METHOD OF PREPARATION OF PILOCARPINES AND INTERMEDIATES THEREOF

Synthesis of (+)-pilocarpine is achieved via homochiral monoprotected propane-1,3-diols prepared in > 98 % e.e. by enzyme catalyzed acylation of the corresponding diol, and lactones derived therefrom, or via acetylenic alcohols which upon imidazolisation and catalysed carbonylation are converted to lactones again leading to pilocarpine and analogues thereof.
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METHOD OF PREPARATION OF PILOCARPINES AND INTERMEDIATES THEREOF.

This invention relates to methods of synthesis of novel compounds, analogues of naturally occurring compounds, and uses of these compounds for pharmaceutical purposes.

According to one aspect of the invention, the problem of producing synthetic alkaloids, particularly plant alkaloids having an imidazole structure such as the pilocarpines or pilosinines, is addressed. The synthesis of pilocarpines has proved difficult and to date it has been necessary to rely on extraction of these alkaloids from the leaves of a number of South American shrubs belonging to the Rutaceae family. Unfortunately these plants defy successful cultivation outside their native habitat and this restriction of source of supply presents economic and other commercial difficulties. Furthermore, recently the plantations have been yielding less than optimum crops which has further limited supply of the natural pilocarpines. These difficulties have stimulated interest in devising a commercially feasible synthetic route to augment or replace the currently preferred Jaborandi leaves extraction process.

(+)-Pilocarpine is of general interest because it exhibits diverse physiological properties, but due to this lack of pharmacological selectivity it is not used extensively in medicine. However it remains the preferred treatment for glaucoma in view of its effective reduction of intraocular pressure for extended periods of time without apparent side effects.

Whereas (+)-pilocarpine is relatively stable to acidic media, in the presence of base and especially on heating it is readily converted to the thermodynamically more stable (+)-isopilocarpine. Unfortunately, only (+)-pilocarpine possesses the desired pharmacological activity. This presents a problem for both extraction and any synthesis strategy because mixtures of the two alkaloids containing between 50% and 66% isopilocarpine cannot be separated by the re-crystallisation of their salts.

Synthesis of both homochiral and racemic forms of pilocarpine has been studied since about 1933. Early
synthetic methods, (e.g. A.V. Chumachenko et al, J. Org. Chem., USSR, 1972, 8, 1112; J.I. DeGraw, Tetrahedron, 1972, 28, 967), commonly involved initial formation of the lactone ring from an achiral starting material and so require a resolution step, usually by means of the tartrate salt. Another method for the synthesis of (+)-pilocarpine, (H. Link and K. Bernauer, Helv. Chim. Acta., 1972, 55, 1053), constructed the lactone ring onto the imidazole ring but yield has not proved sufficient to attract commercial interest. A still further method, (R.S. Compagnone and H. Rapaport, J. Org. Chem., 1986, 51, 1713), starts from D-methionine, the more expensive enantiomer, to provide the correct stereochemistry at the C2 centre. However, this yielded (+)-isopilocarpine, requiring epimerisation via kinetic reprotaction using 2,6-di-t-butyl-4-methylphenol to obtain, at best, 75:25 (+)-pilocarpine:(+)-isopilocarpine. More recently attention has shifted from the difficulties of synthesis of (+)-pilocarpine to the relatively more straightforward preparation of aza-analogues from L-histidine but the pharmacological effects thereof have not been fully investigated.

Considering drug regulations which already apply to the natural extracted material, synthetic (+)-pilocarpine will only be an acceptable replacement if it can be economically synthesized in both homochiral and diastereomerically pure form.

An object of the present invention is to devise steps in such a synthesis and to provide at least one route whereby pure product is obtainable.

A further object of the invention is to obviate or mitigate previous difficulties in alkaloid synthesis by providing novel compounds useful as intermediates or starting materials and processes applicable to synthesis of a variety of alkaloid products.

Thus according to one aspect of the present invention
there is provided a compound of the formula I

![Chemical Structure](image)

wherein $R_1$ is a hydroxyl-protecting group, $R_2$ and $R_2'$, which may be the same or different, represent further more stable protective groups masking an aldehyde functional group, and are each lower alkyl (C$_1$-C$_4$) groups or together represent an alkylene bridge group to form a cyclic acetal having from 2 to 5 carbons in the ring, and $Y$ is an hydroxyl or oxo group. Such a compound e.g. where $R_1$ is an acyl group, preferably an acetyl group, is obtainable in greater than 98% optical yield by enzyme catalysed acylation preferably using the enzyme *Pseudomonas fluorescens* lipase.

No particular preference exists for the protective groups $R_2$ and $R_2'$, and both may be simply methyl groups.

Where $R_1$ is acyl, e.g. acetyl, and $Y$ is oxo, a very useful starting material for production of various lactones is obtained. Conveniently the lactones are formed from the appropriate $\beta$-acyloxy aldehyde by reaction with a suitable unsaturated, substituted or unsubstituted, Grignard reagent such as vinyl magnesium bromide for example, through conversion to the corresponding carbonate with subsequent palladium catalysed decarboxylation-carbonylation. Obviously, use of different Grignard reagents allows introduction of different substituents into the lactone ring. Careful selection of the substituents, which may themselves be unsaturated or contain hetero atoms, on the vinyl group will allow various pilocarpine analogues to be produced.
Useful compounds of the formula I, where $R_1$ is an acyl group are obtainable according to the invention by selective conversion of the diol of formula I'

\[
\begin{align*}
&\text{HO} \\
&\text{OR}_2 \\
&\text{HO} \\
&\text{OR}'_2
\end{align*}
\]

wherein $R_2$ and $R'_2$ are as above, to the (+)-(2R) monoester by enzyme catalysed acylation, preferably using *Pseudomonas fluorescens* lipase (PFL), and, optionally, further oxidising to produce the desired $\beta$-acyloxy aldehyde. Preferably, oxidation is carried out using one of the following reagents, pyridinium dichromate, tetrapropyl-ammonium persruthenate or the Dess-Martin periodinane reagent of the formula

\[
\begin{align*}
&\text{AcO} \\
&\text{I} \\
&\text{OAc}
\end{align*}
\]

which in particular provides a most acceptable ratio of $\beta$-acetoxy aldehyde to $\alpha,\beta$-unsaturated aldehyde.

Conversion of the diol resulting from reaction with the Grignard reagent to the corresponding carbonate may be simply achieved in the usual manner by methods known *per se*, for example by treatment with 1,1'-carbonyldiimidazole (CDI), preferably avoiding presence of excess of that reagent. Methods of such carbonate formation are published in the literature, e.g. T.W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1981, p. 85.; J.P. Kutney and A.H. Ratcliffe, *Synth. Commun.*, 1975, 5, 47.

Production of the corresponding lactone may be accomplished by reaction of the carbonate with carbon monoxide in the presence of a suitable catalyst, preferably a palladium (II) catalyst, such as a solution of palladium acetate and triphenylphosphine. This should be carried out
in a non-interfering solvent, such as an ether, preferably a cyclic ether, e.g. tetrahydrofuran (THF).

Further treatment of the lactone by hydrolysis of the acetal moiety and purification, e.g. by refluxing the lactone with acetone in the presence of catalytic amounts of p-toluenesulphonic acid or salts thereof, preferably pyridinium p-toluene-sulphonate, yields a novel aldehyde in which the lactone structure is preserved.

