.5 (m, aryl), 4.6 (S, CH_2).

The isobutoxy formic anhydride of monic acid A was prepared from monic acid A (1.72 g, 5 mmol), triethylamine (0.75 ml, 5 mmol), and isobutylchloroformate (0.7 ml, 5 mmol). After 20 min at 0°C the m-thiomethylphenacyl ammonium chloride (1.58 g) and triethylamine (1.75 ml) were added and stirred overnight. The reaction mixture was poured into brine, extracted ethyl acetate, and the extract dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (15 g) eluting with a gradient of 0 to 6% methanol in dichloromethane to yield 3-methylthiophenacyl monamide A as a pale yellow oil (630 mg, 25%); ν_{max} ($CHCl_3$) 3400, 1690, 1660, 1630, 1440 cm^{-1}; λ_{max} (EtOH) 232 nm (ε_m 24,743); δH (CD_3OD) 7.85—7.25 (4H, m, aryl), 5.90 (1H, S, H2), 4.70 (2H, S, CH_2-1'), 2.50 (3H, S, SCH_3), 2.15 (3H, S, CH_3-15), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17).

m-Methylthiophenacyl monamide A (491 mg, 0.97 mmol) in dry THF (30 ml) was treated with triethylamine (0.6 ml, 4.3 mmol), trimethylsilyl chloride (0.55 ml, 4.3 mmol) and a few crystals of 4-N.N'-dimethylaminopyridine. After stirring for 1h at room temperature the reaction mixture was filtered and the filtrate evaporated under reduced pressure. To the residue was added acetonitrile (3 ml), pyridine (3 ml), triethylamine (0.3 ml), carbon tetrachloride (0.4 ml) and triphenylphosphine (0.52 g, 2 mmol). The solution darkened after a few minutes and was stirred at room temperature for 1h then evaporated under reduced pressure, and the residue taken up in ethyl acetate and aqueous sodium chloride — sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was treated with THF (50 ml), water (12 ml), and concentrated hydrochloric acid (15 drops) to remove the protecting groups. After 5 min the reaction was quenched with aqueous sodium bicarbonate, extracted with ethyl acetate and the extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by chromatography on silica gel (15 g) eluting with a gradient of 0 to 6% methanol in dichloromethane to yield the title oxazole as a pale yellow oil (151 mg, 30%); ν_{max} (film) 3400, 1650, 1585, 1525, 1505 cm^{-1}; λ_{max} (EtOH) 301 nm (ε_m 14,938); δH ($CDCl_3$) 7.50—7.05 (5H, m, aryl + H4'), 6.25 (1H, 5, H2), 2.50 (3H, S, SCH_3), 2.30 (3H, S, CH_3-15), 1.20 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17).

Example 23

5-m-Methylsulphonylphenyl-2-(1-normon-2-yl)oxazole A

5-m-Methylthiophenyl-2-(1-normon-2-yl) oxazole A (122 mg, 0.25 mmol) was dissolved in methylene chloride (20 ml) and cooled to 0°C. m-Chloroperoxybenzoic acid (69 mg, 0.5 mmol) and sodium hydrogen carbonate (42 mg, 0.5 mmol) were added and reaction stirred for 6h then left standing overnight. The crude product was purified by chromatography on silicagel (7 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to yield the title compound as a pale yellow foam (73 mg, 56%); ν_{max} (film) 3440, 1650, 1610, 1525, 1300, 1150 cm^{-1}; δH ($CDCl_3$) 8.17 (1H, 5, H2''), 7.87 ($2H_1$ d,d, H4'', 6''), 7.63 (1H, t, H5''), 7.50 (1H, S, H4'), 6.30 (1H, S, H2), 3.13 (3H, S, SO_2CH_3), 2.33 (3H, 5, CH_3-15), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17).

Example 24

5-p-Dimethylaminosulphonylphenyl-2-(1-normon-2-yl)oxazole A

The diazonium salt prepared from p-aminoacetophenone (27 g, 0.2 mmol), concentrated hydrochloric acid (140 ml), water (30 ml) and sodium nitrite (14 g, 0.2 mol) was added to a mixture of acetic acid (250 ml), sulphur dioxide (80 g), and cuprous chloride (3 g) at 20°C. After 40 min the mixture was cooled to 0°C and water (1l) added. Filtration, and drying of the residue followed by recrystallisation from carbon tetrachloride then gave p-acetylbenzenesulphonyl chloride as off-white needles (24 g, 55%); m.p. 70—72°C, lit mp* = 85°C; δH ($CDCl_3$) 8.1 (4H, S, aryl), 2.6 (3H, S, Me).

p-Acetylbenzenesulphonyl chloride (4.0 g, 18 mmol), aqueous dimethylamine (10 ml, 55 mmol), and THF (30 ml) were stirred together for 1h at 20°C and then partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure and the resulting residue recrystallised from either water or ether to give p-dimethylaminosulphonylacetophenone as fine white needles (3.8 g, 93%), m.p. 98—99°C (H_2O); δH (dmso-d_6) 8.0 (4H, ABq, aryl), 2.65 (9H, S, 3 × Me).

p-Dimethylaminosulphonylacetophenone (2.3 g, 10 mmol) in chloroform (30 ml) was treated with bromine (0.5 ml, 10 mmol). When the reaction was complete the solution was washed with aqueous sodium carbonate, dried ($MgSO_4$) and evaporated under reduced pressure to give p-dimethylamino-sulphonylphenocyl bromide as white crystals, which could be collected with petrol (2.8 g, 92%); δH ($CCDl_3$) 8.0 (4H, ABq, aryl), 4.5 (2H, S, CH_2), 2.7 (6H, S, CH_3).

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* v. Christof Troltzsch, *J. Prakt. Chem.*, 192 (1963).

p-Dimethylaminosulphonylphenacyl bromide (2.8 g, 9 mmol) was converted to its hexaminium salt with hexamine (1.4 g, 10 mmol) in chloroform (100 ml). This was collected and dissolved in concentrated hdyrochloric acid-ethanol (1:3, 50 ml). After 16h at 20°C the mixture was filtered and the filtration evaporated under reduced pressure to give a solid which was extracted with boiling 2-propanol.

Removal of the 2-propanol under reduced pressure gave p-dimethylaminosulphonylphenacylammonium chloride as a yellow powder after collection with ether (2.4 g, 85%); δH (dmso-d_6) 8.6 (3H, bs, $NH_3^{\oplus}$), 8.1 (4H, ABq, aryl), 4.1 (2H, S CH_2), 2.7 (6H, 3, CH_3).

p-Dimethylaminosulphonylphenacylammonium chloride (1.4 g, 5 mmol) and chloroacetic anhydride (0.5 ml, 6 mmol) in benzene (50 ml) were heated at reflux for 3h; the solution was then cooled and filtered to give p-dimethylaminosulphonylphenacyl chloroacetamide as a yellow powder (1.3 g, 83%); δ_H (dmso-d_6) 8.8 (1H, t, NH), 8.1 (4H, ABq, aryl), 4.8 (2H, d, CH_2N), 4.3 (2H, S, CH_2Cl), 2.7 (6H, S, CH_3).

p-Dimethylaminosulphonylphenacyl chloracetamide (1.3 g, 4 mmol) and phosphoryl chloride (10 ml) were heated together at reflux for 2h and then dissolved in dichloromethane. The mixture was washed with aqueous sodium carbonate, dried ($MgSO_4$) and evaporated under reduced pressure to give a dark oil. This was extracted with boiling benzene. Removal of the benzene under reduced pressure and crystallation of the residue with petrol then gave 2-chloromethyl-5-p-dimethylaminosulphonylphenyloxazole as waxy yellow rhombs (0.65 g, 52%); δH ($CDCl_3$) 7.8 (4H, S, aryl), 7.4 (1H, S, het-H), 4.7 (2H, S, CH_2), 2.7 (6H, S, CH_3).

2-Chloromethyl-5-p-dimethylaminosulphonylphenyloxazole (0.36 g, 1.2 mmol) and triethyl phosphite (0.27 m, 1.8 mmol) were heated at 160°C for 1h. Direct chromatography (5 g silica, 0 to 5% methanol in dichloromethane) then gave diethyl 5-p-dimethylaminosulphonylphenyl-2-oxazolylmethylphosphonate as a yellow gum (0.45 g, 93%), δH ($CDCl_3$) 7.7 (4H, s, aryl), 7.3 (1H, S, het-H), 4.6 (4H, m, OCH_2), 3.4 (1H, d, $^2CH_2$), 2.7 (6H, S, NMe_2), 1.3 (6H, t, CCH_3).

3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]propan-2-one (150 mg, 0.5 mmol) in THF (5 ml) was treated with chlorotrimethylsilane (0.25 ml, 2 mmol), triethylamine (0.28 ml, 2 mmol) and 4-N,N-dimethylaminopyridine (5 mg) for 2h at 20°C. The mixture was then filtered and evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue, (the "protected ketone") dissolved in THF, and set aside for the next stage of the reaction.

To a suspension of sodium hydride (13 mg, 0.5 mmol) in THF (2 ml) at 0°C was added diethyl 5-p-dimethylaminosulphonylphenyl-2-oxazolylmethylphosphonate (0.20 g, 0.5 mmol) in more THF (2 ml). The mixture was stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (*ca.* 1h). The solution was cooled (0°C), the protected ketone *vide supra* added, stirred for 30 minutes at 0°C and then at ambient temperature for 1h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (2.5 ml, 4:1) and treated with acid (6 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product, which was purified by chromatography (20 g silica, 0 to 12% methanol in dichloromethane) to give the title normonyloxazole as a pale yellow oil (75 mg, 27%); ν_{max} (film) 3400, 2950, 1650, 1605, 1340, 1160 cm^{-1}; λ_{max} (EtOH) 321 nm (Em 15,600); δ_H ($CDCl_3$) 7.79 (4H, ABq, aryl), 7.51 (1H, S, het-H), 6.30 (1H, S, H2), 2.72 (6H, S, NMe_2), 2.34 (3H, S, CH_3-15), 1.21 (3H, d, CH_3-14), 0.93 (3H, d, CH_3-17); δ_C (CD_3OD) 163.0 (C1), 149.7 (C3, C4'), 135.3 (C4''), 132.7 (C1''), 128.9 (C3''), 125.5 (C5'), 124.8 (C2''), 113.0 (C2), 75.7 (C5), 70.9 (C13), 70.5 (C7), 69.3 (C6), 65.9 (C16), 61.1 (C11), 56.2 (C10), 43.4 (C12), 43.0 (C4), 40.5 (C8), 38.0 (NMe_2), 32.3 (C9), 20.2 (C14), 19.8 (C15), 12.1 (C17).

Example 25

5-m-Methylsulphinylphenyl-2-(1-normon-2-yl)oxazole A

5-m-Methylthiophenyl-2-(1-normon-2-yl)oxazole A (122 mg, 0.25 mmol) was dissolved in dichloromethane (20 ml) and cooled to 0°C. m-Chloroperoxybenzoic acid (34.5 mg, 0.25 mmol) and sodium hydrogen carbonate (21 mg, 0.25 mmol) were added and stirred for 30 min. The reaction was purified by chromatography on silica gel (7 g) eluting with a gradient of 0 to 6% methanol in dichloromethane to yield the title compound as a pale yellow oil (65 mg, 51%); ν_{max} (film) 3400, 1710, 1650, 1525, 1500, 1410 cm^{-1}; λ_{max} (EtOH) 224 nm (εm 13,531), 304 (εm 19,816; δ_H($CDCL_3$) 7.95—7.50 (4H, m, aryl), 7.48 (1H, S, H4'), 6.30 (1H, S, H2), 2.80 (3H, S, $SOCH_3$), 2.34 (3H, S, CH_3-15), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17); δ_C ($CDCl_3$) 161.9 (C1), 147.9, 147.2 (C3, C5'), 130.1, 129.9, 126.5, 123.4, 123.0, 119.1 (C1'', 2'', 3'', 4'', 5'', 6''), 124.5 (C4'), 113.2 (C2), 75.5 (C5), 71.4 (C13), 70.8 (C7), 69.3 (C6), 65.6 (C16), 61.4 (C11), 55.7 (C10), 43.0 (C4, C12), 39.8 (C8), 32.0 (C9), 21.0 (C14), 19.9 (C15), 12.8 (C17).

Example 26

5-o-Nitrophenyl-2-(1-normon-2-yl)oxazole A

o-Nitroacetophenone (8.3 g, 50 mmol) in ether (100 ml) was treated with aluminium chloride (catalytic amount) followed by bromine (2.55 ml, 50 mmol) over 10 min and the reaction stirred for 30 min. The reaction was quenched with aqueous sodium bicarbonate, the ether layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was taken up in ethyl acetate, the solution was dried ($MgSO_4$), and evaporated under reduced pressure to yield o-nitro phenacyl bromide as a yellow oil (9.45 g,

77%); δ H ($CDCl_3$) 7.2—8.35 (4H, m, aryl), 4.30 (2H, S, CH_2). o-Nitrophenacylbromide (9.45 g, 38 mmol) was dissolved in dichloromethane (100 ml) and hexamethylenetetramine (5.4 g, 38 mmol) added and the mixture stirred for 1h. The reaction was then filtered to yield a pale green solid m.p. 136—138°C (7.38 g, 50%). This solid was added to ethanol (40 ml) and concentrated hydrochloric acid (10 ml) and stirred for 3 h then left standing for 2 days. The reaction mixture was filtered, and the residue was washed with water, and dried to yield a pale yellow solid. This was dissolved in aqueous sodium hydroxide, extracted with ethyl acetate, and the extracts evaporated under reduced pressure. Dilute hydrochloric acid was added to the residue and the resulting solution filtered and the filtrate evaporated under reduced pressure to yield o-nitrophenacylammonium chloride as a dark brown solid (1.45 g, 39%); δ H ($(CD_3)_2SO$) 8.8 (1H, S, NH), 8.4—7.8 (4H, m, aryl), 4.6 (S, CH_2).

The isobutoxy formic mixed anhydride of monic acid A was prepared from monic acid A (1.72 g, 5 mmol), triethylamine (0.75 ml, 5 mmol) and isobutylchloroformate (0.7 ml) and o-nitrophenacyl ammonium chloride (1.09 g, 5 mmol) and triethylamine (0.75 ml, 5 mmol) added and reaction mixture stirred for 4h. The reaction mixture was then poured into brine, extracted with ethyl acetate, the organic layer separated and dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on silicagel (15 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to yield o-nitrophenacyl moamide A as a pale yellow foam (431 mg, 17%); ν max (film) 3400, 2500, 1720, 1660, 1630, 530, 1450 cm^{-1}; λ max (EtOH) 217 nm (εm 19, 675); δ H(CD_3OD) 8.19 (1H, d, $H3^{11}$), 7.85 (1H, t, $H4^{11}$), 7.74 (1H, d, $H6^{11}$), 7.66 (1H, t, $H5^{11}$), 5.78 (1H, S, H2) 4.43 (2H, S, CH_2-1^1), 2.09 (3H, S, CH_3-15), 1.21 (3H, d, CH_3-14), 0.96 (3H, d, CH_3-17); δc (CD_3OD) 200.7 ($C2^1$), 169.7 (C1), 153.3 (C3), 147.3 ($C2^{11}$), 136.7 ($C1^1$), 135.4, 132.3, 129.4, 125.2 ($C3^{11}$, 4^{11}, 5^{11}, 6^{11}), 120.3 (C2), 76.2 (C5), 71.6 (C13), 70.7 (C7), 70.0 (C6), 66.3 (C16), 61.3 (C11), 56.8 (C10), 43.6, 43.5 (C4, C12), 41.4 (C8), 32.9 (C9), 20.3 (C14), 19.0 (C15), 12.2 (C17).