Thus there is provided according to this invention a synthetic method for producing lactones suitable as precursors for pilocarpine-type alkaloids characterised according to the following reaction scheme

15

\[ R_1 O \quad OR_2 \quad (i) \]

\[ \text{1) Oxid.} \quad \text{2) } R_3 MgX \]

\[ R_2' \quad OR_2 \quad (ii) \]

\[ \text{R}_3 \quad \text{OR}_2 \quad \text{OR}_2' \quad \text{OR}_2' \]

\[ \text{Pd}(Z)_2(\text{PPh}_3)_2 \]

\[ 1 \text{ atm. CO/20°C/THF} \quad (iii) \]

\[ \text{W} \quad \text{C=O} \]

wherein, \( R_1, R_2 \) and \( R_2' \) are as defined above, \( R_3 \) is a substituted or unsubstituted vinyl group, \( X \) is a halide, \( Z \) is a suitable ligand, e.g. acetate or a halide such as chloride, and \( W \) is a suitable leaving group, e.g. imidazole or a halide.

Thereby, according to a further aspect of the invention, there is provided a compound of the formula

\[ \text{(II)} \]

\[ \text{R}_3 \quad \text{C=O} \quad \text{H} \]

\[ \text{O} \quad \text{O} \]

wherein \( R_3 \) is a substituted or unsubstituted vinyl group.

The aldehyde of formula III is thus obtainable according to the invention using an unsubstituted vinyl Grignard reagent,
Utilisation of this key aldehyde provides a synthetic route for (+)-pilocarpine which is particularly characterised by conversion of the said aldehyde to the N-alkylimine using a primary amine such as dry methylvamine and treatment with \((p\text{-tolyl-sulphonyl})\)methyl isocyanide (tosMIC) at an elevated temperature in an inert solvent such as dimethoxyethane (DME), whereby the imidazole ring is constructed.

In a similar fashion analogous compounds and derivatives thereof may be obtained using suitably substituted vinyl Grignard reagents, wherein the substituent itself may be any non-reaction hindering unsubstituted, substituted, branched, or hetero atom-containing group.

Thus, it will be appreciated that the invention is generally applicable to production of compounds containing a lactone ring and an imidazole ring as a linked structure via a methylene group between the 5 position of the imidazole and the 3 position of the lactone.

Whilst not wishing to be bound by any theoretical considerations, by way of example, a typical reaction is considered to proceed substantially in accordance with the following reaction scheme:
Hydrogenation of the resulting (E, Z) imidazole lactones at normal temperatures followed by purification yielded a mixture which compared favourably with the natural alkaloids and separation was achievable through recrystallisation of the hydrochloride salts. Subsequent investigations suggested that deviations from typical hydrogenation temperatures and pressures, and changes in solvent had little effect on the hydrogenation and no obvious improvement was obtainable thereby in the ratio of (+)-pilocarpine:(+)-isopilocarpine.

Thus by virtue of the present invention there is provided a synthetic method whereby (+)-pilocarpine is obtainable, which method comprises the enzyme catalysed acylation of 2-(2,2-dimethoxyethyl)propane-1,3-diol to selectively provide the corresponding (2R) butyl monoester which, upon oxidation thereof to the β-acyloxy aldehyde and treatment with a vinyl Grignard reagent, is converted to the carbonate and subjected to palladium-catalysed decarboxylation-carbonylation whereby the lactone ring is constructed, with subsequent imidazolisation of the (2R,3R)-3-(2,2-dimethoxyethyl)-2-vinyl-γ-butylolactone after deprotection of the 3-formylmethylene aldehyde functional group, providing α-alkylidene lactones requiring hydrogenation to produce a mixture of (+)-pilocarpine and (+)-isopilocarpine.

According to another aspect of the invention, (+)-pilocarpine is obtainable by a method involving the use of a compound of formula I, where R₁ is again an acyl
protecting group, $Y$, $R_2$ and $R'_2$ are as defined above, and where $Y$ is the free hydroxyl, which compound is oxidised to produce the corresponding aldehyde, but instead of treating this further to produce a lactone via the carbonate, the aldehyde is treated according to the Corey-Fuchs procedure (Tetrahedron Letters, 1972, 13, 3769) to initially produce a dibromo-protected olefin, the acyl protecting group is removed and replaced by a base-stable protecting group $R_5$ e.g. the $t$-butyl-diphenylsilyl group, whereupon the protected olefin is converted to an acetylenic group by use of an alkyllithium reagent, e.g. $n$-butyllithium, preferably followed by reaction with an alkyl halide, e.g. $\text{CH}_3\text{I}$ to produce a compound of the formula V

![Chemical Structure](Image)

wherein $R_4$ is a lower alkyl group ($C_1$-$C_4$), the $R_2$ groups and $R_5$ are protective groups as defined above, which $R_2$ groups are removed to restore the aldehyde functionality which is readily converted to the imine as before using a primary amine, and thence to the $N$-alkylimidazole derivative using ($p$-tolylsulphonyl)methyl isocyanide in a suitable solvent such as an ether or ether/alcohol mixture, whereupon removal of the base stable protecting group from the protected hydroxyl allows palladium catalysed carbonylation of the imidazole alcohol in the form of an acid addition salt thereof which is convertible to the $\alpha$-alkylidene lactones via a palladium-catalysed carbonylation reaction similar to that discussed hereinbefore.

The invention will now be illustrated and described further by way of the examples presented hereinbelow.
Reference Example

2-(2,2-Dimethoxyethyl)propane-1,3-diol

This is obtainable, via diethyl-(2,2-dimethoxyethyl) malonate, according to a published method, (S. Bailey and M. R. Harnden, J. Chem. Soc. Perkin Trans. 1, 1988, 2767.) as follows. Diethylmalonate (16g, 0.1 moles) was added to a suspension of 60% dispersion of sodium hydride (4.5g = 2.7g NaH, 0.11 mmoles) in N,N-dimethylformamide (150ml) under nitrogen and the reaction mixture stirred for 1 h at 25°C. It was then cooled to 0°C during the dropwise addition of bromoacetaldehyde dimethyl acetal (20g, 0.12 moles) and then stirred at 100°C for 4 h. The reaction mixture was then poured into ice-water (500ml) and the aqueous layer was extracted with ethyl acetate (3 x 500 ml). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure to give an oil, which was distilled under high vacuum to afford the diester (16.05g, 64%) as a clear liquid: published data: ν_max (film) 1740, 1500, 1470, and 1440 cm⁻¹: δ_H(CDCl₃) 1.30 (6H,t,J7Hz,2 x CH₃CH₂), 2.21 (2H,q,J6Hz, CHCH₂CH), 3.35 (6H,s,2 x OCH₃).3.50 [1H,t,J6 Hz, CH(CO₂Et)₂], 4.25 (4H,q,J7 Hz,2 x CH₃CH₂), and 4.42 [1H,t,J6 Hz, CH(OMe)₂].

The target compound, otherwise named as 2-hydroxy-methyl-4,4-dimethoxybutan-1-ol, is then obtainable according to the published method as follows.