To a solution of o-nitrophenacyl monoamide A (410 mg, 0.8 mmol) in dry THF (35 ml) was added trimethylsilylchloride (0.55 ml, 4.3 mmol), triethylamine (0.6 ml, 4.3 mmol) and a few crystals of *p*-dimethylaminopyridine. The reaction was stirred at room temperature for 2h and then filtered. The filtrate was evaporated under reduced pressure to give the protected amide which was dissolved in acetonitrile (3 ml), pyridine (3 ml), triethylamine (0.3 ml, 2 mmol) carbon tetrachloride (0.4 ml, 4 mmol) and treated with triphenylphosphine (0.52 g, 2 mmol). On heating to 60°C the reaction mixture went black after a few minutes. The reaction mixture was stirred at 60°C for 1h and then evaporated under reduced pressure. The residue was taken up in ethyl acetate/aqueous sodium bicarbonate, washed with brine, and the organic layer evaporated under reduced pressure. The resulting residue was deprotected by stirring for 5 min in a mixture of THF (40 ml), water (10 ml) and concentrated hydrochloric acid (20 drops). The reaction was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residual black oil was purified by chromatography on silicagel (10 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to yield the title compound as a bright yellow oil (124 mg, 31%); ν max (film) 3400, 1650, 1530, 1350 cm^{-1}; λ max (EtOH) 205 nm (εm 20, 509), 292 nm (εm 15, 475); δ H ($CDCl_3$) 7.84—7.45 (4H, m, aryl), 7.43 (1H, S, $H4^1$), 6.27 (1H, S, H2), 2.28 (3H, S, CH_3-15), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, $CH_3$17); δ_C ($CDCl_3$), 162.5 (C1), 148.8 (C3), 147.4 ($C5^1$), 144.6 (Cl^{11}), 132.3 ($C5^{11}$), 132.1 ($C2^{11}$), 129.0 ($C4^{11}$, 3^{11}), 127.4 ($C6^{11}$), 124.4 ($C4^1$), 112.9 (C2), 75.4 (C5), 71.3 (C13), 70.6 (C7), 69.1 (C6), 65.5 (C16), 61.3 (C11), 55.6 (C10), 43.0, 42.9 (C4, C12), 39.7 (C8), 31.9 (C9), 20.8 (C14), 19.7 (C15), 12.6 (C17).

Example 27

5-Benzyl-2-(1-normon-2-yl)oxazole A

To diazomethane (40 mmol) in ether (100 ml) at 0°C was added phenylacetyl chloride (2.65 ml, 20 mmol). After 30 min at 0°C the excess diazomethane and the ether were blown off with nitrogen, and then under vacuum to leave 1-diazo-3-phenyl-2-propanone as a yellow oil (3.05 g, 95%); δH ($CDCl_3$) 7.2 (5H, S, aryl), 5.1 (1H, S. CH=N_2), 3.5 (2H, S, CH_2).

1-Diazo-3-phenyl-2-propanone (0.8 g, 5 mmol) in dichloromethane (5 ml) was added to a mixture of boron trifluoride diethyl etherate (1.2 ml,10 mmol), chloroacetonitrile (6.4ml,100mmol) and dichloromethane (5 ml) at 20°C. After 0.5 h at 20°C the solution was washed with cold aqueous 20% sodium hydroxide, dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which was purified by chromatography (10 g silica, dichloromethane) to give 2-chloromethyl-5-benzyl oxazole as a yellow oil (0.64 g, 62%); δH ($CDCl_3$) 7.2 (5H, S, aryl), 6.7 (1H, S, het-H), 4.5 (2H, S, CH_2Cl), 4.2 (2H, S, CH_2Ar), 2-Chloromethyl-5-benzyloxazole (0.6 g, 3 mmol) and triethyl phosphite (0.7 ml, 4.5 mmol) were heated together for 1h at 160°C and then cooled. Direct chromatography (10 g silica, 0 to 5% methanol in dichloromethane) then gave diethyl 5-benzyl-2-oxazolylmethyl phosphonate as a light brown oil (0.65 g, 70%); δH ($CDCl_3$) 7.2 (5H, S, aryl), 6.7 (1H, S, het-H), 4.1 (4H, m, OCH_2), 3.9 (2H, S, CH_2Ar), 3.3 (2H, d, CH_2P), 1.3 (6H, t, Me).

3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyram-2-yl]-propan-2-one (300 mg, 1 mmol) in THF (10 ml) was treated with chlorotrimethylsilane (0.5 ml, 4 mmol), triethylamine (0.6 ml, 4 mmol) and 4-N,N-dimethylaminopyridine (5 mg) for 2h at 20°C. The mixture was then filtered and evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue (the "protected ketone") dissolved in THF, and set aside for the next stage of the reaction.

To a suspension of sodium hydride (25 mg, 1 mmol) in THF (2 ml) at 0°C was added diethyl 5-benzyl-2-

oxazolylmethyl phosphonate (310 mg, 1 mmol) in more THF (2 ml). The mixture was stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (*ca* 0.5 h). The solution was cooled (0°C), the protected ketone *vide supra* added, stirred for 30 minutes at 0°C and then at ambient temperature for 1H. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (50 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was purified by chromatography (20 g silica, 0 to 10% methanol in dichloromethane) to give the title normonyloxazole as a colourless oil (100 mg, 22%); ν max (film) 3400, 2900, 1655, 730 cm^{-1}; λ max (EtOH) 266 nm (ε_m 19,800); δH (CD_3OD) 7.25 (5H, m, aryl), 6.79 (1H, S, het-HO, 6.13 (1H, S, H2), 4.05 (2H, S, CH_2Ar), 21.6 (3H, S, CH_3-15), 1.22 (3H, d, CH_3-14) 0.94 (3H, d, CH_3-17); δ c (CD_3OD) 162.6 (C1), 152.0 (C3), 148.0 (C5), 138.2 ($C1^{11}$), 129.6 ($C2^{11}$, 3^{11}, 5^{11}, 6^{11}), 127.7 ($C4^{11}$), 124.1 ($C4^1$), 113.7 (C2), 76.5 (C5), 71.6 (C13), 70.7 (C7), 70.0 (C6), 66.3 (C16), 61.4 (C11), 56.8 (C10), 43.6 (CH, 12), 41.4 (C8), 32.9 (CH_2Ar) 32.5 (C9), 20.3 (C14), 19.5 (C15), 12.2 (C17).

Example 28

5-[2-(5-Bromo)-thienyl]-2-(1-normon-2-yl)oxazole A

To a solution of 2-acetyl-5-bromothiophene (10.25 g, 50 mmol) in ether (150 ml) containing a few crystals of aluminium chloride was added bromine (12.6 ml, 50 mmol) and reaction mixture stirred for 1h. The mixture was evaporated under reduced pressure and the residue washed with water to yield the bromide as a bright yellow solid m.p. 68—69°C; δ H ($CDCl_3$) 7.05 and 7.45 (2H, ABq, thienyl), 4.20 (2H, S, CH_2).

The bromide was dissolved in methylene chloride (150 ml) and hexamethylenetetramine (7.0 g, 50 mmol) added and stirred for 1h. The precipitate was filtered off, washed with methylene chloride, and dried to yield the hexamine salt as a white solid m.p. 168—170°C (19.64 g, 93%). This salt (19.64 g, 46.5 mmol) was added to a mixture of ethanol (60 ml) and concentrated hydrochloric acid (20 ml) stirred for 3 h, and left standing overnight. Water was added to the residue and the remaining solid filtered and dried to give the amine hydrochloride salt (9.04 g, 76%); δ H ($(CD_3)_2SO$) 8.5 (3H, S (br), NH), 7.95 and 7.45 (2H, ABq, thienyl), 4.45 (2H, S, CH_2).

Isobutoxy formic mixed anhydride of monic acid A was prepared from monic acid A (3.44 g, 10 mmol), triethylamine (1.5 ml, 11 mmol), and isobutylchloroformate (1.4 ml, 11 mmol) at 0°C for 20 min. The amine hydrochloride (2.56 g, 10 mmol) and triethylamine (1.5 ml, 11 mmol) were added and the reaction stirred overnight. The mixture was then poured into brine/aqueous sodium bicarbonate, extracted with ethyl acetate and the extract was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by chromatography using silicagel (20 g) eluting with a gradient of 0 to 4% methanol in dichloromethane to yield N-[2-oxo-2-(2-(5-bromo)-thienyl)ethyl]monamide A as a white foam (1.65 g, 30%); ν max (film) 3400, 1660, 1630, 1520, 1410, cm^{-1}; λ max (EtOH) 221 nm, (εm 17, 097), 294 nm, (εm 10, 784); δ H (CD_3OD) 7.76 (1H, d, thienyl), 7.27 (1H, d, thienyl), 5.88 (1H, S, H2), 4.59 (2H, S, CH_2-1^1), 2.15 (3H, S, CH_3-15), 1.20 (3H, d, CH_3-14), 0.96 (3H, d, CH_3-17); δ c (CD_3OD) 188.1 ($C3^1$), 169.7 (C1), 153.3 (C3), 144.4 ($C4^1$), 134.4 133.0 ($C5^1$, $C6^1$), 124.7 ($C7^1$), 120.6 (C2), 76.3 (C5), 71.6 (C13), 70.7 (C7), 70.0 (C6), 66.3 (C16), 61.4 (C11), 56.8 (C10), 46.6 ($C2^1$), 43.6 (C4, 12), 41.5 (C8), 33.0 (C9), 20.4 (C14), 19.1 (C15), 12.2 (C17).

Example 29

2-(1-Normon-2-yl)-5-phenylthiazole A

A mixture of N-phenacylacetamide (0.70 g, 4 mmol), 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulphide (Lawesson's reagent) (0.80 g, 2 mmol) and toluene (10 ml) was heated for 1.5 h at reflux and then evaporated under reduced pressure. The residue was purified by chromatography (10 g silica, dichloromethane) to give 2-methyl-5-phenylthiazole at a yellowish solid (0.11 g, 16%) m.p. 72—4°C; δ H ($CDCl_3$) 7.85 (1H, S, CH), 7.3—7.7 (5H, m, C_6H_5), 2.7 (3H, S, CH_3).

3-[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl] propan-2-one (300 mg, 1 mmol) in THF (10 ml) was treated with chlorotrimethylsilane (0.5 ml, 4 mmol), triethylamine (0.6, 4 mmol) and 4-N,N-dimethylaminopyridine (5 mg) for 2h at 20°C. The mixture was then filtered and evaporated under reduced pressure and the resulting residue extracted with ether. The combined ether extracts were filtered and evaporated under reduced pressure and the resulting residue (the protected ketone) dissolved in THF, and set aside for the next stage of the reaction.

A solution of 2-methyl-5-phenylthiazole (193 mg, 1.1 mmol) and butyl lithium (1.1 mmol) in dry THF at −78°C was stirred for 10—15 minutes. To the metalated species produced was added trimethylsilyl chloride (0.14 ml, 1.1 mmol) and this mixture stirred at −78°C for 45 minutes, followed by a further 45 minutes at −20°C to −25°C. The resultant solution was cooled to −78°C and a further equivalent of butyl lithium (1.02 mmol) added. Stirring was continued for 45 minutes before adding the protected ketone, *vide supra*, and allowing to warm to room temperature. The mixture was quenched with ammonium chloride solution, extracted with ethyl acetate (3 × 50 ml) and the extracts dried ($MgSO_4$). Solvent removed under reduced pressure gave the protected thiazole which was taken up in THF/water (4:1, 50 ml) and treated with concentrate hydrochloric acid (10 drops) for 5 min, then finally quenched with sodium bicarbonate solution. Extraction with ethylacetate, drying ($MgSO_4$) and solvent removal under reduced pressure gave

the triol which was further purified by column chromatography on silica gel (2 g) using 0 to 6% methanol in dichloromethane as eluent. This gave the title compound as a white foam (0.17 g, 37%); v max (film) 3400, 1640, 810, 730 cm^{-1}; λ max (EtOH) 321 nm (εm 24,100); δ_H (CD_3OD) 8.02 (1H, S, Het-H), 7.3—7.7 (5H, m, C_6H_5), 6.63 (1H, S, H—2), 2.21 (3H, S, CH_3-15), 1.22 (3H, d, CH_3-14), 0.94 (3H, d, CH_3-17); δ_c(CD_3 OD) 166.1 (Cl), 145.5 (C3) 139.8 (HetC—5), 138.5 (HetC—4), 132.5, 130.1, 129.3, 127.5 (C_6H_5), 121.8 (C2), 76.6 (C5), 71.6 (C13), 70.7 (C7), 70.0 (C6), 66.3 (C16), 61.3 (C11) 56.8 (C10), 44.1 (C4), 43.7 (C12), 41.5 (C8), 33.0 (C9), 20.3 (C14), 20.2 (C15), 12.2 (C17); *m/e* (relative intensity) 459 $M^{\oplus}$, 6%), 215 (100) 175 (21) (Found: 459.2040. $C_{25}H_{33}NO_5S$ reqires 459.2077).

Example 30

3-Methyl-5-(1-normon-2-yl) isoxazole A

A mixture of 5-hydroxymethyl-3-methylisoxazole (2.26 g), triphenylphosphine (5.24 g) and dry carbon tetrachloride (40 ml) was heated for 3 h at reflux and then cooled and filtered. The filtrate was evaporated under reduced pressure and the residue taken up in 50% ether-hexane and filtered through a plug of silica. Evaporation of the filtrate under reduced pressure afforded 5-hydroxymethyl-2-methylisoxazole (2.16 g, 82%); δ_H (CCl_4) 6.1 (1H, s, H4), 4.5 (2H, s, CH_2), 2.2 (3H, s, CH_3).

5-Chloromethyl-3-methylisoxazole (1.12 g) was dissolved in triethyl phosphite (2.0 ml) and heated at reflux for 1 h. The residue was then distilled under reduced pressure to give 5-diethylphosphonomethyl-3-methylisoxazole (1.47 g, 74%); bp 122—5°C at 0.5 mm; ν_{max} (film) 2980, 2930, 2910, 1605, 1440, 1420, 1390, 1255, 1160, 1060—1010, 980, 900 cm^{-1}; δ_H ($CDCl_3$) 1.35 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.30 (3H, s, CH_3-het), 3.30 (1H, d, J_{H-P}=24 Hz, CH_2-P), 4.10 (2H, m, $O\underline{CH_2}CH_3$), 6.05 (1H, d, J=3 Hz, CH-Het); δ_C ($CDCl_3$) 11.4 (C5), 16.3, 16.4 ($OCH_2\underline{CH_3}$), 24.6, 26.8 (C1), 62.7, 62.8 ($O\underline{CH_2}CH_3$), 104.1, 104.2 (C3), 160.1 (C4), 163.5, 163.6 (C2); *m/e* (relative intensity) 233 ($M^{\oplus}$, 18%), 192 (47), 177 (41), 136 (50), 109 (100), 97 (82), 96 (35), 81 (76), 43 (32) (Found: 233.0831. $C_9H_{16}NO_4P$ requires 233.0816).

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran-2S-yl acetone (604 mg, 2.0 mmol) in dry THF (20 ml) was added triethylamine (0.87 ml, 6.20 mmol), trimethylsilyl chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

To a suspension of sodium hydride (106 mg, 50% in oil, washed, 2.20 mmol) in dry dimethoxyethane (DME, 10 ml) at 0°C was added 5-diethylphosphonomethyl-3-methylisoxazole (489 mg, 2.10 mmol) in 1,2-dimethoxyethane (5 ml). The cooling bath was removed and the mixture stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (*ca.* 2 h). The solution was cooled (0°C), the protected ketone added, stirred for 30 minutes at 0°C and then ambient for 1 h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops concentrated hydrochloric acid) for 5 min. After this time the solution was quenched with sodium bicarbonate and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product, which was chromatographed to afford the title compound as an inseparable mixture of E and Z isomers (4:1 respectively) (250 mg, 0.66 mmol, 32%); ν_{max} (film) (mixture of isomers) 3600—3200, 2970, 2930, 1720, 1655, 1585, 1570, 1450, 1415, 1110, 1050, 910, 730 cm^{-1}; λ_{max} (EtOH) (mixture of isomers) 259 nm (ε_m 17,160); δ_H ($CDCl_3$) (E-isomer only) 0.93 (3H, d, J=7 Hz, CH_3-17), 1.21 (3H, d, J=7 Hz, CH_3-14), 1.32 (1H, q, J=7 Hz, CH-12), 1.75 (2H, m, CH_2-9), 2.05 (4H, s + m, CH_3-15, CH—8), 2.30 (3H, s, CH_3-het), 2.36 (1H, dd, J=14, 10 Hz, CH—4), 2.60 (1H, m, CH—4'), 2.72 (1H, dd, J=8, 2 Hz, CH—11), 2.83 (1H, m, CH—10), 3.45—3.60 (2H, m), 3.70—4.00 (4H, m), 5.95 (1H, s, CH—2), 6.25 (1H, s, CH-2'); δ_C ($CDCl_3$) (E-isomer) 11.3 (CH_3-het), 12.4 (C17), 19.5 (C15), 20.6 (C14), 31.8 (C9), 39.7 (C8), 42.7 (C4 + 12), 55.7 (C10), 61.0 (C11), 65.4 (C16), 68.9 (C6), 70.4 (C7), 70.8 (C13), 75.3 (C5), 102.8 (C2'), 113.1 (C2), 144.5 (C3), 159.6 (C3'), 168.6 (C1); Z-isomer shows 25.6 (C15), 36.2 (C4), 39.6 (C8), 103.0 (C2'), 113.0 (C2), 145.7 (C3), 168.4 (Cl); *m/e* (relative intensity) 381 ($M^{\oplus}$, 1%), 279 (3), 227 (7), 149 (19), 137 (100), (14), 95 (14), 69 (22), 55 (20), 43 (37), 41 (27) (Found: 381.2166. $C_{20}H_{31}NO_6$ requires 381.2152).

Example 31

5-(1-Normon-2-yl)-3-phenylisoxazole A

(a) 5-Bromomethyl-3-phenylisoxazole

To a solution of propargyl bromide (1.51 ml, 20 mmol) in dichloromethane (15 ml) and aqueous sodium hypochlorite (22.4 ml, 10% 30 mmol) at 0°C was added dropwise with stirring benzaldoxime (2.42 g, 20 mmol) in dichloromethane (15 ml). When addition was complete the ice bath was removed and the reaction stirred for a further 2 h. The organic layer was separated and the aqueous layer washed with dichloromethane (2 × 20 ml) then the combined organic layers dried ($MgSO_4$). Solvent removal under reduced pressure gave a solid which was recrystallized from 40—60°C petroleum ether fraction to give the desired isoxazole (2.64 g, 11.1 mmol, 55%); mp 82—3°C, δ_H ($CDCl_3$) 4.40 (2H, s, $C\underline{H_2}$-Br), 6.50 (1H, s, CH—4), 7.3—7.9 (5H, m, C_6H_5).

(b) 5-Diethylphosphonomethyl-3-phenylisoxazole

5-Bromomethyl-3-phenylisoxazole (7.14 g, 30 mmol) and triethyl phosphite (10.4 ml, 60 mmol) was heated at 150°C until no more ethyl bromide distilled, then the temperature maintained for a further 1 h. The mixture was then distilled under reduced pressure to give 5-diethylphosphonomethyl-3-phenylisoxazole bp 190—192°C at 0.5 mm Hg (8.15 g, 27.6 mmol, 92%); ν_{max} (film) 2980, 2900, 1605, 1580, 1465, 1440, 1410, 1250, 1160, 1020, 970, 770, 690, 670 cm^{-1}; δ_H ($CDCl_3$) 1.30 (6H, t, J 7Hz, $OCH_2\underline{CH_3}$), 3.45 (1H, d, J_{H-P} 22 Hz, $C\underline{H_2}$-P), 4.10 (4H, m, $OC\underline{H_2}CH_3$), 6.55 (1H, d, J3 Hz, CH-4), 7.40 (3H, m, Ph), 7.65 (2H, m, Ph); δ_C ($CDCl_3$) 16.3, 16.4 ($OCH_2\underline{CH_3}$), 24.7, 26.9 ($\underline{C}H_2$-P), 62.8, 62.9 ($O\underline{C}H_2CH_3$), 101.5, 101.6 (C-4), 126.8, 128.9, 130.0 (Ph), 162.8 (C—3), 164.3, 164.4 (C—2).

(c) 5-(1-Normon-2-yl)-3-phenylisoxazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran-2S-yl acetone (604 mg, 2.0 mmol) in dry THF (20 ml) was added triethylamine (0.87 ml, 6.20 mmol), trimethylsilyl chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

To a suspension of sodium hydride (106 mg, 50% in oil, washed, 2.20 mmol) in dry tetrahydrofuran (THF, 10 ml) at 0°C was added 5-diethylphosphono methyl 3-phenyl isoxazole (620 mg, 2.10 mmol) in the THF (5 ml). The cooling bath was removed and the mixture stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (*ca.* 1h). The solution was cooled (0°C), the protected ketone added, stirred for 30 minutes at 0°C and then ambient for 1h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed to give the title compound (272 mgs, 0.61 mmol, 31%); ν_{max} (film) 3600—3200, 2970, 2920, 1655, 1590, 1570, 1465, 1405, 1105, 1050, 910, 770, 690 cm^{-1}; λ_{max} (EtOH) 240 nm (εm 22,600); δH ($CDCl_3$) 0.93 (3H, d, J7Hz, CH_3-17), 1.22 (3H, d, J7Hz, CH_3-14), 1.32 (1H, m, CH-12), 1.74 (2H, m, CH_2-9), 2.04 (1H, m, CH-8), 2.13 (3H, s, CH_3-15), 2.38 (1H, dd, J 14, 10Hz, CH-4), 2.50—2.75 (2H, m, CH-11 + CH-4a), 2.80 (1H, dt, J5Hz, CH-10) 3.5—4.0 (6H, m), 6.32 (1H, s, CH-2), 6.43 (1H, s, CH-2'), 7.46 (3H, m, Ph), 7.80 (2H, m, Ph); δc ($CDCl_3$), 12.6 (C17), 19.7 (C15), 20.7 (C14), 31.7 (C9), 39.6 (C8), 42.8 (C12,4), 55.7 (C10), 61.2 (C11), 65.5 (C16), 68.9 (C6), 70.4 (C7), 71.1 (C13), 75.3 (C5), 100.1 (C2'), 113.2 (C2), 126.8, 129.0 130.0 (Ph), 145.0 (C3), 162.4 (C3'), 169.4 (CI); *m/e* (relative intensity) 443 ($M^{\oplus}$, 3%), 199 (100), 83 (8), 69 (14), 67 (9), 55 (11), 45 (8), 43 (15), 41 (14) (Found: 443.2322. $C_{25}H_{33}NO_6$ requires 443.2308) and the z isomer (47.4 mgs, 0.11 mmol, 5%); ν_{max} 3600—3200, 2970, 2920, 1650, 1590, 1570, 1465, 1405, 1105, 1045, 770, 730, 690 cm^{-1}; λ_{max} (EtOH) 241 nm (m 23,380); δH ($CDCl_3$), 0.92 (3H, d, J 7Hz, CH_3-17), 1.22 (3H, d, J 7Hz, CH_3-14), 1.37 (1H, q, J 7Hz, CH-12),1.74 (2H, m, CH_2-9), 2.05 (4H, m+s, CH-8 + CH_3-15), 2.61 (1H, dd, J14, 10H2, CH-4), 2.73 (1H, dd, J8, 2Hz, CH-11), 2.82 (1H, dt, J 2,6Hz, CH-10), 3.03 (1H, dd, J 14, 2Hz, CH-4a), 3.55 (2H, m,), 3.75—4.00 (4H, m), 6.29 (1H, s, CH-2), 6.59 (1H, s, CH-2'), 7.45 (3H, m, Ph), 7.80 (2H, m, Ph); δc ($CDCl_3$), 12.4 (C17), 20.5 (C14), 25.8 (C15), 31.9 (C9), 36.5 (C9), 36.5 (C4), 39.6 (C8), 42.7 (C12), 55.8 (C10), 61.2 (C11), 65.5 (C16), 69.5 (C6), 70.3 (C7), 70.9 (C13), 76.2 (C5), 100.4 (C2') 1130 (C2), 126.8, 129.0 130.0 (Ph), 146.4 (C3), 162.5 (C3'), 169.3 (CI); *m/e* (relative intensity) 443 ($M^{\oplus}$, 1%), 200 (17), 199 (100), 77 (14), 69 (17), 67 (12), 55 (22), 45 (19), 43 (26), 41 (28) (Found: 443.2345 $C_{25}H_{33}NO_6$ requires 443.2305.

Example 32

3-(1-Normon-2-yl)isoxazole A

(a) 3-Hydroxymethyl isoxazole

A solution of ethyl isoxazole-3-carboxylate (9.92 g, 70 mmol) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.67 g, 70 mmol) in ether (100 ml). The mixture was then refluxed until tlc indicated the reaction was complete (*ca.* 30 min) then the reaction was cautiously quenched with 2% sulphuric acid. The ether layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the 3-hydroxymethyl(isoxazole (4.23 g, 42.7 mmol, 61%); δ_H ($CDCl_3$) 4.00 (1H, bs, O$\underline{H}$), 4.70 (2H, s, $C\underline{H_2}$-OH), 6.40 (1H, d, J2 Hz, CH-4), 8.30 (1H, d, J2 Hz, CH-5).

(b) 3-Chloromethyl isoxazole

A solution of 3-hydroxymethyl isoxazole (4.23 g, 43 mmol) and triphenylphosphine (11.3 g, 42 mmol) in carbon tetrachloride (100 ml) was heated at reflux for 18 h. Solvent was removed under reduced pressure then the residue taken up in ether and filtered. The filtrate was concentrated under reduced pressure and further purified by short path distillation (bp 60°C at 10 mm Hg) to give the desired chloride (1.41 g, 12 mmol, 28%); δ_H ($CDCl_3$) 4.50 (2H, s, $C\underline{H_2}$-Cl), 6.40 (1H, d, J2 Hz, CH-4), 8.40 (1H, d, J2 Hz, CH-5).

(c) 3-Diethylphosphonomethyl isoxazole

3-Chloromethyl isoxazole (1.41 g, 12 mmol) and triethylphosphite (3.13 ml, 18 mmol) were heated at 140°C for 1 h. Distillation (short path) yielded the phosphonate 390 mg, 1.78 mmol, 15%); bp 110—120°C at

0.7 mm Hg; δ_H ($CDCl_3$) 1.30 (6H, t, J7 Hz, $OCH_2\underline{CH_3}$), 3.30 (2H, d, J_{P-H} 22 Hz, $\underline{CH_2}$-P), 4.10 (4H, m, $O\underline{CH_2}CH_3$), 6.40 (1H, s, CH-4), 8.35 (1H, s, CH-5).

(d) 3-(1-Normon-2-yl) isoxazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-, methylhexyl)tetrahydropyran-2S-yl acetone (302 mg, 1,00 mmol) in dry THF (20 ml) was added triethylamine (0.6 ml, 3.90 mmol), trimethylsilyl chloride (0.5 ml, 3.90 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next state of the reaction.

To a solution of lithium diisopropylamide [from diisopropylamine (0.14 ml) and butyl lithium (1.06 ml of a 0.94 M solution, 1.00 mmol)] in THF (10 ml) at −78°C was added 3-diethylphosphonomethylisoxazole (229 mg, 1.00 mmol) in THF (5 ml). The solution was stirred for 30 minutes then raised to 0°C and stirred for a further 30 minutes. The protected ketone was added and the reaction stirred at 0°C for 30 minutes then room temperature for 18 h before quenching with ammonium chloride, extracting the ethyl acetate and drying ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product (310 mg) which was chromatographed (0—5% MeOH/CH_2Cl_2, 5 g, SiO_2) to give the title compound as an inseparable mixture with the Z-isomer (42 mg, 0.11 mmol, 11%); ν_{max} (film) 3600—3200, 2970, 2930, 1650, 1625, 1550, 1450, 1380, 1110, 1050, 850 cm^{-1}; λ_{max} (EtOH) 220 nm (ε_m 7,620); δ_H ($CDCl_3$) 0.94 (3H, d, J 7 Hz, CH_3-17), 1.22 (3H, d, J 7 Hz, CH_2-14), 1.35 (1H, m, CH-12), 1.72 (2H, m, CH_2-9), 2.00 (1H, m, CH-8), 2.08 + 2.10 (3H, 2 × s, CH_3-15), 2.2—2.4 (1H, m, CH-4), 2.55—2.90 (3H, m), 3.5—4.0 (6H, m), 6.25 (1H, s, CH-2), 6.36 (1H, d, J 2 Hz, CH-2'), 8.35 (1H, d, J 2 Hz, CH-3').

Example 33

5-Methyl-3-(1-normon-2-yl) isoxazole A

(a) Ethyl 5-methylisoxazole-3-carboxylate

A mixture of ethyl 2,4-dioxovalerate (25 ml, 178 mmol), hydroxylamine hydrochloride (13.7 g, 197 mmol) and sodium bicarbonate (15.4 g, 183 mmol) in ethanol (125 ml) were heated at reflux for 2.5h, cooled and the solvent removed under reduced pressure. The residue was taken up in chloroform and washed with water, the organic layer separated and dried ($MgSO_4$). Solvent removal and distillation under reduced pressure gave the desired product (15.44 g, 100 mmol, 56%); b.p. 82—86°C at 0.5 mm Hg; ν_{max} (film) 3120, 2980, 2930, 1730, 1600, 1450, 1270, 1200, 1100, 1020, 915, 930, 780 cm^{-1}; δ_H ($CDCl_3$) 1.40 (3H, t, J 7Hz, $OCH_2\underline{CH_3}$), 2.50 (3H, s, CH_3-5), 4.40 (2H, q, J 7Hz, $O\underline{CH_2}CH_3$), 6.40 (1H, s, CH-4).

(b) 3-Hydroxymethyl-5-methylisoxazole

Ethyl 5-methylisoxazole-3-carboxylate (15.44 g, 100 mmol) in dry ether was added dropwise to a stirred suspension of lithium aluminium hydride (3.5 g, 100 mmol) in ether (100 ml). The mixture was then refluxed until tlc indicated the reaction was complete (*ca* 30 min) then the reaction was cautiously quenched with 2% sulphuric acid. The ether layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to leave an oil which was further purified by distillation to give 3-hydroxymethyl-5-methylisoxazole (5.85 g, 52 mmol, 52%); b.p. 80°C at 0.5 mm Hg; ν_{max} (film), 3600—3100, 2930, 1610, 1480, 1255, 1130, 1050, 1000, 890, 800, 760 cm^{-1} δ_H ($CDCl_3$), 2.40 (3H, s, CH_3-5), 4.30 (1H, bs, OH), 4.65 (2H, s, $\underline{CH_2}$-OH), 6.05 (1H, s, CH-4).

(c) 3-Chloromethyl-5-methylisoxazole

A solution of 3-hydroxymethyl-5-methyl isoxazole (6.50 g, 57.5 mmol) and triphenylphosphine (15.1 g, 57.5 mmol) in carbon tetrachloride (120 ml) were heated at reflux for 18h. Solvent was removed from the cooled mixture under reduced pressure then the residue taken up in ether and filtered. The filtrate was concentrated under reduced pressure then flash chromatographed through silica using 1:1 ether: 40—60°C petroleum ether fraction as eluant to give 3-chloromethyl-5-methylisoxazole (5.43 g, 41.3 mmol, 72%); ν_{max} (film) 3130, 2960, 2920, 1610, 1475, 1400, 1270, 1250, 1160, 1130, 1010, 920, 890, 800, 750 cm^{-1}; δ_H ($CDCl_3$) 2.40 (3H, s, CH_3-5), 4.55 (2H, s, $\underline{CH_2}$-Cl), 6.10 (1H, s, CH-4).