A solution of the diester obtained above (8.5g, 34.3 mmol) in ether (10ml) was added dropwise to a cooled (-10°C) suspension of lithium aluminium hydride (2.9g, 75.5 mmol) in ether (25ml), and the mixture was stirred at 20°C for 16 h. The reaction mixture was then diluted with ether (50ml), and water (7ml), and 10% aqueous sodium hydroxide (4ml) added slowly: stirring was then continued for a further 2 h. The solids were filtered off and the filtrate evaporated under reduced pressure. The residue obtained was dissolved in ethyl acetate and the solution dried (MgSO₄) and evaporated to afford the desired diol (3.4g, 61%) as a clear liquid: published data: ν_max (film) 3400, 1470, 1440, and 1 380 cm⁻¹: δ_H(CDCl₃) 1.72 [3 H,m,
CHCH₂CH(OMe)₂], 3.10 (2H, br s, D₂O exchangeable, 2 x OH), 3.34 (6H, s, 2 x OCH₃), 3.71 (4H, m, 2 x CH₂OH), and 4.49 [1 H, t, J 5.5 Hz, CH(OMe)₂]].

Repetition of such steps yielded material for the present purpose: ¹H n.m.r. data, δH 4.50 [1H, t, J 5.4 Hz, CH₂CH(OCH₃)₂], 3.72 [4H, m, CHCH₂OH], 3.36 [6H, s, CH₂CH(OCH₃)₂], 2.61 (2H, br s, OH), 1.89 (1H, m, CHCH₂OH), 1.70 [2H, dd, J 6.9 and 5.5 Hz, CH₂CH(OCH₃)₂].

**Example 1**

The PFL-catalysed acetylation of 2-((2,2-dimethoxyethyl)propane-1,3-diol to give (+)-(2R)-2-hydroxymethyl-4,4-dimethoxybutyl acetate.

To a solution of the diol obtained according to the Reference Example, (2.377g) in dichloromethane (10ml) was added vinyl acetate (1.73ml) and PFL (10mg) and the mixture gently stirred until an aliquot withdrawn from the reaction mixture showed the monoacetate, none of the diol and only a trace of the diacetate. Filtration of the reaction mixture to remove the enzyme, followed by removal of solvent in vacuo, afforded the monoacetate as an oil (3.522g, 98% yield), [α]D + 13.6 (c 1.0 CHCl₃).

(Found: C, 52.6; H, 9.0. C₉H₁₈O₅ requires C, 52.4; H, 8.8%);

Vmax. 1730 (C=O) cm⁻¹; δH 4.50 [1H, t, J 5.5 Hz, CH₂CH(OCH₃)₂], 4.15, 4.08 [2H ABX system, Jₐ₈ 11.2 Hz, Jₐₓ 5.2 Hz, Jₐₓ 6.6 Hz, CHCH₂OAc], 3.58 (2H, t, J 5.7 Hz, CHCH₂OH), 3.35, 3.34 [2 3H, s, CH₂CH(OCH₃)₂], 2.47 (1H, t, J 6.3 Hz, OH), 2.07 (6H, s, CH₃C=O), 2.01 (1H, m, CHCH₂OH), 1.68 [2H, t, J 5.7 Hz, CH₂CH(OCH₃)₂]; δC 171.7 (C=O), 103.1 [CH₂CH(OCH₃)₂], 64.6 (CH₂OAc), 62.3 (CHCH₂OH), 53.1, 52.6 [CH₂CH(OCH₃)₂], 36.6(CHCH₂OH), 31.0 [CH₂CH(OCH₃)₂], 20.6 (CH₃C=O); m/z=224 (M⁺+NH₄⁺).

In the presence of 0.77 equivalents of Eu(hfc)₃ the ¹H n.m.r. spectrum of the monoacetate showed only a single acetyl signal at δ2.93, e.e. greater than 98%. After four months storage at room temperature the enantiomeric excess of the sample had dropped to 92%.

(hfc = 3-(heptafluoropropylhydroxymethylene)-(+)—camphorato)
Example 2

(2S)-2-Formyl-4,4-dimethoxybutyl acetate

To a suspension of the Dess-Martin periodinane reagent

(2.68g) in dichloromethane (25ml) was added pyridine (1.02g) with stirring at 0°C. A solution of the monoacetate, as obtained in Example 1, (1.00g) in dichloromethane (20ml) was then added dropwise at 0°C, the mixture allowed to warm to room temperature and stirred for one hour. Diethyl ether (50ml) was added to the reaction mixture followed by a solution of sodium thiosulphate (11g) in saturated sodium bicarbonate solution (40ml). This mixture was stirred for a further five minutes. The ether layer was separated and the aqueous layer extracted with a further 40ml of ether, pyridine was removed to trace levels from the combined ether layers by standard procedures.

The organic layer was dried (Na₂SO₄) and solvent removed to give the crude product as an oil (0.95g, 96%) δH 9.68 (1H, d, J 1.6 Hz, CHCHO), 4.46 [1H, t, J 5.5 Hz, CH₂CH(OCH₃)₂], 4.33 [2H, d, J 5.7 Hz, CHCH₂OAc], 3.34, 3.33 [2 3H, s, CH₂CH(OCH₃)₂], 2.79 (1H, m, CHCH₂OAc), 2.06, 1.78 [2 1H, m, CH₂CH(OCH₃)₂], 2.05 (3H, s, CH₃=0).

Example 3

(28,3R)-2-(2,2-Dimethoxyethyl)pent-4-en-1,3-diol and (28,3S)-2-(2,2-Dimethoxyethyl)pent-4-en-1,3-diol.

A solution of vinyl magnesium bromide (1 M in THF) was added dropwise via syringe at 0°C to a solution of the crude aldehyde, as obtained in Example 2, (0.95g) in THF (20ml), the solution was then allowed to warm to room temperature. After stirring for five minutes at room temperature the reaction was quenched by the addition of saturated NH₄Cl solution. The organic layer was separated and the aqueous
layer extracted with dichloromethane, the combined extracts were dried (Na₂SO₄) and the solvent removed in vacuo to afford the target diol (a yellow oil, 0.7g) as a 50:50 mixture of diastereoisomers. (Found: C, 56.5; H, 9.8 C₉H₁₈O₄ requires C, 56.8; H, 9.5%); [α]D²₀ -5.7 (c 1.0 CHCl₃);

δH 5.97-5.84 [1H and 1H', m, CH(OH)CH=CH₂], 5.37-5.20 [2H and 2H', m, CH(OH)CH=CH₂], 4.55-4.49 [1H and 1H', m, CH(OCH₃)₂], 4.37 [1H', m, CH(OH)CH=CH₂], 4.22 [1H, m, CH(OH)CH=CH₂], 3.90-3.62 (2H and 2H', m, CH₂OH), 3.37, 3.36, 3.35, 3.34 [2 3H and 2 3H', s, CH(OCH₃)₂], 2.78-2.66 (2H and 2H', m, OH and OH'), 1.91-1.69 [3H and 3H', m, CHCH₂CH(OCH₃)₂]; δC 139.5, 138.7 [CH(OH)CH=CH₂], 115.9, 115.7 [CH(OH)CH=CH₂], 103.5 [CH(OCH₃)₂], 75.6, 75.1 [CH(OH)CH=CH₂], 64.3, 63.1 (CH₂OH), 53.4, 53.3, 52.6, 52.4 [CH(OCH₃)₂], 40.8 (CHCH₂OH), 30.9, 28.8 [CH₂CH(OCH₃)₂]; m/z = 144 (M⁺-46).