(d) 3-Diethylphosphonomethyl-5-methylisoxazole

3-Chloromethyl-5-methylisoxazole (3.95 g, 30 mmol) and triethylphosphite (10.4 ml, 60 mmol) were heated at reflux for 2h. Distillation under reduced pressure yielded the phosphonate (5.03 g, 21.6 mmol, 72%); b.p. 125°C at 0.5 mm Hg; ν_{max} (film) 2980, 2930, 1610, 1475, 1440, 1420, 1390, 1250, 1060—1010, 960, 900, 810 cm^{-1}; δ_H ($CDCl_3$) 1.30 (6H, t, J 7Hz, $OCH_2\underline{CH_3}$), 2.40 (3H, s, CH_3-5), 3.20 (2H, d, J_{H-P} 22Hz, CH_2-P), 4.10 (2H, m, $O\underline{CH_2}CH_3$), 6.10 (1H, s, CH-4); δ_H ($CDCl_3$) 12.2 (CH_3-5), 16.3, 16.4 ($OCH_2\underline{CH_3}$), 23.5, 25.7 (CH_2-P), 62.4, 62.6 ($O\underline{CH_2}CH_3$), 102.5 (C-4), 155.9, 156.0 (C-3), 169.9 (C-5).

(e) 5-Methyl-3-(1-Normon-2-yl)-isoxazole

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl) tetrahydropyran-2S-yl acetone (604 mg, 2.0 mmol) in dry THF (20 ml) was added triethylamine (0.87 ml, 6.20 mmol), trimethylsilyl chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethyl-amino)pyridine. After stirring at room temperature for 2h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

To a solution of lithium diisopropylamide (from diisopropyl amine (0.31 ml) and butyl lithium (1.42 ml of a 1.55 M solution, 2.20 mmol)) in THF (10 ml) at −78°C was added 3-diethyl-phosphonomethyl-5-methyl-isoxazole (489 mgs, 2.10 mmol) in THF (5 ml). The solution was stirred for 30 minutes then raised to 0°C and stirred for a further 30 minutes. The ketone was added and the reaction stirred at 0°C for 30 minutes then room temperature for 3h before quenching with ammonium chloride, extracting with ethyl acetate and drying ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 minutes. After this time, the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed (0—5% $MeOH/CH_2Cl_2$, 15g SiO_2) to give the title compound (250 mgs, 0.65 mmol, 33%); ν_{max} (film), 3600—3200, 2970, 2930, 1650, 1600, 1450, 1380, 1110, 1050, 910, 730 cm^{-1}; λ_{max} (EtOH) 232 nm (ε_m 10,900); δ_H ($CDCl_3$) 0.92 (3H, d, J 7Hz, CH_3-17) 1.22 (3H, d, J 7Hz, CH_3-14), 1.34 (1H, q, J CH-12), 2.72 (2H, t, J 6Hz, CH_2-9), 2.03 (4H, s+m, CH_2-15 + CH-8), 2.40 (4H, s+m, CH_3-het + CH-4), 2.63 (1H, dd, J 14,2 CH-4a), 2.70 (1H, dd, J 9,2 Hz, CH-11), 2.82 (1H, dt, J 2,5 Hz, CH-10), 3.54 (2H, m), 3.75-3.95 (4H, m), 6.01 (1H, s, CH-het), 6.20 (1H, s, CH-2); δ_C($CDCl_3$), 12.1 (C4), 12.5 (C17), 19.3 (C15), 20.7 (C14), 31.7 (C9), 39.5 (C8), 42.6 (C4), 42.7 (C12), 55.6 (C10), 61.1 (C11), 65.4 (C16), 68.9 (C6), 70.4 (C7), 71.0 (C13), 75.3 (C5), 102.2 (C2), 114.5 (C2), 144.1 (C3), 160.7 (Cl), 168.6 (C3'); m/e (relative intensity) 381 ($M^{\oplus}$, 1%), 227 (5), 138 (18), 137 (100), 122 (19), 69 (18), 55 (19), 45 (21), 43 (52), 41 (31) (Found: 381,2172.$C_{20}H_{31}NO_6$ requires 381.2151) and the Z-isomer (60.5 mgs, 0.15 mol, 8%); ν_{max} (film) 3600—3200, 2970, 2930, 1645, 1605, 1450, 1110, 1050, 910, 730 cm^{-1}; λ_{max} (EtOH) 232 nm (ε_m 11,000) δ_H ($CDCl_3$), 0.94 (3H, d, J 7Hz, CH_3-17), 1.21 (3H, d, J 7Hz, CH_3-14), 1.34 (1H, q, J 7Hz, CH-12), 1.59 (1H, m, CH-9), 1.82 (1H, m, CH-9a), 2.04 (4H, d, J 1Hz +m, CH_3-15 + CH-8), 2.80 (3H, m), 3.5-4.0 (6H, m), 5.88 (1H, s, CH-2'), 6.05 (1H, s, CH-2); δ_C ($CDCl_3$), 12.0 (C4'), 12.7 (C17), 20.7 (C14), 26.8 (C15), 31.8 (C9), 36.8 (C4), 38.9 (C8), 42.9 (C12), 56.0 (C10), 61.4 (C11), 65.5 (C16), 67.3 (C6), 70.3 (C7), 71.3 (C13), 76.8 (C5), 103.0 (C2'), 114.2 (C2), 146.9 (C3), 160.1 (Cl), 168.8 (C3'); *m/e* (relative intensity) 382 ($MH^{\oplus}$, 2%), 381 ($M^{\oplus}$, 1%), 227 (7), 166 (42), 150 (54), 137 (100), 45 (50), 43 (88), 41 (48) (Found: 381.2127. $C_{20}H_{31}NO_6$ requires 381.2149).

Example 34

3-(1-Normon-2-yl)-5-phenylisoxazole A

(a) 3-Hydroxymethyl-5-phenylisoxazole

A solution of ethyl 5-phenylisoxazole-3-carboxylate (5.90 g, 27 mmol) in ether (30 ml) was added dropwise to a suspension of lithium aluminium hydride in ether (20 ml). When addition was complete, the mixture was heated at reflux for 1h then a further quantity of lithium aluminium hydride (0.25 g) was added and reflux continued for 0.5 h. The reaction was cautiously quenched with 2% sulphuric acid and the ether layer separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield 3-hydroxymethyl-5-phenylisoxazole (2.10 g, 12 mmol, 44%); δ_H ($CDCl_3$) 3.60 (1H, br, OH), 4.75 (2H, s, CH_2), 6.35 (1H, s, CH), 7.2—7.8 (5H, m, C_6H_5).

(b) 3-Chloromethyl-5-phenylisoxazole

3-Hydroxymethyl-5-phenylisoxazole (2.10 g, 12 mmol) was refluxed with triphenylphosphine (3.14 g, 12 mmol) in carbon tetrachloride (40 ml) overnight. After cooling the solvent was removed under reduced pressure and the residue taken up in ether, the solution filtered and concentrated to give an oil. This material was filtered through a plug of silica gel (5g, ether-hexane 1:1) to remove triphenylphosphine oxide then crystallised to give the title compound (1.33 g, 6.9 mmol, 58%); m.p. 48-9°C; ν_{max} ($CHCl_3$) 3000, 1610, 1590, 1570, 1450, 1265, 945, 690 cm^{-1}; δ_H ($CDCl_3$) 4.55 (2H, s, CH_2Cl), 6.55 (1H, s, CH-het) 7.2—8.0 (5H, m, Ph).

(c) 3-Diethylphosphonomethyl-5-phenylisoxazole

3-Chloromethyl-5-phenylisoxazole (2.07 g, 10 mmol) and triethylphosphite (1.72 ml, 10 mmol) were heated at reflux for 2h then the mixture distilled under reduced pressure to yield the title compound (1.85 g, 6.27 mmol, 63%); b.p. 192°C at 0.5 mm Hg; ν_{max} (film) 2980, 2900, 1610, 1590, 1570, 1500, 1450, 1420, 1390, 1250, 1160, 1060—1010, 970, 760, 690 cm^{-1}; δ_H ($CDCl_3$) 1.30 (3H, t, J 7Hz, $OCH_2\underline{CH_3}$), 3.30 (2H, d, J 21Hz, CH_2-P), 4.20 (2H, m, $O\underline{CH_2}CH_3$), 6.60 (1H, s, CH-het), 7.2—7.9 (5H, m, Ph).

(d) 3-(1-Normon-2-yl)-5-phenyl izoxazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran-2S-yl acetone (604 mg, 2.0 mmol) in dry THF (20 ml) was added triethylamine (0.87 ml, 6.20 mmol), trimethylsilyl chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethyl-amino)pyridine. After stirring at

room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

To a suspension of sodium hydride (106 mg, 50% in oil, washed, 2.20 mmol) in dry tetrahydrofuran (THF, 10 ml) at 0°C was added 3-diethylphosphonomethyl-5-phenylisoxazole (620 mg, 2.10 mmol) in THF (5 ml). The cooling bath was removed and the mixture stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (ca. 2 h). The solution was cooled (0°C), the protected ketone added, stirred for 30 minutes at 0°C and then at ambient temperature for 1 h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed to give the title compound (110 mg, 0.24 mmol, 12%); ν_{max} (film) 3600—3200, 2970, 2920, 1655, 1615, 1590, 1575, 1495, 1450, 1420, 1380, 1110, 1050, 910, 865, 830 cm^{-1}; λ_{max} (EtOH) 266 nm (ε_m 21,230); δ_H ($CDCl_3$) 0.93 (3H, d, J 7 Hz, CH_3-17), 1.22 (3H, J 7 Hz, CH_3-14), 1.33 (1H, q, J 7 Hz, CH-12), 1.74 (2H, m, CH_2-9), 2.02 (1H, m, CH-8), 2.11 (3H, s, CH_3-15), 2.42 (1H, dd, J 12, 9 Hz, CH-4), 2.65 (1H, m, CH-4'), 2.72 (1H, dd, J 8, 2 Hz, CH-11), 2.83 (1H, dt, J 2, 5 Hz, CH-10), 3.5—4.0 (6H, m), 6.27 (1H, s, CH-2), 6.54 (1H, s, CH-2'), 7.44 (3H, m, Ar), 7.78 (2H, m, Ar); δ_C ($CDCl_3$) 12.6 (C17), 19.6 (C15), 20.8 (C14), 31.7 (C9), 39.5 (C8), 42.6, 42.7 (C12, 4), 55.7 (C10), 61.2 (C11), 65.4 (C16), 69.0 (C6), 70.4 (C7) 71.1 (C13), 75.3 (C5), 100.0 (C2'), 114.4 (C2), 125.8, 129.0, 130.1 (Ar), 144.7 (C3), 161.1 (C1), 169.2 (C3'); *m/e* (relative intensity) 443 ($M^{\oplus}$, 3%), 200 (23), 199 (100), 105 (36), 94 (16), 69 (24), 57 (16), 55 (22), 43 (29), 41 (23) (Found 443.2286. $C_{25}H_{33}NO_6$ requires 443.2306) and the Z-isomer (33.5 mg, 0.08 mmol, 4%); ν_{max} (film) 3600—3200, 2970, 2930, 1655, 1615, 1590, 1575, 1495, 1450, 1420, 1110, 1050, 910, 865, 830, 790 cm^{-1}; λ_{max} (EtOH) 266 nm; δ_H ($CDCl_3$) 0.94 (3H, d, J 7Hz, CH_3-17), 1.20 (3H, d, J 7 Hz, CH_3-14), 1.31 (1H, q, J 7 Hz, CH-12), 1.62 (1H, m, CH-9a), 1.82 (1H, m, CH-9b), 2.09 (4H, m + s, CH-8 + CH_3-15), 2.68 (1H, dd, J 8, 2Hz, CH-11), 2.82 (3H, m, CH-10 + CH_2-4), 3.5—4.0 (6H, m,), 6.15 (1H, s, CH-2), 6.43 (1H, s, CH-2'), 7.45 (3H, m, Ar), 7.75 (2H, m, Ar); δ_C ($CDCl_3$) 12.7 (C17), 20.8 (C14), 26.8 (C14), 26.8 (C15), 31.8 (C9), 37.0 (C4) 43.0 (C12), 56.0 (C10), 61.5 (C11), 65.5 (C16), 67.5 (C6), 70.3 (C7), 71.4 (C13), 76.8 (C5), 100.8 (C2'), 114.1 (C2), 120.1, 129.0, 130.4 (C_6H_5), 147.5 (C3), 160.6 (C1), 169.4 (C3'); *m/e* (relative itensity) 443 ($M^{\oplus}$, 1%), 340 (6;, 228 (34), 211 (50), 199 (65), 105 (100), 77 (50), 45 (50), 43 (45), 41 (56) (Found: 443.2303. $C_{25}H_{33}NO_6$ requires 443.2303).

Example 35
5-(1-Normon-2-yl)-2-phenyloxazole A

(a) 5-Chloromethyl-2-phenyl oxazole

A solution of chloroacetyl chloride (freshly distilled, 1.59 ml, 20 mmol) in ether (10 ml) was added dropwise to a cooled (0°C) solution of diazomethane in ether (40 mmol, ex 10.8 g Diazald) and stirred until nitrogen evolution had ceased (ca. 10—15 mins). The solvent was blown off using nitrogen and the residual oil containing the diazoketone used without further purification. The 1-chloro-3-diazo propanone was taken up in dichloromethane (50 ml) and added dropwise to a solution of boron trifluoride etherate (4.9 ml, 40 mmol) and benzonitrile (10.2 ml, 100 mmol) in dichloromethane (150 ml) and stirred until nitrogen evolution had ceased. The mixture was then poured onto 20% aqueous sodium hydroxide solution (300 ml), the organic layer separated, washed with brine and dried ($MgSO_4$). Solvent removal then distillation at reduced pressure gave an oil which was further purified by column chromatography (CH_2Cl_2 as eluant, 20 g silica) to give the title compound (870 mg, 4.50 mmol, 22%); ν_{max} (film), 3060, 2960, 1665, 1610, 1550, 1545, 1480, 1450, 1355, 1280, 1125, 1040, 1020, 990, 900, 875, 840, 780, 700 cm^{-1}; δH ($CDCl_3$) 4.60 (2H, s, CH_2-Cl), 7.10 (1H, s, CH-4), 7.40 (3H, m, Ph), 7.90 (2H, m, Ph).

(b) 5-Diethylphosphonomethyl-2-phenyl oxazole

5-Chloromethyl-2-phenyl oxazole (870 mg, 4.50 mmol) and triethylphosphite (1.17 ml, 6.75 mmol) were heated at reflux for 3 h, cooled, the excess triethylphosphite removed under reduced pressure and the residue column chromatographed (0 to 5% MeOH/CH_2Cl_2, 10g silica) to give the title compound (794 mg, 2.69 mmol, 60%); δH ($CDCl_3$) 1.30 (6H, t, J 7Hz, $OCH_2\underline{CH_3}$), 3.30 (2H, d, J_{P-H} 22Hz, CH_2-P) 4.10 (4H, m, $O\underline{CH_3}$), 7.00 (1H, d, J_{P-H} 3Hz, CH-4), 7.40 (3H, m, Ph), 8.00 (2H, m, Ph).

(c) 5-(1-Normon-2-yl)-2-phenyl oxazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)tetrahydropyran-2S-yl acetone (604 mg, 2.0 mmol) in dry THF (20 ml) was added triethylamine (0.87 ml, 6.20 mmol), trimethylsilyl chloride (0.78 ml, 6.20 mmol) and a catalytic amount of 4-(N,N-dimethyl-amino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil taken up in dry THF ready for the next stage of the reaction.

To a suspension of sodium hydride (96 mg, 50% in oil, washed, 2.00 mmol) in dry tetrahydrofuran (THF, 10 ml) at 0°C was added 5-diethylphosphono methyl-2-phenyl oxazole (590 mg, 2.00 mmol) in THF (5 ml). The cooling bath was removed and the mixture stirred at room temperature until hydrogen

evolution had ceased and the solution was homogeneous (*ca.* 1.5h). The solution was cooled (0°C) the protected ketone added, stirred for 30 minutes at 0°C and then ambient for 1 h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed (0—5% MeOH/CH_2Cl_2 on silica) to give the title compound as an inseparable mixture with the Z isomer (91 mgs, 0.21 mmol, 10%) E:Z 3:1; ν_{max} (film) (both isomers) 3600—3200, 2970, 2910, 1640, 1480, 1450, 1380, 1110, 1050, 905, 750, 710, 690 cm^{-1}; λ_{max} (EtOH) (both isomers) 306 nm (Em 16, 170); δH ($CDCl_3$) (E isomer) 0.93 (3H, d, J 7Hz, CH_3-17), 1.22 (3H, d, J 7Hz, CH_3-14), 1.33 (1H, m, CH-12), 1.76 (2H, m, CH_2-9), 2.12 (3H, s, CH_3-15), 2.39 (1H, dd, J 14,9 CH-4), 2.5—2.9 (3H, m), 3.4—4.0 (6H, m), 6.26 (1H, s, CH-2), 7.03 (1H, s, CH-2), 7.45 (3H, m, Ph), 8.02 (2H, m, Ph).