Example 4

(4R,5S)-5-(2,2-Dimethoxyethyl)-4-vinyl-1,3-dioxan-2-one and (4S,5S)-5-(2,2-Dimethoxyethyl)-4-vinyl-1,3-dioxan-2-one.

A solution of 1,1'-carbonyldiimidazole (1.02g) in dichloromethane (30ml) was added dropwise over three hours to a solution of the diol, as obtained in Example 3, (1.00g) in dichloromethane (30ml). Stirring was continued until analysis of an aliquot showed an acceptable level of unreacted starting material, then water (20ml) was added and the organic layer removed. The aqueous layer was extracted with dichloromethane, the combined organic extracts dried (Na₂SO₄) and solvent removed in vacuo to afford the carbonate as a 50:50 mixture of diastereoisomers (1.137g, 90%) (Found: C, 55.4; H, 7.8. C₁₀H₁₆O₅ requires C, 55.55; H, 7.5%); [α]D²₀ -2.2 (c 1.0 CHCl₃); vₚₚₚₚₚₚₚₚₚₚₚₚₚₚₚₚₚₚₚ₁₇₃₅ (C=O) cm⁻¹;

δH 5.88-5.76 [1H and 1H', m, CH(OCO₂)CH=CH₂], 5.50-5.41 [2H and 2H', m, CH(OCO₂)CH=CH₂], 4.63 [1H,m, CH(OOCO₂)CH=CH₂], 4.55-4.09 [3H and 3H', m, CH₂OCO₂ and CH(OCH₃)₂], 3.35, 3.35, 3.34, 3.33 [2 3H and 2 3H', s, CH(OCH₃)₂], 2.47 [1H', m, CHCH₂CH(OCH₃)₂], 2.16 [1H,m, CHCH₂CH(OCH₃)₂], 1.85-1.54 [2H and 2H', m, CHCH₂CH(OCH₃)₂]; δC 148.5, 148.4 (C=O), 133.5, 131.1 [CH(OOCO₂)CH=CH₂], 120.7, 119.9 [(OCO₂)CH=CH₂], 102.9,
102.5 [CH(OCH₃)₂], 83.8, 80.9 [CH(OCO₂)CH=CH₂], 70.2, 69.7 (CH₂CO₂), 53.9, 53.7, 52.4, 52.1 [CH(OCH₃)₂], 31.9, 30.6 (CHCH₂CO₂), 30.5, 28.2 [CH₂CH(OCH₃)₂]; m/z = 234 (M⁺+NH₄⁺).

**Example 5**

(2R,3R)-3-(2,2-Dimethoxyethyl)-2-vinyl-γ-butyrolactone

A solution of the carbonate produced according to Example 4 (1.5g) in THF (15ml) was added to a previously prepared solution of palladium (II) acetate (46mg) and triphenylphosphine (109mg) in THF (20ml) under a nitrogen atmosphere. A balloon filled with carbon monoxide was added to the sealed flask and the solution stirred at room temperature until t.l.c. analysis showed no remaining starting material and the solvent was removed in vacuo, to afford the title compound as an oil and as a single diastereoisomer in which the two substituents have a trans relationship (1.28g, 92%) (Found: C, 60.1; H, 8.4 C₁₀H₁₆O₄ requires C, 60.0; H, 8.05%); [α]D²⁰ +24.3 (c 1.0 CHCl₃); νmax 1760 (C=O) cm⁻¹; δH 5.83-5.72 (1H, ddd, J 17.2 and 10.3 and 7.7 Hz, CHCH=CH₂), 5.36 (1H, d, J 10.3 Hz, CHCH=CH₂), 5.30 (1H, d, J 17.2 Hz, CHCH=CH₂), 4.50 (1H, ddd, J 9.3 and 7.6 Hz, CHCH₂O), 4.40 [1H, ddd, J 6.0 and 4.4 Hz, CH(OCH₃)₂], 3.91 (1H, dd, J 9.6 and 9.5 Hz, CHCH₂O), 3.35, 3.33 [2 3H, s, CH(OCH₃)₂], 2.86 (1H, m, CHCH=CH₂), 2.55 (1H, m, CHCH₂O), 1.96 [1H, ddd, J 14.1 and 4.4 and 4.4 Hz, CHCH₂CH(OCH₃)₂], 1.70 [1H, ddd, J 14.1 and 9.7 and 6.0 Hz, CHCH₂CH(OCH₃)₂]; δC 176.7 (C=O), 132.0 (CHCH=CH₂), 120.4 (CHCH₂CH₂), 103.1 [CH(OCH₃)₂], 72.1 (CH₂O), 53.9, 53.0 [2 CH(OCH₃)₂], 49.9 (CHCH=CH₂), 38.1 (CHCH₂O), 34.5 [CH₂CH(OCH₃)₂]; m/z = 218 (M⁺+NH₄⁺).

**Example 6**

(2R,3R)-3-(2-Formylmethyl)-2-vinyl-γ-butyrolactone

A solution of the lactone obtained in Example 5 (0.50g) in acetone (30ml) containing a catalytic quantity of pyridinium p-toluenesulphonate was refluxed until an aliquot withdrawn from the reaction mixture and examined by ¹H n.m.r. spectroscopy after removal of solvent showed the
absence of any acetal. Removal of the solvent in vacuo afforded the desired aldehyde as a colourless oil (0.358g, 93%), $\nu_{max}$ 1765 (C=O) 1715 (C=O) cm$^{-1}$; $\delta_H$ 9.85 (1H, s, \text{CH}_2\text{CHO}), 5.83-5.71 (1H, m, \text{CHCH}=\text{CH}_2), 5.36 (1H, d, $J$ 10.3 Hz, \text{CHCH}=\text{CH}_2), 5.28 (1H, d, $J$ 17.1 Hz, \text{CHCH}=\text{CH}_2), 4.66 (1H, dd, $J$ 9.2 and 6.9 Hz, \text{CHCH}_2\text{O}), 3.85 (1H, dd, $J$ 9.1 and 8.9 Hz, \text{CHCH}_2\text{O}), 2.96-2.55 (4H, m, \text{CHCH}=\text{CH}_2 \text{ and CHCH}_2\text{O and CH}_2\text{CHO}); $\delta_C$ 199.7 (CHO), 176.2 (C=O), 131.3 (CHCH=CH_2), 120.7 (CHCH=CH_2), 71.0 (CH_2O), 49.0 (CHCH=CH_2), 45.1 (CH_2CHO), 35.8 (CHCH_2O); m/z = 172 (M$^+$+NH$_4$).

**Example 7**

(Z)-(3R)-2-Ethylidene-3-(1-methyl-5-imidazolyl)methyl-$\gamma$-butyro lactone and (E)-(3R)-2-ethy lidene-3-(1-methyl-5-imidazolyl)methyl-$\gamma$ -butyrolactone.

Methylamine gas was bubbled into a solution of the aldehyde obtained according to Example 6 (0.200g) in dimethoxyethane (DME) (20ml) at 0°C in the presence of molecular sieves for two minutes, the reaction mixture was then allowed to stir overnight at room temperature. TosMIC (0.380g) was added and the solution warmed slowly to 80°C and held at that temperature for about 24 hours. The solution was decanted from the molecular sieves and evaporated in vacuo. Saturated NaHCO$_3$ solution (5ml) was added and extracted with chloroform (4x20ml), the combined extracts were dried and the solvent removed to afford the desired imidazole lactones respectively in a ratio of 83:17 as a brown viscous oil (0.186g, 70%).