Example 36

3-(4-Methylsulfinylphenyl)-5-(1-normon-2-yl) isoxazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran-2S-yl acetone (585 mg, 1.94 mmol) in dry THF (20 ml) was added triethylamine (1.20 ml, 8.60 mmol), trimethylsilyl chloride (1.00 ml, 8.60 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

To a suspension of sodium hydride (93 mg, 50% in oil, washed, 1.94 mmol) in dry tetrahydrofuran (THF, 10 ml) at 0°C was added 5-(diethylphosphonomethyl)-3-(4-methylsulphinylphenyl) isoxazole (678 mg, 1.94 mmol) in THF (5 ml). The cooling bath was removed and the mixture stirred at room temperature until hydrogen evolution had ceased and the solution was homogeneous (*ca.* 3 h). The solution was cooled (0°C), the protected ketone added, stirred for 30 minutes at 0°C and then ambient for 3 h. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed to give the title compound as a 4:1 mixture with the Z-isomer (410 mg, 8.12 mmol, 42%).

Example 37

3-(4-Methylsulfonylphenyl)-5-(1-normon-2-yl) isoxazole A

A mixture of 3-*p*-methylsulfinylphenyl-5-(1-normon-2-yl) isoxazole A (0.20 g, 0.4 mmol), sodium hydrogen carbonate (75 mg, 0.90 mmol) and *m*-chloroperbenzoic acid (91 mg, 0.45 mmol) in dichloromethane (10 ml) was stirred for 2 h at 20°C, and then diluted with ethyl acetate. The solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography (silicagel, 0 to 10% methanol in dichloromethane) to give the title compound (90 mg, 1.73 mmol, 43%) as a white foam.

Example 38

5-(4-Methylthiophenyl)-2-(1-normon-2-yl) thiazole A

To a solution of 3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran-2S-yl acetone (151 mg, 0.5 mmol) in dry THF (20 ml) was added triethylamine (0.6 ml, 4.3 mmol), trimethylsilyl chloride (0.5 ml, 4.0 mmol) and a catalytic amount of 4-(N,N-dimethylamino)pyridine. After stirring at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution concentrated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent removed under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

A solution of 2-methyl-5-(4-methylsulphinylphenyl)thiazole (0.5 mmol) and butyl lithium (0.5 mmol) in dry THF at −78°C was stirred for 30 minutes. To the metalated species produced was added trimethylsilyl chloride (64 µl, 0.5 mmol) and this mixture stirred at −78°C for 15 minutes, followed by a further 15 minutes at −78° to 0°C. The resultant solution was cooled to −78°C and a further equivalent of butyl lithium (0.49 mmol) added. Stirring was continued for 45 minutes before adding the protected ketone, *vide supra*, and allowing to warm to room temperature. The mixture was quenched with ammonium chloride then extracted with ethyl acetate and dried ($MgSO_4$). Solvent removal under reduced pressure gave an oil which was taken up in THF/water (100 ml, 4:1) and treated with acid (10 drops, concentrated hydrochloric acid) for 5 min. After this time the mixture was quenched with sodium bicarbonate and extracted with ethyl acetate. Drying ($MgSO_4$) and solvent removal under reduced pressure gave the crude product which was chromatographed using 0 to 5% methanol/dichloromethane as eluant to give the title compound (84 mg, 0.17 mmol, 33%), mp 128—34°C.

Example 39

4,5-Dimethyl-2-(1-normon-2-yl)oxazole A

A solution of 3-[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]propan-2-one (604 mg) in THF (20 ml) was treated with chlorotrimethylsilane (0.84 ml), triethylamine (0.92 ml) and a catalytic amount of 4-N,N-dimethylaminopyridine. After 2 h at 20°C the reaction mixture was filtered and the filtrate evaporated under reduced pressure. The resultant oil was taken up in anhydrous ether, filtered, the solvent evaporated under reduced pressure, then the oil (the protected ketone) taken up in dry THF ready for the next stage of the reaction.

A solution of 2,4,5-trimethyloxazole (244 mg) in dry THF (20 ml) was cooled to −78°C under an atmosphere of argon. A solution of n-butyl lithium in hexane (1.8 ml, 1.2 M) was added, followed after 10 min by chlorotrimethylsilane (0.30 ml). After 45 min at −78°C the solution was warmed to 0°C for 45 min and then recooled to −78°C. A further quantity of n-butyl lithium (1.8 ml) was added and the solution stirred at −78°C for 45 min. The solution of the protected ketone was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was quenched with ammonium chloride solution, extracted with ethyl acetate and the combined extracts dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting oil was dissolved in THF/water (4:1, 25 ml) and concentrated hydrochloric acid (6 drops) added. After stirring for 12 min excess sodium bicarbonate solution was added and the mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to an oil which was purified on silica (10 g) eluting with 0 to 4% methanol in dichloromethane. The title oxazole was isolated as a colourless oil (0.185 g, 23%); ν_{max} (film) 3400, 1650, 730 cm^{-1}; λ_{max} 275 nm (ε_m 14,700); δ_H ($CDCl_3$) 6.11 (1H, s, H2), 2.24, 2.09 (6H, 2S, Het-C$\underline{H}_3$), 2.21 (3H, s, CH_3-15), 1.23 (3H, d, CH_3-14), 0.92 (3H, d, CH_3-17); δ_C ($CDCl_3$) 159.3 (C1), 144.9 (C3), 142.1 (oxazole C5), 130.7 (oxazole C4), 113.2 (C2), 75.5 (C5), 71.0 (C13), 70.4 (C7), 68.9 (C6), 65.4 (C16), 61.1 (C11), 55.6 (C10), 42.7 (C4), 42.6 (C12), 39.5 (C8), 31.8 (C9), 20.7 (C14), 19.4 (C15), 12.5 (C17), 11.0 and 9.9 (2 × Het-$\underline{C}H_3$); *m/e* (relative intensity) 395 ($M^{\oplus}$, 9%), 151 (100), 111 (21), 84 (27) (Found: 395.2313. $C_{21}H_{33}NO_6$ requires 395.2308).

Example 40

4-Methyl-2-(1-normon-2-yl)-5-phenyloxazole A

A solution of 2,4-dimethyl-5-phenyloxazole (190 mg) in dry THF (10 ml) was cooled to −78°C under argon. A solution of n-butyl lithium in hexane (0.9 ml, 1.2 M) was added, followed after 10 min by chlorotrimethylsilane (0.15 ml). After 45 min at −78°C the solution was warmed to 0°C for 45 min and then recooled to −78°C. A further quantity of n-butyl lithium (0.9 ml) was added and the solution stirred at −78°C for 45 min. The solution of the protected ketone (1 mM) (prepared as in example 39) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was quenched with ammonium chloride solution, extracted with ethyl acetate and the combined extracts dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting oil was dissolved in THF/water (4:1, 25 ml) and concentrated hydrochloric acid (6 drops) added. After stirring for 12 min excess sodium bicarbonate solution was added and the mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to an oil which was purified on silica (10 g) eluting with 0 to 4% methanol in dichloromethane. The title oxazole was isolated as a white foam (0.25 g, 55%); ν_{max} (film) 3400, 1655, 910 cm^{-1}; λ_{max} (EtOH) 225 (ε_m 15,600), 305 nm (ε_m 22,200); δ_H ($CDCl_3$) 7.25—7.65 (5H, m, C_6H_5), 6.24 (1H, s, H2), 2.43 (3H, s, Het-C$\underline{H}_3$), 2.31 (3H, s, CH_3-15), 1.21 (3H, d, CH_3-14), 0.95 (3H, d, CH_3-17); δ_C ($CDCl_3$) 159.4 (C1), 146.4 (C3), 144.2 (Het-C5), 132.3 (Het-C4), 129.2, 128.7, 127.4, 125.1 (C_6H_5), 113.1 (C2), 75.4 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6), 65.5 (C16), 61.2 (C11), 55.6 (C10), 42.8 (C4, 12), 39.5 (C8), 31.7 (C9), 20.8 (C14), 19.6 (C15), 13.3 (Het-$\underline{C}H_3$), 12.6 (C17); *m/e* (relative intensity) 457 ($M^{\oplus}$, 6%), 213 (100), 173 (21) (Found: $M^{\oplus}$ 457.2448. $C_{28}H_{35}NO_6$ requires 457.2461).

Example 41

4,5-Diphenyl-2-(1-normon-2-yl)oxazole A

A solution of 4,5-diphenyl-2-methyloxazole (0.57 g) in dry THF (20 ml) was cooled to −78°C under argon. A solution of n-butyl lithium in hexane (1.8 ml, 1.2 M) was added, followed after 10 min by chlorotrimethylsilane (0.30 ml). After 45 min at −78°C the solution was warmed to 0°C for 45 min and then recooled to −78°C. A further quantity of n-butyl lithium (1.8 ml) was added and the solution stirred at −78°C for 45 min. The solution of the protected ketone (2 mM) (prepared as in example 39) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was quenched with ammonium chloride solution, extracted with ethyl acetate and the combined extracts dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting oil was dissolved in THF/water (4:1, 25 ml) and concentrated hydrochloric acid (6 drops) added. After stirring for 12 min excess sodium bicarbonate solution was added and the mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to an oil which was purified on silica (10 g) eluting with 0 to 4% methanol in dichloromethane. The title oxazole was isolated as a white foam (0.30 g, 29%); ν_{max} (film) 3400, 1655, 910 cm^{-1}; λ_{max} (EtOH) 229 nm (ε_m 20,800), 304 nm (ε_m 18,000); δ_H ($CDCl_3$) 7.2—7.7 (10H, 2m, aryl), 6.31 (1H, s, H2), 2.34 (3H, s, CH_3-15), 1.20 (3H, d, CH_3-14), 0.92 (3H, d, CH_3-17); δ_C ($CDCl_3$) 160.1 (C1), 147.3 (C4''), 144.3 (C3), 135—126 (aryl), 126.3 (C5'), 113.0 (C2), 75.5 (C5), 71.1 (C13), 70.4 (C7), 68.9 (C6),

65.4 (C16), 61.2 (C11), 55.6 (C10), 42.8 (C4, C12), 39.5 (C8), 31.7 (C9), 20.8 (C14), 19.7 (C15), 12.6 (C17); *m/e* (relative intensity) 519 ($M^{\oplus}$, 12%), 275 (100), 235 (34) (Found: $M^{\oplus}$, 519.2646. $C_{31}H_{37}NO_6$ requires 519.2618).

Biological Data

a) Mycoplasma

The activity of the compounds of the Examples against various mycoplasmal organisms was assayed *in vitro* in Friis broth solidified with 0.9% agarose and inoculated with 10^3 to 10^5 C.F.U. The minimum inhibitory concentrations (MIC's) were determined after incubation for 6 days at 37°C and are shown in Table I.

b) Veterinary Bacteria

The activity of the compounds of the Examples against various veterinarily important bacteria, was assayed *in vitro* using two-fold serial dilutions in Diagnostic Sensitivity Test Agar inoculated with 10^4 organisms. The MIC's were determined after incubation for 18 hours at 37°C and are shown in Table 2.

c) Human Bacteria

The activity of the compounds of the Examples against various bacteria which are important in diseases of humans, was assayed *in vitro* using serial dilutions in nutrient agar with 5% chocolated horse blood. The MIC's were determined after incubation for 18 hours at 37°C and are shown in Table 3.

TABLE 1

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.						
	1	2*	3	4	5	9	10
M. suipneumoniae NB12	1.0	>10	0.1	0.5	0.05	0.5	0.05
M. suipneumoniae JF 435	1.0	>10	0.25	1.0	0.1	0.5	0.05
M. suipneumoniae HK(2)	1.0	10	0.25	1.0	0.1	0.5	0.05
M. suipneumoniae Str. 11	0.5	10	0.1	0.5	0.05	0.5	0.025
M. suipneumoniae J2206/183[b]	1.0	10	0.25	1.0	0.1	0.5	0.05
M. suipneumoniae MS 16	0.5	5.0	0.05	0.5	0.05	0.5	0.025
M. suipneumoniae PW/C/210	0.5	5.0	0.1	0.5	0.05	0.5	0.025
M. suipneumoniae LABER	0.5	10	0.1	0.5	0.05	0.5	0.025
M. suipneumoniae UCD 1	1.0	10	0.25	1.0	0.1	0.5	0.05
M. suipneumoniae TAM 6N	1.0	>10	0.25	1.0	0.1	0.5	0.05
M. suipneumoniae ATCC 25095	0.5	10	0.1	0.5	0.05	0.5	0.025
M. suipneumoniae NCTC 10110	1.0	10	0.25	1.0	0.1	0.5	0.05
M. hyorhinis ATCC 23234	0.5	10	0.1	0.5	0.05	0.5	0.025
M. hyorhinis ATCC 25021	0.5	5.0	0.05	0.5	0.05	0.5	0.025
M. hyosynoviae ATCC 25591	0.5	5.0	0.25	0.5	0.25	0.5	0.05
M. bovis NCTC 10131	≤0.01	0.25	0.25	0.025	≤0.01	0.05	0.01
M. bovigenitalium ATCC 14173	NG	0.5	0.5	0.05	0.025	0.1	0.025
M. dispar NCTC 10125	0.1	2.5	0.05	0.25	0.025	0.1	0.025
M. gallisepticum S6	2.5	>10	0.5	2.5	0.5	1.0	0.1
M. pneumoniae ATCC 15492	2.5	NG	0.5	NG	0.25	1.0	0.1

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	6	7	11	12
M. suipneumoniae NB12	0.05	>10	0.1	>10
M. suipneumoniae JF 435	0.05	>10	0.25	>10
M. suipneumoniae HK(2)	0.05	>10	0.25	>10
M. suipneumoniae Str. 11	0.05	10	0.1	10
M. suipneumoniae J2206/183[b]	0.05	>10	0.25	>10
M. suipneumoniae MS 16	0.025	10	0.1	10
M. suipneumoniae PW/C/210	0.025	10	0.1	10
M. suipneumoniae LABER	0.05	10	0.1	>10
M. suipneumoniae UCD 1	0.05	>10	0.25	>10
M. suipneumoniae TAM 6N	0.1	>10	0.5	>10
M. suipneumoniae ATCC 25095	0.05	10	0.25	10
M. suipneumoniae NCTC 10110	0.05	10	0.25	>10
M. hyorhinis ATCC 23234	0.025	10	0.1	5.0
M. hyorhinis ATCC 25021	0.025	10	0.1	5.0
M. hyosynoviae ATCC 25591	0.5	5.0	0.25	5.0
M. bovis NCTC 10131	0.025	0.1	≤0.01	0.05
M. bovigenitalium ATCC 14173	0.05	1.0	0.1	1.0
M. dispar NCTC 10125	0.025	2.5	0.1	5.0
M. gallisepticum S6	1.0	>10	0.5	>10
M. pneumoniae ATCC 15492	1.0	>10	0.5	>10

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	13	14	15	16
M. suipneumoniae NB12	0.1	5.0	0.5	0.5
M. suipneumoniae JF 435	0.25	5.0	0.5	0.5
M. suipneumoniae HK(2)	0.25	5.0	0.5	0.5
M. suipneumoniae Str. 11	0.1	2.5	0.5	0.25
M. suipneumoniae J2206/183[b]	0.25	5.0	0.5	0.5
M. suipneumoniae MS 16	0.1	2.5	0.25	0.25
M. suipneumoniae PW/C/210	0.1	2.5	0.25	0.25
M. suipneumoniae LABER	0.1	2.5	0.5	0.25
M. suipneumoniae UCD 1	0.25	5.0	0.5	0.5
M. suipneumoniae TAM 6N	0.25	5.0	0.5	0.5
M. suipneumoniae ATCC 25095	0.25	2.5	0.5	0.25
M. suipneumoniae NCTC 10110	0.25	5.0	0.5	0.5
M. hyorhinis ATCC 23234	0.1	2.5	0.25	0.25
M. hyorhinis ATCC 25021	0.1	2.5	0.25	0.25
M. hyosynoviae ATCC 25591	0.25	5.0	0.5	0.5
M. bovis NCTC 10131	≤0.01	0.05	0.05	0.05
M. bovigenitalium ATCC 14173	0.025	0.1	0.05	0.1
M. dispar NCTC 10125	0.05	0.5	0.1	0.1
M. gallisepticum S6	0.5	>10	1.0	2.5
M. pneumoniae ATCC 15492	0.5	>10	1.0	1.0

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	17	18	19	20
M. suipneumoniae NB12	2.5	0.5	1.0	0.5
M. suipneumoniae JF 435	5.0	0.5	2.5	1.0
M. suipneumoniae HK(2)	10	1.0	2.5	1.0
M. suipneumoniae Str. 11	2.5	0.25	1.0	0.5
M. suipneumoniae J2206/183[b]	5.0	1.0	5.0	1.0
M. suipneumoniae MS 16	2.5	0.25	0.5	0.5
M. suipneumoniae PW/C/210	NG	0.25	0.25	0.5
M. suipneumoniae LABER	2.5	0.25	1.0	0.5
M. suipneumoniae UCD 1	5.0	0.5	2.5	1.0
M. suipneumoniae TAM 6N	10	1.0	2.5	1.0
M. suipneumoniae ATCC 25095	5.0	0.5	.10	0.5
M. suipneumoniae NCTC 10110	>10	1.0	5.0	1.0
M. hyorhinis ATCC 23234	5.0	0.25	1.0	0.5
M. hyorhinis ATCC 25021	5.0	0.5	1.0	0.5
M. hyosynoviae ATCC 25591	>10	0.5	0.5	0.5
M. bovis NCTC 10131	2.5	0.05	0.025	≤0.01
M. bovigenitalium ATCC 14173	5.0	0.1	0.1	0.05
M. dispar NCTC 10125	2.5	0.25	0.5	0.25
M. gallisepticum S6	>10	1.0	10	2.5
M. pneumoniae ATCC 15492	>10	1.0	1.0	0.5

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	21	22	23	24
M. suipneumoniae NB12	0.25	1.0	0.5	0.1
M. suipneumoniae JF 435	0.5	1.0	1.0	0.25
M. suipneumoniae HK(2)	0.5	1.0	1.0	0.25
M. suipneumoniae Str. 11	0.25	0.5	0.5	0.1
M. suipneumoniae J2206/183[b]	0.5	1.0	1.0	0.25
M. suipneumoniae MS 16	0.25	0.5	0.5	0.1
M. suipneumoniae PW/C/210	0.25	0.5	0.5	0.1
M. suipneumoniae LABER	0.25	0.5	0.5	0.1
M. suipneumoniae UCD 1	0.25	1.0	1.0	0.25
M. suipneumoniae TAM 6N	0.5	1.0	1.0	0.25
M. suipneumoniae ATCC 25095	0.25	1.0	0.5	0.1
M. suipneumoniae NCTC 10110	0.5	1.0	1.0	0.25
M. hyorhinis ATCC 23234	0.25	1.0	0.5	0.1
M. hyorhinis ATCC 25021	0.25	0.5	0.5	0.1
M. hyosynoviae ATCC 25591	0.1	1.0	1.0	0.25
M. bovis NCTC 10131	0.025	0.05	0.025	0.025
M. bovigenitalium ATCC 14173	0.05	1.0	1.0	0.1
M. dispar NCTC 10125	0.1	0.5	0.5	0.1
M. gallisepticum S6	0.25	5.0	1.0	0.5
M. pneumoniae ATCC 15492	0.25	5.0	1.0	0.5

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	25	26	27	28
M. suipneumoniae NB12	0.25	2.5	5.0	NG
M. suipneumoniae JF 435	0.5	2.5	10	1.0
M. suipneumoniae HK(2)	0.1	5.0	10	0.5
M. suipneumoniae Str. 11	0.5	2.5	5.0	0.25
M. suipneumoniae J2206/183[b]	0.1	5.0	10	0.5
M. suipneumoniae MS 16	0.25	1.0	5.0	0.25
M. suipneumoniae PW/C/210	0.25	1.0	5.0	NG
M. suipneumoniae LABER	0.25	2.5	5.0	0.25
M. suipneumoniae UCD 1	0.1	2.5	10	0.25
M. suipneumoniae TAM 6N	0.1	5.0	10	0.5
M. suipneumoniae ATCC 25095	0.5	2.5	5.0	0.25
M. suipneumoniae NCTC 10110	0.1	5.0	10	0.5
M. hyorhinis ATCC 23234	0.1	2.5	10	0.5
M. hyorhinis ATCC 25021	0.5	2.5	5.0	0.5
M. hyosynoviae ATCC 25591	0.1	0.5	2.5	1.0
M. bovis NCTC 10131	0.025	0.025	0.05	0.05
M. bovigenitalium ATCC 14173	0.25	0.25	0.25	0.1
M. dispar NCTC 10125	0.25	1.0	2.5	0.1
M. gallisepticum S6	2.5	2.5	>10	2.5
M. pneumoniae ATCC 15492	2.5	2.5	10	5.0

* Only the Z-isomer was tested

TABLE 1 (continued)

MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.			
	29	30	31	33
M. suipneumoniae NB12	10	5.0	10	2.5
M. suipneumoniae JF 435	>10	5.0	10	2.5
M. suipneumoniae HK(2)	>10	2.5	10	2.5
M. suipneumoniae Str. 11	10	2.5	5.0	1.0
M. suipneumoniae J2206/183[b]	>10	2.5	10	1.0
M. suipneumoniae MS 16	10	2.5	5.0	1.0
M. suipneumoniae PW/C/210	10	NG	NG	NG
M. suipneumoniae LABER	10	2.5	10	2.5
M. suipneumoniae UCD 1	>10	2.5	10	1.0
M. suipneumoniae TAM 6N	>10	5.0	10	2.5
M. suipneumoniae ATCC 25095	10	2.5	5.0	1.0
M. suipneumoniae NCTC 10110	>10	2.5	10	2.5
M. hyorhinis ATCC 23234	>10	0.5	5.0	1.0
M. hyorhinis ATCC 25021	10	0.5	5.0	1.0
M. hyosynoviae ATCC 25591	>10	1.0	10	2.5
M. bovis NCTC 10131	0.5	0.25	1.0	0.25
M. bovigenitalium ATCC 14173	1.0	0.25	5.0	0.5
M. dispar NCTC 10125	2.5	0.25	2.5	0.5
M. gallisepticum S6	>10	>10	>10	>10
M. pneumoniae ATCC 15492	>10	10	>10	10

* Only the Z-isomer was tested

TABLE 1 (continued)
MIC's (µg/ml) against Mycoplasma

Organism	Compound of Example No.				
	34	35	39	40	41
M. suipneumoniae NB12	2.5	NG	>10	>10	>10
M. suipneumoniae JF 435	2.5	>10	>10	>10	>10
M. suipneumoniae HK(2)	2.5	>10	>10	>10	>10
M. suipneumoniae Str. 11	1.0	>10	>10	>10	>10
M. suipneumoniae J2206/183[b]	2.5	>10	>10	>10	>10
M. suipneumoniae MS 16	1.0	>10	>10	>10	>10
M. suipneumoniae PW/C/210	NG	NG	>10	>10	>10
M. suipneumoniae LABER	1.0	>10	>10	>10	>10
M. suipneumoniae UCD 1	2.5	>10	>10	>10	>10
M. suipneumoniae TAM 6N	2.5	>10	>10	>10	>10
M. suipneumoniae ATCC 25095	1.0	>10	>10	>10	>10
M. suipneumoniae NCTC 10110	2.5	>10	>10	>10	>10
M. hyorhinis ATCC 23234	2.5	>10	>10	>10	>10
M. hyorhinis ATCC 25021	1.0	>10	>10	>10	>10
M. hyosynoviae ATCC 25591	5.0	>10	>10	>10	>10
M. bovis NCTC 10131	0.25	2.5	5.0	5.0	2.5
M. bovigenitalium ATCC 14173	1.0	5.0	5.0	10	2.5
M. dispar NCTC 10125	0.5	>10	>10	>10	>10
M. gallisepticum S6	>10	>10	>10	>10	>10
M. pneumoniae ATCC 15492	5.0	>10	>10	>10	>10

* Only the Z-isomer was tested

TABLE 2
MIC's (µg/ml) against Veterinary Bacteria

Organism	Compound of Example No.					
	1	2*	3	4	5	6
E. coli NCTC 10418	>80	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	80	>80	40	>80	80	80
Bord. bronchiseptica B09	20	>80	5.0	20	40	20
Past. multocida PA1	10	>80	5.0	5.0	5.0	10
ast. multocida PA2	1.25	20	0.625	5.0	2.5	1.25
Past. haemolytica PA5	80	>80	10	40	40	80
Erysipelothrix rhusiopathiae NCTC 8163	80	>80	>80	>80	80	>80
Corynebacterium pyogenes CY1	80	>80	80	>80	80	>80
Staph. aureus B4 (pen. resistant)	1.25	20	0.312	5.0	1.25	1.25
Staph. aureus 152 (pen. sens)	1.25	20	0.312	5.0	0.625	1.25
Staph. aureus Oxford	1.25	20	0.312	0.625	0.625	1.25
Step. suis (group D) SPS11	20	>80	2.5	20	10	10
Strep. uberis SPU1	0.625	5.0	0.039	0.312	0.07	0.07
Strep. dysgalacticiae SPD1	0.625	10	0.312	1.25	0.312	0.625
Strep. agalactiae SPA1	1.25	20	1.25	NG	0.625	2.5
B. subtilis ATCC 6633	—	—	—	—	—	—

* Only the Z-isomer was tested

TABLE 2 (continued)

MIC's (μg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	7	9	10	11	12
E. coli NCTC 10418	>80	>80	>80	>80	>40
E. coli E1	>80	>80	>80	>80	>40
S. dublin S7	>80	>80	>80	>80	>40
S. typhimurium S18	>80	>80	>80	>80	>40
Bord. bronchiseptica B08	40	40	>80	>80	>40
Bord. bronchiseptica B09	40	40	40	40	20
Past. multocida PA1	40	20	5.0	5.0	2.5
Past. multocida PA2	20	5.0	1.25	0.625	0.156
Past. haemolytica PA5	>80	40	40	40	40
Erysipelothrix rhusiopathiae NCTC 8163	>80	80	>80	>80	>40
Corynebacterium pyogenes CY1	>80	80	>80	>80	>40
Staph. aureus B4 (pen. resistant)	5.0	1.25	5.0	5.0	2.5
Staph. aureus 152 (pen. sens)	5.0	0.625	2.5	2.5	0.625
Staph. aureus Oxford	5.0	0.625	2.5	2.5	0.625
Step. suis (group D) SPS11	80	10	10	5.0	20
Strep. uberis SPU1	1.25	0.16	0.625	0.312	0.625
Strep. dysgalacticiae SPD1	2.5	0.625	2.5	1.25	0.625
Strep. agalactiae SPA1	5.0	10	2.5	2.5	20
B. subtilis ATCC 6633	—	—	—	—	—

* Only the Z-isomer was tested

TABLE 2 (Continued)

MIC's (µg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	13	14	15	16	17
E. coli NCTC 10418	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	>80	>80	80	>80	>80
Bord. bronchiseptica B09	20	>80	20	40	40
Past. multocida PA1	2.5	10	10	40	10
Past. multocida PA2	0.312	10	<0.039	<0.039	1.25
Past. haemolytica PA5	40	>80	80	>80	>80
Erysipelothrix rhusiopathiae NCTC 8163	>80	>80	>80	80	80
Corynebacterium pyogenes CY1	>80	>80	>80	>80	>80
Staph. aureus B4 (pen. resistant)	1.25	10	2.5	5.0	10
Staph. aureus 152 (pen. sens)	1.25	10	0.625	1.25	10
Staph. aureus Oxford	1.25	10	1.25	1.25	20
Step. suis (group D) SPS11	10	>80	20	20	40
Strep. uberis SPU1	0.312	2.5	0.625	0.312	1.25
Strep. dysgalacticiae SPD1	0.625	2.5	1.25	1.25	2.5
Strep. agalactiae SPA1	10	>80	1.25	1.25	40
B. subtilis ATCC 6633	—	—	—	—	—

* Only the Z-isomer was tested

TABLE 2 (Continued)

MIC's (μg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	18	19	20	21	22
E. coli NCTC 10418	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	40	>80	80	40	>80
Bord. bronchiseptica B09	10	20	10	10	40
Past. multocida PA1	10	—	2.5	2.5	20
Past. multocida PA2	1.25	NG	0.312	0.625	10
Past. haemolytica PA5	40	>80	80	20	80
Erysipelothrix rhusiopathiae NCTC 8163	40	>80	80	40	80
Corynebacterium pyogenes CY1	>80	>80	>80	>80	>80
Staph. aureus B4 (pen. resistant)	0.156	1.25	0.63	1.25	1.25
Staph. aureus 152 (pen. sens)	0.312	1.25	0.63	0.625	1.25
Staph. aureus Oxford	0.625	2.5	2.55	2.5	2.5
Step. suis (group D) SPS11	10	80	40	10	20
Strep. uberis SPU1	>0.039	0.625	0.156	0.156	0.156
Strep. dysgalacticiae SPD1	0.156	2.5	0.625	0.625	1.25
Strep. agalactiae SPA1	0.625	10	1.25	1.25	10
B. subtilis ATCC 6633	—	—	10	2.5	0.625

* Only the Z-isomer was tested

TABLE 2 (Continued)

MIC's (µg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	23	24	25	26	27
E. coli NCTC 10418	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	>80	80	>80	80	>80
Bord. bronchiseptica B09	40	40	40	20	80
Past. multocida PA1	5.0	5.0	5.0	10	20
Past. multocida PA2	2.5	2.5	2.5	5.0	5.0
Past. haemolytica PA5	80	40	80	C	C
Erysipelothrix rhusiopathiae NCTC 8163	>80	40	>80	>80	>80
Corynebacterium pyogenes CY1	>80	80	>80	>80	>80
Staph. aureus B4 (pen. resistant)	5.0	1.25	10	2.5	2.5
Staph. aureus 152 (pen. sens)	2.5	0.625	10	2.5	10
Staph. aureus Oxford	10	1.25	20	2.5	10
Step. suis (group D) SPS11	10	2.5	20	10	>80
Strep. uberis SPU1	0.625	0.312	0.625	0.156	1.25
Strep. dysgalacticiae SPD1	1.25	0.625	1.25	0.625	2.5
Strep. agalactiae SPA1	2.5	1.25	2.5	2.5	20
B. subtilis ATCC 6633	12.25	0.312	2.5	0.312	2.5

* Only the Z-isomer was tested

TABLE 2 (Continued)

MIC's (µg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	28	29	30	31	33
E. coli NCTC 10418	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	80	>80	>80	>80	>80
Bord. bronchiseptica B09	20	>80	>80	80	>80
Past. multocida PA1	20	>80	2.5	—	1.3
Past. multocida PA2	2.5	80	0.312	NG	0.625
Past. haemolytica PA5	80	>80	10	>80	20
Erysipelothrix rhusiopathiae NCTC 8163	40	>80	>80	>80	>80
Corynebacterium pyogenes CY1	>80	>80	>80	>80	>80
Staph. aureus B4 (pen. resistant)	0.156	10	1.25	10	1.3
Staph. aureus 152 (pen. sens)	0.312	10	2.5	10	2.5
Staph. aureus Oxford	0.625	10	2.5	20	2.5
Step. suis (group D) SPS11	10	>80	>80	>80	>80
Strep. uberis SPU1	>0.039	5.0	10	40	5.0
Strep. dysgalacticiae SPD1	0.312	20	40	>80	5.0
Strep. agalactiae SPA1	1.25	40	40	—	10
B. subtilis ATCC 6633	0.07	—	—	—	—

*Only the Z-isomer was tested.