**Example 8**

General procedure for the heterogeneous catalytic hydrogenation of (Z)-(3R)-2-ethylidene-3-(1-methyl-5-imidazolyl)methyl-$\gamma$-butyrolactone and (E)-(3R)-2-ethylidene-3-(1-methyl-5-imidazolyl)methyl-$\gamma$-butyrolactone to (±)-pilocarpine and (±)-isopilocarpine.

The hydrogenation of the 83:17 mixture of $\alpha$-alkylidene lactones obtained according to Example 7 (150mg) was carried out in methanol (5ml) in the presence of platinum oxide
(10mg) under three atmospheres of hydrogen. After 24 hours the reaction mixture was filtered through Celite (Trade Mark of Johns-Mansville Products Corp) and the solvent removed in vacuo. The $^1$H n.m.r. spectrum of the product (obtained in near quantitative yield) showed it to be a 72:28 mixture of pilocarpine and isopilocarpine by comparison of the spectrum with that of a 72:28 mixture of the authentic alkaloids. The specific rotation of the synthetic mixture was $\alpha_D^{20} +89.7$ (c 1.0 CHCl$_3$) comparing well to that of the mixture of natural alkaloids, $\alpha_D^{20} +85.2$ (c 1.0 CHCl$_3$), confirming the (3R) absolute configuration in the synthetic material.

Example 9

(+)-Pilocarpine.

The mixture of alkaloids resulting from the procedure of Example 8 (450mg) was dissolved in ethanol (1ml) and the solution cooled to 0°C. A solution of 12 N HCl (0.177ml, one equivalent) in ethanol (0.5ml) was then added dropwise and the mixture refrigerated overnight. The crystals of pilocarpine hydrochloride so produced were removed by filtration and twice recrystallised from ethanol to yield pure (+)-pilocarpine hydrochloride (88mg, 23%), m.p. 201-202°C alone or when mixed with authentic material (H. A. D. Jowett, J. Chem. Soc., 1900, 77, 473), m.p. 204-205°C. The specific rotation of the synthetic material was $\alpha_D^{20} +90.1$ (c 2.0 H$_2$O), (United States Pharmacopoeia XXII, 22nd Ed., United States Pharmacopoeical Convention Inc., 1982, p 1082) $[\alpha]_D$ between +88.5 and +91.5 (c 2.0 H$_2$O)] confirming both its identity and purity.

The usual therapeutic uses are envisaged for the material obtainable by the methods of this invention, either as purified, or as converted to the corresponding physiologically-absorbable acids, esters or salts thereof with pharmaceutically acceptable acids, which may of course be formulated in the usual way for topical administration, especially for ophthalmic preparations.
Example 10

(2R)-4,4-Dibromo-2-(2,2-dimethoxyethyl)but-3-enyl acetate.

Zinc dust (0.32g) was added to a solution of carbon tetrabromide (1.634g) and triphenylphosphine (1.284g) in dichloromethane (50ml) and the mixture stirred at 25°C under a nitrogen atmosphere for 24 hours (observe formation of a pink/brown precipitate during this time). To this solution, a solution of the crude aldehyde (cf Example 2) prepared from the oxidation of the alcohol obtained in Example 1 (0.505g) in dichloromethane (15ml) was added resulting in the disappearance of the precipitate. The red/brown solution was stirred at room temperature for 12 hours. Work-up and purification gave the title compound as an oil (0.706g, 80%) (Found: C, 33.45; H, 4.5. C_{10}H_{16}O_{4}Br_{2} requires C, 33.4; H, 4.5%; [α]_{D}^{20} -19.0 (c 1.0 CHCl_{3}); ν_{max}: 1730 (C=O) cm^{-1}; δ_{H} 6.28 (1H, d, J 9.8Hz, CH=CBr_{2}), 4.38 [1H, dd, J 7.0 and 4.6Hz, CH_{2}CH(OCH_{3})_{2}], 4.03 [2H, d, J 6.0Hz, CHCH_{2}OAc], 3.36, 3.34 [2 3H, s, CH_{2}CH(OCH_{3})_{2}], 2.91 (1H, m, CHCH_{2}OAc), 2.08 (3H, s, CH_{3}C=O), 1.82, 1.62 [2 1H, m, CH_{2}CH(OCH_{3})_{2}]; δ_{C} 171.0 (C=O), 138.5 (CH=CBr_{2}), 102.5 [CH(OCH_{3})_{2}], 90.8 (CH=CBr_{2}), 65.2 (CH_{2}OAc), 53.4, 52.7 [2 CH(OCH_{3})_{2}], 39.5 (CHCH_{2}OAc), 33.5 [CH_{2}CH(OCH_{3})_{2}], 20.7 (CH_{3}C=O); m/z=378 (M^{+}+NH_{4}).

Example 11

(2R)-4,4-Dibromo-2-(2,2-dimethoxyethyl)-but-3-en-1-ol.

A solution of the acetate obtained in Example 10 (0.50g) in methanol (5ml) containing potassium carbonate (30mg) was stirred at room temperature for one hour. The solution was then filtered, the solvent removed in vacuo and the residue purified to give the title compound as a colourless oil (0.433g, 98%) (Found: C, 30.5; H, 4.4. C_{8}H_{14}O_{3}Br_{2} requires C, 30.2; H, 4.4%); [α]_{D}^{20} -25.8 (c 1.0 CHCl_{3}); δ_{H} 6.36 (1H, d, J 9.7Hz, CH=CBr_{2}), 4.42[1H, dd, J 6.7 and 4.3Hz, CH_{2}CH(OCH_{3})_{2}] 3.62, 3.60 [2H, ABX system, J_{AB} 5.7Hz, J_{AX} 2.5Hz, J_{BX} 3.0Hz, CHCH_{2}OH], 3.38, 3.35 [2 3H, s, CH_{2}CH(OCH_{3})_{2}], 2.75 (1H, m,
CH\textsubscript{2}CH\textsubscript{2}OH), 2.04 (H, t, J 6.2Hz, OH), 1.87, 1.69 [2 1H, m, CH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], δ\textsubscript{C} 139.4 (CH=CBr\textsubscript{2}), 102.9 [CH(OCH\textsubscript{3})\textsubscript{2}], 90.0 (CH=CBR\textsubscript{2}), 64.1 (CH\textsubscript{2}OH), 53.6, 52.6 [2 CH(OCH\textsubscript{3})\textsubscript{2}], 42.6 (CH\textsubscript{2}CH\textsubscript{2}OH), 33.3 [CH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}]; m/z=336 (M\textsuperscript{+}+NH\textsubscript{4}).

**Example 12**

(2R)-O-(tert-Butyldiphenylsilyl)-4,4-dibromo-2-(2,2-dimethoxyethyl)but-3-en-1-ol.

Tert-Butyldiphenylsilyl chloride (TBDPS) (0.39ml), was added via syringe to a solution of the alcohol of Example 11 triethylamine (0.23ml) and 4-dimethylaminopyridine (10mg) in dichloromethane (20ml) and the solution stirred overnight. Water (10ml) was added and the organic layer removed, the aqueous layer was then extracted with dichloromethane and the combined extracts dried (Na\textsubscript{2}SO\textsubscript{4}). After removal of solvent the residue was purified to afford the TBDPS ether as a colourless oil (0.616g, 88%), [α]\textsubscript{D}\textsuperscript{20} -12.0 (c 1.0 CHCl\textsubscript{3}); δ\textsubscript{H} 7.68-7.64 (4H, m, Ph), 7.45-7.37 (6H, m, Ph), 6.32 (1H, d, J 9.7Hz, CH=CBR\textsubscript{2}), 4.35 [1H, dd, J 7.2 and 4.5Hz, CH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], 3.63, 3.57 [2H, ABX system, J\textsubscript{AB} 10.0Hz, J\textsubscript{AX} 5.4Hz, J\textsubscript{BX} 5.6Hz, CHCH\textsubscript{2}OSi], 3.33, 3.31 [2 3H, s, CH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], 2.76 (1H, m, CHCH\textsubscript{2}OSi), 1.91 [1H, ddd, J 13.9 and 7.2 and 4.8Hz, CHCH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], 1.63 [1H, ddd, J 13.9 and 9.4 and 4.5Hz, CHCH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], 1.07 [9H, s, SiC(CH\textsubscript{3})\textsubscript{3}]; δ\textsubscript{C} 140.1, 135.7 [C\textsubscript{6}H\textsubscript{5}(CH) and CH=CBR\textsubscript{2}], 133.4 (C\textsubscript{6}H\textsubscript{5}, Cipso), 129.9, 127.8 [C\textsubscript{6}H\textsubscript{5}(CH)], 102.8 [CH(OCH\textsubscript{3})\textsubscript{2}], 89.6 (CH=CBR\textsubscript{2}), 65.3 (CH\textsubscript{2}OSi), 53.0, 52.6 [CH(OCH\textsubscript{3})\textsubscript{2}], 42.6 (CHCH\textsubscript{2}OSi), 33.3 [CH\textsubscript{2}CH(OCH\textsubscript{3})\textsubscript{2}], 26.7 [SiC(CH\textsubscript{3})\textsubscript{3}], 19.1 [SiC(CH\textsubscript{3})\textsubscript{3}]; m/z=525 (M\textsuperscript{+}-31).

**Example 13**

(2R)-O-(tert-Butyldiphenylsilyl)-2-(2,2-dimethoxyethyl)pent-3-yn-1-ol.

n-Butyllithium (0.5ml, 2.5 M in hexanes) was added dropwise via syringe to a solution of the TBDPS ether obtained according to Example 12 (0.348g) in THF (10ml) at -78°C under a nitrogen atmosphere and the solution stirred for one hour. The reaction mixture was allowed to warm to
room temperature and stirring continued for another hour, methyl iodide (0.2ml, excess) was then added and the solution stirred for a further 15 minutes. Removal of solvent afforded the title compound as a colourless oil (0.238g, 92%) (Found: C, 73.05; H, 8.6. C_{25}H_{34}O_{3}Si requires C, 73.1; H, 8.35%).

\[
\begin{align*}
[a]_D & = -10.1 \text{ (c 1.0 CHCl}_3) ; \delta_H 7.71-7.67 \text{ (4H, m, Ph), 7.46-7.36 (6H, m, Ph), 4.69 [1H dd, J 8.4 and 3.6Hz, CH}_2\text{CH(OCH}_3)_2] , 3.73, 3.58 \text{ [2H, ABX system, } J_{AB} 9.6Hz, J_{AX} 5.3Hz, J_{BX} 7.8Hz, \text{ CHCH}_2\text{OSi}], 3.36, 3.35 \text{ [2 3H, s, CH}_2\text{CH(OCH}_3)_2] , 2.65 \text{ (1H, m, CHCH}_2\text{OSi), 2.10 [1H, m, CH}_2\text{CH(OCH}_3)_2] , 1.77 \text{ (3H, d, J 2.3Hz, C}=\text{C-CH}_3), 1.62 \text{ [1H, m, CHCH}_2\text{CH(OCH}_3)_2] , 1.07 \text{ [9H, s, SiC(CH}_3)_3] ; \delta_C 135.7 \text{ [C}_6\text{H}_5 \text{(CH)}], 133.7 \text{ [C}_6\text{H}_5 \text{, Cipso)], 129.7, 127.7 \text{ [C}_6\text{H}_5 \text{(CH)}], 103.0 \text{ [CH(OCH}_3)_2] , 79.0, 77.8 \text{ [C}=\text{C}], 66.6 \text{ (CH}_2\text{OSi), 53.0, 52.1 \text{ [CH(OCH}_3)_2] , 34.3 \text{ [CH}_2\text{CH(OCH}_3)_2] , 30.7 \text{ (CHCH}_2\text{OSi), 26.6 [SiC(CH}_3)_3], 19.1 [SiC(CH}_3)_3], 3.3 \text{ (C}=\text{C-CH}_3); m/z=379 (M^+ -31).
\end{align*}
\]

Example 14

(3R)-3-[(tert-Butyldiphenylsilyloxy)methyl]-hex-4-ynal.

A solution of the acetal prepared according to Example 13 (1.787g) in acetone (100ml) containing a catalytic quantity of p-toluenesulphonic acid (10mg) was refluxed until an analysis of an aliquot by H\textsuperscript{1} n.m.r. showed an absence of acetal. Triethylamine (0.1 ml) was added and solvent removed in vacuo. The residue was purified to give the target aldehyde which was used directly in the next step (1.539g, 97%), \delta_H 9.84 (1H, t, J 2.1 Hz, CH\textsubscript{2}CHO), 7.68-7.64 (4H, m, Ph), 7.47-7.37 (6H, m, Ph), 3.78, 3.59 (2H, ABX system, J\textsubscript{AB} 9.8Hz, J\textsubscript{AX} 4.9Hz, J\textsubscript{BX} 8.2Hz, CH\textsubscript{2}CH\textsubscript{2}OSi), 3.06 (1H, m, CH\textsubscript{CH}2OSi), 2.77 (1H, ddd, J 16.5 and 5.6 and 2.0Hz, CH\textsubscript{2}CHO), 2.56 (1H, ddd, J 16.5 and 8.0 and 2.2Hz, CH\textsubscript{2}CHO), 1.75 (3H, d, J 2.3Hz, C=CH\textsubscript{3}, 1.06 [9H, s, SiC(CH\textsubscript{3})\textsubscript{3}].
Example 15

(2R)-O-(tert-Butyldiphenylsilyl)-2-(1-methyl-5-imidazolyl)methyl-pent-3-yn-1-ol.

Dry methylamine gas was bubbled into a solution of the aldehyde obtained in Example 14 (0.100g) in DME (10ml) for two minutes at 0°C in the presence of molecular sieves, the reaction mixture was then allowed to stir for 30 minutes at room temperature. TosMIC (0.107g) in methanol (10ml) was added and the solution warmed slowly to 80°C and held at that temperature for 12 hours. The solution was decanted from the molecular sieves (which were washed with further DME) and evaporated in vacuo. Saturated NaHCO₃ solution (5ml) was added and extracted with chloroform, the combined extracts were dried and the solvent removed to afford a brown oil which was purified to provide the desired ether (0.09g, 79%) (Found: C, 74.9; H, 8.1; N, 6.4.