TABLE 2 (Continued)

MIC's (µg/ml) against Veterinary Bacteria

Organism	Compound of Example No.				
	34	35	39	40	41
E. coli NCTC 10418	>80	>80	>80	>80	>80
E. coli E1	>80	>80	>80	>80	>80
S. dublin S7	>80	>80	>80	>80	>80
S. typhimurium S18	>80	>80	>80	>80	>80
Bord. bronchiseptica B08	>80	>80	>80	>80	>80
Bord. bronchiseptica B09	40	>80	>80	>80	>80
Past. multocida PA1	—	80	80	80	40
Past. multocida PA2	NG	NG	40	80	20
Past. haemolytica PA5	>80	>80	80	>80	>80
Erysipelothrix rhusiopathiae NCTC 8163	>80	>80	>80	>80	>80
Corynebacterium pyogenes CY1	>80	>80	>80	80	40
Staph. aureus B4 (pen. resistant)	2.5	>80	>80	80	40
Staph. aureus 152 (pen. sens)	2.5	>80	>80	80	40
Staph. aureus Oxford	5.0	>80	>80	80	40
Step. suis (group D) SPS11	80	>80	>80	>80	>80
Strep. uberis SPU1	5.0	80	>80	40	10
Strep. dysgalacticiae SPD1	10	>80	>80	>80	20
Strep. agalactiae SPA1	40	>80	NG	>80	40
B. subtilis ATCC 6633	—	>80	—	—	—

* Only the Z-isomer was tested

TABLE 3

MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.						
	1	2*	3	4	5	9	10
E. coli NCTC 10418	>100	>50	>100	>100	>50	>100	>128
E. coli ESS	10	25	0.5	2.5	1.2	5.0	8.0
P. mirabilis 889	>100	>50	50	>100	>50	>100	>128
K. aerogenes A	>100	>50	100	>100	>50	>100	>128
Ps. aeruginosa NCTC 10662	>100	>50	>100	>100	>50	>100	>128
Pasteurella multocida 1633	10	>50	0.5	25	5.0	5.0	8.0
Haemophilus influenzae Q1	1.0	12.5	0.1	2.5	1.2	5.0	1.0
Haemophilus influenzae Wy21	1.0	12.5	0.1	2.5	1.21	50	2.0
Neisseria catarrhalis 1502	10	>50	0.5	10	5.0	10	8.0
Bacillus subtilis 6633	2.5	25	0.5	5.0	1.2	1.0	2.0
Corynebacterium xerosis 9755	>100	>50	>100	>100	>50	>100	>128
Sarcina lutea 8340	≥100	>50	>100	>100	>50	>100	>128
Staph. aureus Oxford	5.0	25	0.2	2.5	1.2	2.5	8.0
Staph. aureus Russell	5.0	>50	5.0	5.0	5.0	5.0	8.0
Staph. aureus W2827	5.0	>50	1.0	5.0	5.0	5.0	8.0
Strep. faecalis I	≥100	>50	50	>100	50	>100	>128
Strep. pyogenes R80/421-A	1.0	>50	0.5	5.0	—	10	8.0
Strep. agalactiae 2788-B	5.0	>50	0.5	5.0	2.5	10	8.0
Strep. spp. 64/848-C	2.5	>50	0.5	5.0	—	5.0	4.0
Strep. pneumoniae CN33	2.5	>50	0.5	5.0	2.5	10	8.0

Only the Z-isomer was tested

TABLE 3 (Continued)

MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.					
	6	7	11	12	13	14
E. coli NCTC 10418	>128	>100	>128	>16	>128	>128
E. coli ESS	16	0.5	128	>16	2.0	32
P. mirabilis 889	>128	>100	>128	>16	>128	>128
K. aerogenes A	>128	>100	>128	>16	>128	>128
Ps. aeruginosa NCTC 10662	>128	>100	>128	>16	>128	>128
Pasteurella multocida 1633	16	2.5	8.0	4.0	2.0	16
Haemophilus influenzae Q1	2.0	0.5	2.0	1.0	0.5	2.0
Haemophilus influenzae Wy21	2.0	1.0	4.0	2.0	1.0	2.0
Neisseria catarrhalis 1502	4.0	5.0	8.0	16	4.0	16
Bacillus subtilis 6633	2.0	2.5	4.0	4.0	1.0	4.0
Corynebacterium xerosis 9755	>128	>100	>128	>16	64	>128
Sarcina lutea 8340	>128	>100	>128	>16	128	>128
Staph. aureus Oxford	8.0	2.5	16	8.0	4.0	16
Staph. aureus Russell	16	25	16	8.0	4.0	16
Staph. aureus W2827	16	25	16	8.0	4.0	16
Strep. faecalis I	>128	>100	>128	>16	>128	>128
Strep. pyogenes R80/421-A	4.0	25	4.0	16	4.0	32
Strep. agalactiae 2788-B	4.0	25	4.0	16	2.0	32
Strep. spp. 64/848-C	—	10	2.0	4.0	1.0	—
Strep. pneumoniae CN33	4.0	25	4.0	16	4.0	32

TABLE 3 (Continued)

MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.					
	15	16	17	18	19	20
E. coli NCTC 10418	>128	>64	>64	>128	>128	>128
E. coli ESS	16	32	16	8.0	16	4.0
P. mirabilis 889	>128	>64	>64	>128	>128	>128
K. aerogenes A	>128	>64	>64	>128	>128	>128
Ps. aeruginosa NCTC 10662	>128	>64	>64	>128	>128	>128
Pasteurella multocida 1633	32	16	8.0	16	32	4.0
Haemophilus influenzae Q1	4.0	2.0	NG	NG	C	C
Haemophilus influenzae Wy21	4.0	2.0	2.0	4.0	4.0	0.5
Neisseria catarrhalis 1502	4.0	8.0	8.0	4.0	C	C
Bacillus subtilis 6633	2.0	1.0	32	1.0	4.0	0.5
Corynebacterium xerosis 9755	>128	>64	>64	>128	>128	>128
Sarcina lutea 8340	>128	>64	NG	NG	>128	>128
Staph. aureus Oxford	2.0	4.0	32	2.0	4.0	4.0
Staph. aureus Russell	8.0	4.0	>64	8.0	4.0	4.0
Staph. aureus W2827	8.0	4.0	>64	8.0	4.0	4.0
Strep. faecalis I	>128	>64	>64	>128	>128	>128
Strep. pyogenes R80/421-A	8.0	4.0	4.0	2.0	2.0	0.25
Strep. agalactiae 2788-B	8.0	4.0	32	8.0	16	2.0
Strep. spp. 64/848-C	—	—	32	4.0	16	2.0
Strep. pneumoniae CN33	8.0	4.0	64	4.0	NG	NG

* Only the Z-isomer was tested

TABLE 3 (Continued)

MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.					
	21	22	23	24	25	26
E. coli NCTC 10418	>128	>128	>64	>64	>128	>128
E. coli ESS	4.0	64	4.0	4.0	4.0	8.0
P. mirabilis 889	>128	>128	>64	>64	>128	>128
K. aerogenes A	>128	>128	>64	>64	>128	>128
Ps. aeruginosa NCTC 10662	>128	>128	>64	>64	>128	>128
Pasteurella multocida 1633	8.0	32	2.0	16	16	16
Haemophilus influenzae Q1	C	C	C	C	C	C
Haemophilus influenzae Wy21	2.0	4.0	1.0	4.0	2.0	0.25
Neisseria catarrhalis 1502	C	C	C	C	C	C
Bacillus subtilis 6633	1.0	4.0	2.0	4.0	2.0	0.25
Corynebacterium xerosis 9755	>128	>128	>128	>128	128	>128
Sarcina lutea 8340	>128	>128	>128	>128	128	>128
Staph. aureus Oxford	4.0	4.0	4.0	4.0	4.0	4.0
Staph. aureus Russell	4.0	16	16	4.0	32	4.0
Staph. aureus W2827	4.0	16	16	4.0	32	4.0
Strep. faecalis I	>128	>128	>128	>128	>128	>128
Strep. pyogenes R80/421-A	1.0	8.0	0.5	2.0	2.0	1.0
Strep. agalactiae 2788-B	4.0	16	2.0	2.0	2.0	2.0
Strep. spp. 64/848-C	4.0	16	2.0	4.0	2.0	2.0
Strep. pneumoniae CN33	NG	NG	NG	NG	NG	NG

* Only the Z-isomer was tested

TABLE 3 (Continued)

MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.					
	27	29	30	31	33	34
E. coli NCTC 10418	>64	>100	>128	>128	>128	>128
E. coli ESS	16	>100	8.0	64	8.0	16
P. mirabilis 889	>64	>100	>128	>128	>128	>128
K. aerogenes A	>64	>100	>128	>128	>128	>128
Ps. aeruginosa NCTC 10662	>64	>100	>128	>128	>128	>128
Pasteurella multocida 1633	32	>100	8.0	64	2.0	64
Haemophilus influenzae Q1	C	50	NG	NG	NG	NG
Haemophilus influenzae Wy21	2.0	50	>0.06	16	0.25	2.0
Neisseria catarrhalis 1502	C	50	8.0	8.0	4.0	4.0
Bacillus subtilis 6633	4.0	50	8.0	64	1.0	4.0
Corynebacterium xerosis 9755	>64	>100	>128	>128	>128	>128
Sarcina lutea 8340	>64	>100	NG	NG	NG	NG
Staph. aureus Oxford	8.0	25	8.0	64	8.0	8.0
Staph. aureus Russell	16	100	16	128	8.0	16
Staph. aureus W2827	16	50	16	128	8.0	16
Strep. faecalis I	>64	>100	>128	>128	>128	>128
Strep. pyogenes R80/421-A	4.0	50	32	128	8.0	8.0
Strep. agalactiae 2788-B	16	50	128	>128	64	64
Strep. spp. 64/848-C	16	25	>128	>128	32	64
Strep. pneumoniae CN33	NG	50	128	>128	32	64

*Only the Z-isomer was tested.

TABLE 3 (Continued)

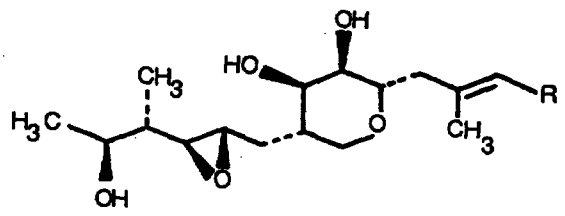
MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.			
	35	39	40	41
E. coli NCTC 10418	>128	>100	>100	>100
E. coli ESS	128	>100	100	50
P. mirabilis 889	>128	>100	>100	>100
K. aerogenes A	>128	>100	>100	>100
Ps. aeruginosa NCTC 10662	>128	>100	>100	>100
Pasteurella multocida 1633	>128	50	100	25
Haemophilus influenzae Q1	C	5	50	10
Haemophilus influenzae Wy21	128	2.5	50	25
Neisseria catarrhalis 1502	C	25	50	25
Bacillus subtilis 6633	>128	>100	100	100
Corynebacterium xerosis 9755	>128	>100	>100	>100
Sarcina lutea 8340	>128	>100	>100	>100
Staph. aureus Oxford	>128	100	100	100
Staph. aureus Russell	>128	>100	100	>100
Staph. aureus W2827	>128	>100	>100	>100
Strep. faecalis I	>128	>100	>100	>100
Strep. pyogenes R80/421-A	>128	—	—	>100
Strep. agalactiae 2788-B	>128	>100	>100	>100
Strep. spp. 64/848-C	>128	—	—	100
Strep. pneumoniae CN33	NG	100	>100	>100

* Only the Z-isomer was tested

Claims

1. A compound of formula (I)



(I)

TABLE 3 (Continued)

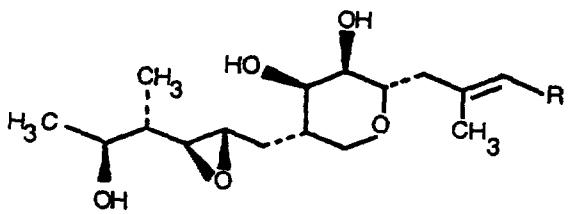
MIC's (µg/ml) against Human Bacteria

Organism	Compound of Example No.			
	35	39	40	41
E. coli NCTC 10418	>128	>100	>100	>100
E. coli ESS	128	>100	100	50
P. mirabilis 889	>128	>100	>100	>100
K. aerogenes A	>128	>100	>100	>100
Ps. aeruginosa NCTC 10662	>128	>100	>100	>100
Pasteurella multocida 1633	>128	50	100	25
Haemophilus influenzae Q1	C	5	50	10
Haemophilus influenzae Wy21	128	2.5	50	25
Neisseria catarrhalis 1502	C	25	50	25
Bacillus subtilis 6633	>128	>100	100	100
Corynebacterium xerosis 9755	>128	>100	>100	>100
Sarcina lutea 8340	>128	>100	>100	>100
Staph. aureus Oxford	>128	100	100	100
Staph. aureus Russell	>128	>100	100	>100
Staph. aureus W2827	>128	>100	>100	>100
Strep. faecalis I	>128	>100	>100	>100
Strep. pyogenes R80/421-A	>128	—	—	>100
Strep. agalactiae 2788-B	>128	>100	>100	>100
Strep. spp. 64/848-C	>128	—	—	100
Strep. pneumoniae CN33	NG	100	>100	>100

* Only the Z-isomer was tested

Claims

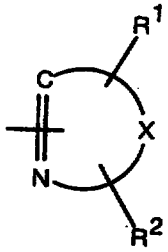
1. A compound of formula (I)



(I)

* C L M S *

wherein R is a group



wherein

R is a group

R^1 and R^2 are the same or different and each is selected from:

a) hydrogen,

b) phenyl or a 5 or 6-membered heterocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, optionally substituted with a substituent selected from halogen, C_{1-6} alkoxy, hydroxy, carboxy, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6}) alkyl carbamoyl, sulphamoyl, mono- and di-(C_{1-6})sulphamoyl, cyano, nitro, amino, mono- and di-(C_{1-6})alkylamino, C_{1-6} acylamino, ureido, C_{1-6} alkoxycarbonylamino, 2,2,2-trichloroethoxy-carbonylamino, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanesulphinyl, and C_{1-6} alkanesulphonyl,

c) C_{1-20} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, optionally substituted with a substituent selected from halogen, carboxy, C_{1-6} alkoxy-carbonyl, carbamoyl, mono- or di-(C_{1-6})alkyl carbamoyl, sulphamoyl, amino, mono- and di-(C_{1-6})-alkylamino, C_{1-6} acylamino, ureido, C_{1-6} alkoxycarbonylamino, 2,2,2-trichloroethoxy carbonylamino, phenyl, a 5 or 6-membered heterocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, hydroxy, C_{1-6} alkoxy, oxo, 2-thenoyl, C_{1-6} alkylthio, C_{1-6} alkanesulphinyl, C_{1-6} alkanesulphonyl, hydroxyimino, hydrazono, benzohydroximoyl, and 2-thiophenecarbohydroximoyl, and

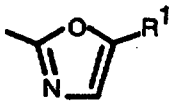
d) C_{3-7} cycloalkyl,

X is a divalent group —Y—C=C— and

Y is oxygen or sulphur.

2. A compound as claimed in claim 1 wherein R is substituted or unsubstituted oxazolyl.

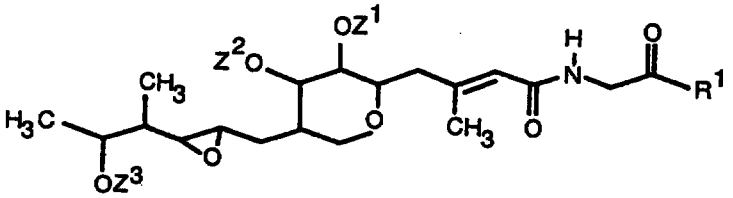
3. A compound as claimed in claim 2 wherein R is



wherein R^1 is as defined in claim 1.