C₂₆H₃₂N₂O₂Si requires C, 74.95; H, 7.7; N, 6.7%; [α]D₂ -14.2 (c 1.0 CHCl₃); δH 7.70-7.65 (4H, m, Ph), 7.47-7.36 (7H, m, Ph and 4-H), 6.91 (1H, s, 2-H), 3.79, 3.64 (2H, ABX system, Jₐ₈ 9.9Hz, Jₐₓ 4.5Hz, Jₓₓ 7.9Hz, CH₂OSi), 3.58 (3H, s, NCH₃), 3.02 (1H, m, CH₂het.), 2.70 (2H, m, CH₂het. and CH₂OSi), 1.73 (3H, d, J 2.1Hz, C=CH₃), 1.10 [9H, s, Si(CH₃)₃]; δC 137.5, 135.7, 135.6 [C₆H₅ (CH) or 2-CH], 133.4 (C₆H₅, Cipso), 129.8 [C₆H₅ (CH) or 4-CH], 129.5 (5-C), 127.8 [C₆H₅ (CH) or 4-CH], 78.6, 76.4 (C=C), 65.5 (CH₂OSi), 34.7 (CH₂OSi), 31.3 (NCH₃), 26.6 [SiC(CH₃)₃], 25.3 (CH₂het.), 19.1 [SiC(CH₃)₃], 3.2 (C=C-CH₃); m/z=360 (M⁺-57).

Example 16

(-)-(2R)-2-(1-Methyl-5-imidazolyl)methyl-pent-3-yn-1-ol.

The TBDPS ether obtained in Example 15 (0.50g) was dissolved in a 5% solution of 40% HF in acetonitrile (40ml) and left for 48 hours at room temperature after which time t.l.c. analysis indicated that no starting material remained. An excess of powdered potassium carbonate was added and the solution well stirred until the pH of the solution was greater than eight. The solid was removed by
filtration and washed with further acetonitrile. Removal of solvent and purification then afforded the pure target alcohol as a pale yellow oil (0.214g, 92%), $[\alpha]_D^{20} = -25.9$ (c 1.0 CHCl₃); (Found: C, 67.3; H, 8.0; N, 15.9. C₁₀H₁₄N₂O requires C, 67.4; H, 7.9; N, 15.7%) $\delta_H$ 7.35 (1H, s, 2-H), 6.86 (1H, s, 4-H), 3.61 (2H, d, J 5.3 Hz, CH₂OH), 3.59 (3H, s, NCH₃), 3.17 (1H, br s, OH), 2.78 (3H, m, CH₂het. and CH₂OH), 1.78 (3H, d, J 2.1 Hz, C=CH₃); $\delta_C$ 137.3 (2-CH), 129.8 (5-C), 127.2 (4-CH), 78.8, 77.2 (2 C=C), 64.0 (CH₂OH), 34.9 (CH₂CH₂OH), 31.2 (NCH₃), 25.3 (CH₂het.), 3.2 (C≡C-CH₃); m/z = 179 (M⁺+1)

**Example 17**

**Palladium-catalysed carbonylation of (-)-(2R)-2-(1-methyl-5-imidazolyl)-methyl-pent-3-yn-1-ol.**

A solution of the alcohol obtained in Example 16 (0.20g) in methanol (3ml) was treated with HCl gas until the pH of the solution was acidic. Removal of the solvent then gave the hydrochloride salt of the imidazole alcohol as a yellow viscous oil.

A solution of palladium (II) chloride (13.9mg), anhydrous tin (II) chloride (14.7mg), triphenylphosphine (41.1mg) and the hydrochloride salt prepared above (0.24g) was carbonylated in DMF (10ml) under an atmosphere of carbon monoxide at 110°C. After five hours a palladium mirror had been deposited upon the walls of the flask and the solution was allowed to cool. The crude reaction mixture obtained after removal of solvent was dissolved in saturated sodium bicarbonate solution (5ml) and extracted with dichloromethane, the combined organic extracts were dried (Na₂SO₄) and solvent removed in vacuo. Purification of the residue afforded a small amount (30mg) of the α alkylidene lactones (equivalents of those obtained in Example 7) in a 12:88 ratio.

**Example 18**

(+)-Pilocarpine [(+)-1].

The mixture of lactones (100mg) obtained by methods according to Example 17 in repeated runs of the reaction was dissolved in methanol (5ml) and hydrogenated over Adam's
catalyst at three atmospheres of hydrogen for 24 hours. After filtration of the reaction mixture through Celite (TM) and removal of solvent, purified product, a 72:28 mixture of pilocarpine and isopilocarpine, $\left[\alpha\right]_D^{20} +83.0$ (c 1.0 CHCl$_3$) according to the $^1$H n.m.r. comparison proved to be identical to a 72:28 reference mixture of authentic alkaloids $\left[\alpha\right]_D^{20} +85.2$ (c 1.0 CHCl$_3$).

**Example 19**
Example 1 was repeated using toluene (10 ml) as the solvent. The required monoacetate was obtained in high yield (>90%).

**Example 20**
Example 1 was repeated again but this time using diethyl ether (10 ml) as the solvent. The required monoacetate was once more obtained in high yield (>90%).

**Example 21**
The procedure of Example 1 was repeated using petroleum ether 60/80 (10 ml) as the solvent. The required monoacetate was again obtained in high yield (>90%).

**Example 22**
Following the procedure of Example 1 again 2-(2,2-diethoxyethyl)propane-1,3-diol (2.78 g) was used instead of 2-(2,2-dimethoxyethyl)propane-1,3-diol. The corresponding monoacetate was formed in high yield (>90%).

$\left[\alpha\right]_D^{20} +39.6^\circ$, (CHCl$_3$).

**Example 23**
Example 1 was repeated but this time using ethylene glycol as the aldehyde protecting group. From 2.34 g of

![Chemical structure](image)

(2-(2-hydroxymethyl,-3-hydroxypropyl)-1,3-dioxolane), the corresponding monoacetate was produced in high yield (>90%)

$\left[\alpha\right]_D^{20} +3.2^\circ$, (CHCl$_3$).
Example 24

Example 4 was repeated but instead of using carbonyldiimidazole, a combination of phosgene and triethylamine was used to form the required carbonate (44% yield).

Example 25

Substituting 1,2-dimethoxyethane (20 ml) for THF in the procedure of Example 5 resulted in the required lactone being produced in moderate yield (>40%).

Example 26

Repeating Example 5 again using dichloroethane (20 ml), as the solvent instead of THF gave the required lactone again in moderate yield (>40%).

Example 27

Following Example 5 once more, but using acetone (20 ml), as the solvent instead of THF gave the required lactone again in moderate yield (>40%).
Claims

1. A compound of the formula I

\[
\begin{align*}
R_1O & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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5. (+)-(2R) AcO

6. A process for producing a compound of the formula II

wherein \( R_3 \) is a substituted or unsubstituted vinyl group, comprising oxidation of a compound of the formula

wherein \( R_1, R_2 \) and \( R_2' \) are as defined in claim 1, and reaction thereof with a Grignard reagent \( R_3\text{MgX} \), wherein \( X \) is a halide, followed by methods known per se to obtain the carbonate of the formula
reacting said carbonate with carbon monoxide in the presence of a suitable catalyst in a non-interfering solvent to form a lactone, and subjecting the acetal moiety to hydrolysis, e.g. by reflux with acetone in the presence of catalytic amounts of p-toluenesulphonic acid or salts thereof.