4. A process for producing a compound of formula (I) as defined in claim 1 which process comprises either

a) cyclising a compound of formula (II):

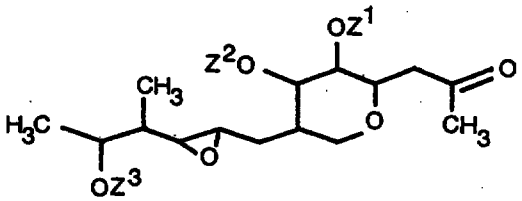


(II)

wherein R^1 is as defined in relation to formula (I);
and Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group

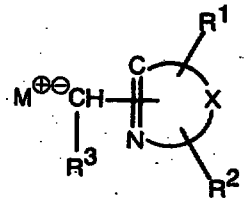
to form a compound of formula (I) wherein R is substituted or unsubsituted oxaloyl or

b) reacting a compound of formula (III):



(III)

wherein Z^1, Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group, with a compound of formula (IV):



(IV)

wherein

R^1 and R^2 are as defined in relation to formula (I) $M^{\oplus}$ is a metal cation, and

R^3 is an anion-stabilising group which will spontaneously eliminate with a β-hydroxyl group to produce an olefin,

and, where necessary, removing any hydroxyl-protectiong groups and, if desired, converting one compound of formula (I) into a further compound of formula (I).

5. A process as claimed in claim 4 wherein the compound of formula (II) is treated with a chlorinating agent in the presence of a tertiary amine or with a carboxylic anhydride or mixed anhydride.

6. A process as claimed in claim 5 wherein the compound of formula (II) is treated with triphenylphosphine and carbontetrachloride in the presence of triethylamine and an inert solvent.

7. A pharmaceutical or veterinary composition comprising a compound of formula (I) as defined in claim 1 and a pharmaceutically or veterinarily acceptable carrier or excipient.

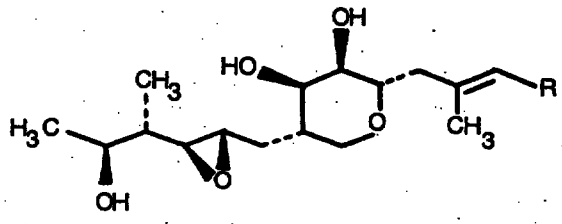
8. A composition as claimed in claim 7 in unit dosage form comprising 50 to 500 mg of a compound of formula (I).

9. A compound of formula (II) as defined in claim 4.

10. A compound of formula (I) as defined in claim 1 for use in therapeutical treating the human or animal body.

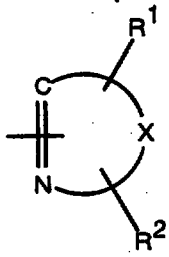
Patentansprüche

1. Eine Verbindung der Formel (I)



(I)

in welcher R eine Gruppe



in welcher

R ein Gruppe

bedeutet, R^1 und R^2 gleich oder verschieden sind und jeweils ausgewählt sind aus:

a) Wasserstoff,

b) Phenyl oder einem 5- oder 6-gliedrigen Ring enthaltend 1 bis 3 Heteroatome, ausgewählt aus Sauerstoff, Stickstoff und Schwefel, gegebenenfalls substituiert mit einem Substituenten, ausgewählt aus Halogen, C_{1-6}-Alkoxy, Hydroxy, Carboxy, C_{1-6}-Alkyl, C_{1-6}-Alkoxycarbonyl, Carbamoyl, Mono- oder Di-(C_{1-6})alkyl-carbamoyl, Sulfamoyl, Mono- und Di-(C_{1-6})sulfamoyl, Cyano, Nitro, Amino, Mono- und Di-(C_{1-6})alkylamino, C_{1-6}-Acylamino, Ureido, C_{1-6}-Alkoxycarbonylamino, 2,2,2-Trichloräthoxy-carbonylamino, C_{1-6}-Alkylthio, C_{1-6}-Alkanoyl, C_{1-6}-Alkansulfinyl, und C_{1-6}-Alkansulfonyl,

c) C_{1-60}-Alkyl, C_{2-6}-Alkenyl oder C_{2-6}-Alkynyl, gegebenenfalls substituiert mit einem Substituenten, ausgewählt aus Halogen, Carboxy, C_{1-6}-Alkoxy-carbonyl, Carbamoyl, Mono- oder Di-(C_{1-6})alkyl-carbamoyl, Sulfamoyl, Mono- und Di-(C_{1-6})alkyl-sulfamoyl, Amino, Mono- und Di(C_{1-6})-alkylamino, C_{1-6}-

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Acylamino, Ureido, C_{1-6}-Alkoxycarbonylamino, 2,2,2-Trichloräthoxycarbonylamino, Phenyl, ein 5- oder 6-gliedriger heterocyclischer Ring, enthaltend 1 bis 3 Heteroatome, ausgewählt aus Sauerstoff, Stickstoff und Schwefel, Hydroxy, C_{1-6}-Alkansulfinyl, C_{1-6}-Alkansulfonyl, Hydroxyimino, Hydrazono, Benzohydroximoyl, und 2-Thiophencarbohydroximoyl, und

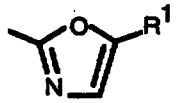
d) C_{3-7}-Cycloalkyl,

X eine zweiwertige Gruppe —Y—C=C— ist, und

Y Sauerstoff oder Schwefel bedeutet.

2. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher R substituiertes oder unsubstituiertes Oxazolyl ist.

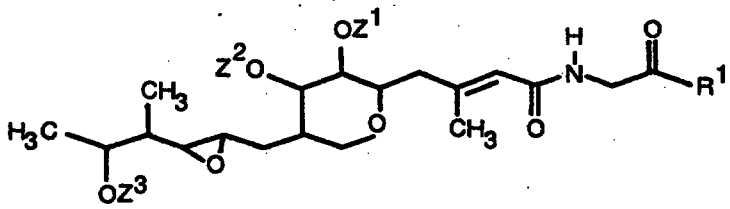
3. Eine Verbindung wie in Anspruch 2 beansprucht, in welcher R



ist, wobei R^1 wie in Anspruch 1 definiert ist.

4. Ein Verfahren zur Herstellung einer Verbindung der Formel (I) wie in Anspruch 1 definiert, welches Verfahren entweder

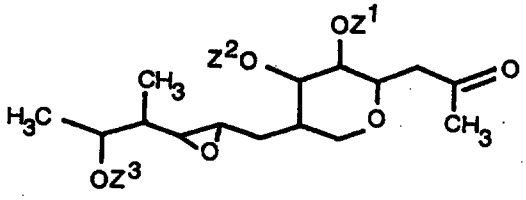
a) das Cyklisieren einer Verbindung der Formel (II):



(II)

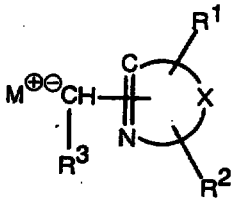
in welcher R^1 wie in bezug auf Formel (I) definiert ist; und Z^1, Z^2 und Z^3 gleich oder verschieden sind, und jeweils Wasserstoff oder eine Hydroxyl-Schutzgruppe bedeuten,
zur Bildung einer Verbindung der Formel (I), in welcher R substituiertes oder unsubstituiertes Oxazolyl ist, oder

(b) die Umsetzung einer Verbindung der Formel (III):



(III)

in welcher Z^1, Z^2 und Z^3 gleich oder verschieden sind und jeweils Wasserstoff oder eine Hydroxyl-Schutzgruppe sind,
mit einer Verbindung der Formel (IV):



(IV)

in welcher R^1 und R^2 wie in bezug auf Formel (I) definiert sind, $M^{\oplus}$ ein Metallkation ist, und

R^3 eine anionstabiliserende Gruppe ist, welche mit einer β-Hydroxylgruppe zur Bildung eines Olefins spontan eliminiert werden kann,
und, falls notwendig, das Entfernen jeglicher Hydroxyl-Schutzgruppe, und, falls gewünscht, die Umwandlung einer Verbindung der Formel (I) in eine weitere Verbindung der Formel (I), umfaßt.

5. Ein Verfahren wie in Anspruch 4 beansprucht, in welchem die Verbindung der Formel (II) mit einem Chlorierungsmittel in Gegenwart eines tertiären Amins oder mit einem Carbonsäureanhydrid oder einem gemischen Anhydrid behandelt wird.

6. Ein Verfahren wie in Anspruch 5 beansprucht, in welchem die Verbindung der Formel (II) mit Triphenylphosphin und Kohlenstofftetrachlorid in Gegenwart von Triäthylamin und einem inerten Lösungsmittel behandelt wird.

7. Eine pharmazeutische oder veterinärmedizinische Zusammensetzung enthaltend eine Verbindung der Formel (I), wie in Anspruch 1 definiert und einen pharmazeutisch oder veterinärmedizinisch verträglichen Träger.

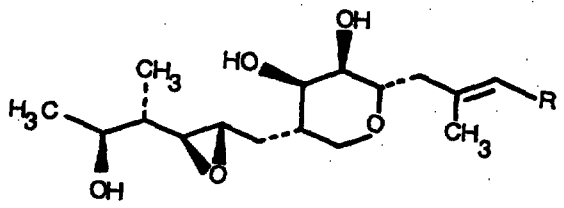
8. Eine Zusammensetzung wie in Anspruch 7 beansprucht in Einzeldosisform, enthaltend 50 bis 500 mg einer Verbindung der Formel (I).

9. Eine Verbindung der Formel (II), wie in Anspruch 4 definiert.

10. Eine Verbindung der Formel (I) wie in Anspruch 1 definiert zur Verwendung bei der therapeutische Behandlung von Mensch und Tier.

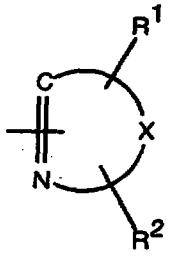
Revendications

1. Composé de formule (I):



(I)

où R est un groupe



où R est un groupe

R^1 et R^2 sont identiques ou différents et sont chacun choisis parmi:

a) un atome d'hydrogène,

b) un groupe phényle ou un noyau hétérocyclique à 5 ou 6 chaînons contenant 1 à 3 hétéroatomes choisis parmi les atomes d'oxygène, d'azote et de soufre, éventuellement substitué avec un substituant choisi parmi un atome d'halogène, un groupe alcoxy en C_{1-6}, hydroxy, carboxy, alcoyle en C_{1-6}, alcoxy(C_{1-6})carbonyle, carbamoyle, mono- ou dialcoyl(C_{1-6})carbamoyle, sulfamoyle, mono- et dialcoyl(C_{1-6})sulfamoyle, cyano, nitro, amino, mono- et dialcoyl(C_{1-6})amino, acyl(C_{1-6})amino, uréido, alcoxy(C_{1-6})carbonylamino, 2,2,2-trichloroéthoxycarbonylamino, alcoyl(C_{1-6})thio, alcanoyle en C_{1-6}, alcane(C_{1-6})sulfinyle et alcane(C_{1-6})sulfonyle,

c) un groupe alcoyle en C_{1-20}, alcényle en C_{2-8} ou alcynyle en C_{2-8}, éventuellement substitué avec un substituant choisi parmi un atome d'halogène, un groupe carboxy, alcoxy(C_{1-6})carbonyle, carbamoyle, mono- ou dialcoyl(C_{1-6})carbamoyle, sulfamoyle, mono- et dialcoyl(C_{1-6})sulfamoyle, amino, mono- et dialcoyl-(C_{1-6})amino, acyl(C_{1-6})amino, uréido, alcoxy(C_{1-6})carbonylamino, 2,2,2-trichloroéthoxycarbonyl-amino, phényle, un noyau hétérocyclique à 5 ou 6 chaînons contenant 1 a 3 hétéroatomes choisis parmi des atomes d'oxygène, d'azote et de soufre, un groupe hydroxy, alcoxy en C_{1-6}, oxo, 2-thénoyle, alcoyl(C_{1-6})thio, alcane(C_{1-6})sulfinyle, alcane(C_{1-6})sulfonyle, hydroxyimino, hydrazono, benzo-hydroxyimoyle et 2-thiophènecarbohydroxyimoyle, et

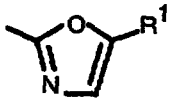
d) un groupe cycloalcoyle en C_{3-7},

X est un groupe divalent —Y—C=C—,

et Y est un atome d'oxygène ou de soufre.

2. Composé suivant la revendication 1, dans lequel R est un groupe oxazolyle substitué ou non substitué.

3. Composé suivant la revendication 2, dans lequel R est un radical

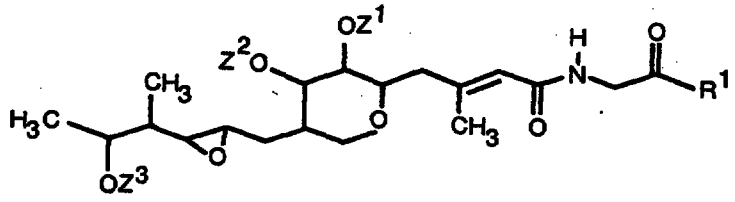


dans lequel R^1 est tel que défini dans la revendication 1.

4. Procédé de production d'un composé de formule (I) telle que définie dans la revendication 1, lequel composé comprend soit:

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a) la cyclisation d'un composé de formule (II):



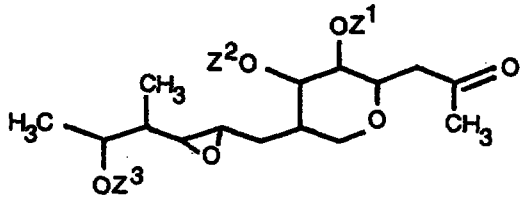
(II)

dans laquelle R^1 est tel que défini à propos de la formule (I); et

Z^1, Z^2 et Z^3 sont identiques ou différents et sont chacun et atome d'hydrogène ou un groupe hydroxy-protecteur,

pour former un composé de formule (I) dans laquelle R est un groupe oxazolyle substitué ou non-substitué, soit

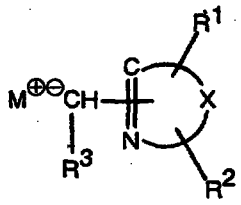
b) la réaction d'un composé de formule (III)



(III)

dans laquelle Z^1, Z^2, Z^3 sont identiques ou différents et sont chacun un atome d'hydrogène ou un groupe hydroxy-protecteur,

avec un composé de formule (IV)



(IV)

dans laquelle R^1 et R^2 sont tels que définis à propos de la formule (I), $M^{\oplus}$ est un cation métallique et R^3 est un groupe stabilisant l'anion qui va s'éliminer spontanément avec un groupe β-hydroxy pour produire une oléfine, et, si cela est nécessaire, l'élimination de quelconques groupes hydroxy-protecteurs, et si cela est désiré, la conversion d'un composé de formule (I) en un autre composé de formule (I).

5. Procédé suivant la revendication 4, dans lequel le composé de formule (II) est traité avec un agent chlorurant en présence d'une amine tertiaire ou avec un anhydride carboxylique ou un anhydride mixte.

6. Procédé suivant la revendication 5, dans lequel le composé de formule (II) est traité avec de la triphénylephosphine et du tétrachlorure de carbone en présence de triéthylamine et d'un solvant inerte.

7. Composition pharmaceutique ou vétérinaire comprenant un composé de formule (I), telle que définie dans la revendication 1 et un support ou excipient acceptable du point de vue pharmaceutique ou vétérinaire.

8. Composition suivant la revendication 7 sous forme de dose unitaire comprenant 50 à 500 mg d'un composé de formule (I).

9. Composé de formule (II) telle que définie dans la revendication 4.

10. Composé de formule (I) telle que définie dans la revendication 1, utile dans le traitement thérapeutique du corps humain ou animal.

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