7. A process according to claim 6 wherein the catalyst for lactone formation is a palladium (II) catalyst.

8. A process according to claim 6 wherein the catalyst for lactone formation comprises a solution of palladium acetate and triphenyl-phosphine.

9. A process according to any one of claims 6 to 8 wherein oxidation is carried out using one of, pyridinium dichromate, tetrapropylammonium perruthenate or the Dess-Martin periodinane reagent of the formula

10. A process according to any one of claims 6 to 9 wherein the oxidation is carried out using the Dess-Martin periodinane reagent of the formula
11. A compound of the formula (II)

\[
\begin{align*}
  &\text{R}_3' \\
  &\text{O} \\
  &\text{C} \\
  &\text{H} \\
\end{align*}
\]

(II)

wherein \( \text{R}_3 \) is a substituted or unsubstituted vinyl group.

12. A compound of the formula (III)

\[
\begin{align*}
  &\text{O} \\
  &\text{C} \\
  &\text{H} \\
\end{align*}
\]

(III)

13. Lactones obtainable by a process characterised by the following reaction steps

\[
\begin{align*}
  &\text{R}_1'O \\
  &\text{HO} \\
  &\text{OR}_2' \\
  &\text{OR}_2 \\
  &\text{(i)} \\
\end{align*}
\]

1) Oxid. 
2) \( \text{R}_3\text{MgX} \)

\[
\begin{align*}
  &\text{HO} \\
  &\text{OR}_2' \\
  &\text{OR}_2 \\
  &\text{(ii)} \\
\end{align*}
\]

\[
\begin{align*}
  &\text{O} \\
  &\text{C} \\
  &\text{H} \\
\end{align*}
\]

\[\text{Pd(Z)}_2(\text{PPh}_3)_2\]

1 atm.\( \text{CO}/20^\circ\text{C}/\text{THF} \)

(ivi)

wherein, \( \text{R}_1, \text{R}_2 \) and \( \text{R}_2' \) are as defined above, \( \text{R}_3 \) is a substituted or unsubstituted vinyl group, \( \text{X} \) is a halide, \( \text{Z} \) is a suitable ligand, and \( \text{W} \) is a suitable leaving group, e.g. imidazole or halide.
14. Lactones obtainable by a process characterised by the following reaction steps

\[
\begin{align*}
\text{AcO} & \text{OR}_2 & \text{HO} \rightarrow & \text{OR}_2 \quad \text{(i)} \\
\text{(v)} & \text{O} & \text{Pd}(Z)_2(PPh_3)_2 & \text{1 atm.CO/20°C/THF} \\
\text{OR}_2 & \text{OR}_2' & \text{(ii)} & \text{(iv)} \\
\end{align*}
\]

wherein \( R_2 \) and \( R_2' \) are as defined in claim 1, \( X \) is a halide and \( Z \) is acetate or a halide.

15. Pilocarpines or analogues thereof obtainable by a process comprising conversion of an aldehyde of formula (II)

\[
\begin{align*}
\text{R}_3 & \quad \text{(II)} \\
\end{align*}
\]

wherein \( R_3 \) is a substituted or unsubstituted vinyl group, to the corresponding N-alkylimine using a primary amine and treatment with (p-tolyl-sulphonyl)methyl isocyanide at an elevated temperature in an inert solvent such as dimethoxyethane, whereby the imidazole ring is constructed, followed by hydrogenation and purification.

16. (+)-Pilocarpine obtainable by a process comprising conversion of the aldehyde of the formula III

\[
\begin{align*}
\text{(III)} \\
\end{align*}
\]
to the corresponding N-methylimine using dry methylamine and
treatment with (p-tolyl-sulphophenyl)methyl isocyanide at an
elevated temperature in an inert solvent such as
dimethoxyethane, whereby the imidazole ring is constructed,
followed by hydrogenation and purification.

17. (+)-Pilocarpine obtainable by a process which comprises
enzyme catalysed acylation of 2-(2,2-dimethoxyethyl)-
propane-1,3-diol to selectively provide the corresponding
(2R) butyl monoester, oxidation of said monoester to the β-
acyloxy aldehyde and treatment with a vinyl Grignard reagent
to obtain the vinyl diol which is converted to the
corresponding carbonate, which carbonate is subjected to
palladium-catalysed decarboxylation-carbonylation whereby
the lactone ring is constructed, with subsequent
imidazolisation of the (2R,3R)-3-(2,2-di-methoxyethyl)-2-
vinylox-y-butyrolactone after deprotection of the 3-
formylmethylenaldehyde functional group, to provide α-
alkylidene lactones which are subjected to hydrogenation to
yield a mixture of (+)-pilocarpine and (+)-isopilocarpine
capable of resolution by methods known per se.

18. (+)-Pilocarpine and analogues thereof obtainable by a
process comprising treatment of a compound of the formula IV

\[
\begin{align*}
\text{HO} & \quad \text{OR}_2 \\
\quad & \quad \text{OR}_2' \\
R_4 & \quad \text{OR}_2
\end{align*}
\]

wherein the R_2 groups are aldehyde protective groups as
defined in claim 1 and R_4 is a lower alkyl group (C_1-C_4), to
achieve imidazolisation and obtain the N-alkylimidazole
derivative using a primary amine and (p-tolylsulphophenyl)-
methyl isocyanide in a suitable solvent to provide α-
alkylidene lactones which are subjected to hydrogenation to
yield a mixture of (+)-pilocarpine and (+)-isopilocarpine
capable of resolution by methods known per se.
19. (+)-Pilocarpine and analogues thereof obtainable by a process which comprises enzyme catalysed acylation of 2-(2,2-dimethoxyethyl)-propane-1,3-diol to selectively provide the corresponding (2R) butyl monoester, oxidation of the remaining unprotected hydroxyl to produce the corresponding aldehyde, treating the aldehyde according to the Corey-Fuchs procedure to initially produce a dihalo-protected olefin, then removing the acyl protecting group and replacing same by a base-stable protecting group R₅ e.g. the t-butyl-diphenylsilyl group, converting the olefin to an acetylenic group by use of an alkyllithium reagent, followed by reaction with an alkyl halide to produce a compound of the formula V

\[
\begin{align*}
R_5O & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
21. (+)-Pilocarpine obtainable by a process according to claim 12 or claim 13 wherein the alkyl halide is CH₃I.

22. Synthetic alkaloids obtainable by processes in accordance with the Examples hereinbefore.

23. Pharmaceutical compositions comprising a synthetic alkaloid obtained according to a process substantially as hereinbefore described in a pharmaceutically acceptable vehicle or carrier.
INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 92/00275

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int. Cl.5 | C 07 D 319/06 | C 07 D 307/33 | C 07 D 317/24 | C 07 C 43/315
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Documentation searched other than Minimum Documentation
to the extent that such Documents are included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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"Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the International filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search
14-05-1992

Date of Mailing of this International Search Report
7 JUN 1992

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Form PCT/ISA/210 (second sheet) (January 1985)
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V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers Authority, namely: because they relate to subject matter not required to be searched by this

2. ☒ Claim numbers 22, 23 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   Claims 22, 23 cannot be searched because of lack of ready comprehensibility. The term "synthetic alkaloid" is not clear and concise.

3. ☐ Claim numbers the second and third sentences of PCT Rule 8.4(a). because they are dependent claims and are not drafted in accordance with

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application

2. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.