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A practical and scaleable total synthesis of the jaborandi alkaloid (+)-pilocarpine

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ABSTRACT

The total synthesis of (+)-pilocarpine (as its nitrate salt) has been achieved in nine steps and 30% overall yield starting from racemic 2-(2′,2′-dimethoxyethyl)propane-1,3-diol, which was desymmetrised via an enzymatic protocol. A high yielding synthesis of a key α-ethylidene lactone precursor has been developed, which involves the palladium-catalysed decarboxylation/carbonylation of a 1,3-dioxan-2-one for formation of the γ-butyrolactone ring. Subsequent hydrogenation of the α-ethylidene lactone introduces the C(3)-stereochemistry to give a 72:28 mixture of (+)-pilocarpine and (+)-isopilocarpine, which are readily separable via recrystallisation of the (+)-pilocarpine nitrate salt.

1. Introduction

Pilocarpine **1** is a naturally occurring imidazole alkaloid, which was first independently isolated by Hardy[1] and Gerrard[2] in 1875 from the leaves of *Pilocarpus jaborandi*, but it was not until 1900 that its structure was proposed.[3] In addition to pilocarpine **1**, five other closely related imidazole alkaloids, including isopilocarpine **2** [the C(3)-epimer of pilocarpine] and pilosinine **3**, have been extracted from the same source and are collectively known as the jaborandi alkaloids.[4] The physiological properties of pilocarpine **1** are diverse: it is a peripheral stimulant of the parasympathetic system[5] and has been used both as a miotic[6] and diaphoretic[7] agent. Pilocarpine **1** is even reported to stimulate the growth of hair and has been used in hair lotions.[4a] Primarily because of this lack of pharmacological selectivity, pilocarpine **1** is no longer used extensively in medicine, but remains the treatment of choice for glaucoma since it effectively reduces the intraocular pressure for long periods of time without side effects.[8] It is most commonly administered in eye drops as a buffered isotonic solution ranging from 0.5 to 10% in concentration as either the nitrate or hydrochloride salt (Fig. 1).[9]

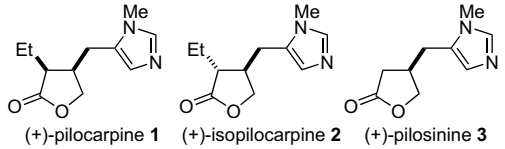

Figure 1. The jaborandi alkaloids (+)-pilocarpine **1**, (+)-isopilocarpine **2** and (+)-pilosinine **3**.

To date, ten total syntheses[10] and three formal syntheses[11] of pilocarpine **1** have been reported,[12,13] including enantiospecific syntheses starting from L-histidine,[10f] D-methionine[10g] and L-aspartic acid;[10j] however, the reported isolated overall yields of pilocarpine **1** are too low to have industrial application and a practical synthesis of homochiral (+)-pilocarpine is yet to be described. The facile epimerisation of either pilocarpine **1** or its precursors to the more stable C(3)-epimeric series make it desirable to introduce the C(3)-stereocentre as late as possible in any synthesis. This approach was followed by Link and Bernauer,[10e] whose strategy involved the elaboration of resolved (+)-pilosinine **3** via acetylation and reduction to give α-hydroxyethyl lactone **4**. Subsequent elimination via the corresponding acetate and hydrogenation of the resulting α-ethylidene lactone **5** gave a 93:7 mixture of pilocarpine **1** and isopilocarpine **2**. However, the critical point of this synthesis was the classical resolution of pilosinine **3**, which proceeded in an unacceptably low (~2%) yield (Scheme 1).

We proposed that a more efficient synthesis of α-ethylidene lactone **5** would provide a practical solution for the industrial preparation of (+)-pilocarpine **1** and report herein our full investigations within this area. Part of this work, concerning our initial efforts towards the synthesis of racemic pilocarpine **1**, has been recently communicated.[14]

2. Results and discussion

Two alternative approaches towards α-ethylidene lactone **5** were envisaged. The first approach required the palladium-catalysed carbonylation of homopropargylic alcohol **6** to afford α-ethylidene lactone **5**, with **6** arising from triple bond isomerisation of terminal bishomopropargylic alcohol **7**. The second strategy involved a palladium-catalysed decarboxylation/carbonylation of 1,3-

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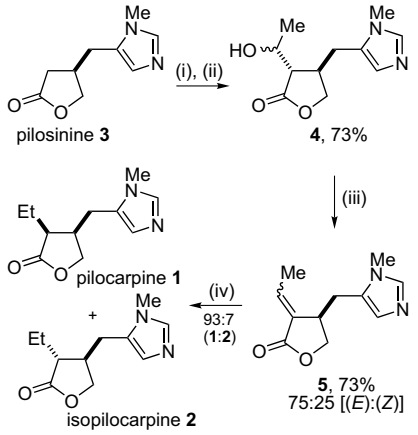


Scheme 1. Reagents and conditions: (i) KO^{t}Bu, EtOAc, ^{t}BuOH; (ii) PtO_2, H_2 (50 atm), MeOH, rt; (iii) Ac_2O, AcOH, 70 °C to 130 °C; (iv) PtO_2, H_2 (50 atm), MeOH, rt.

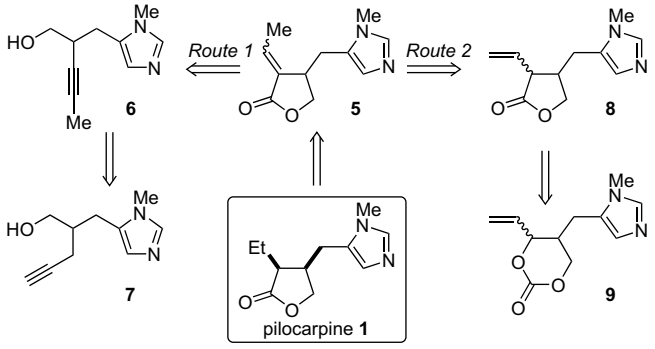


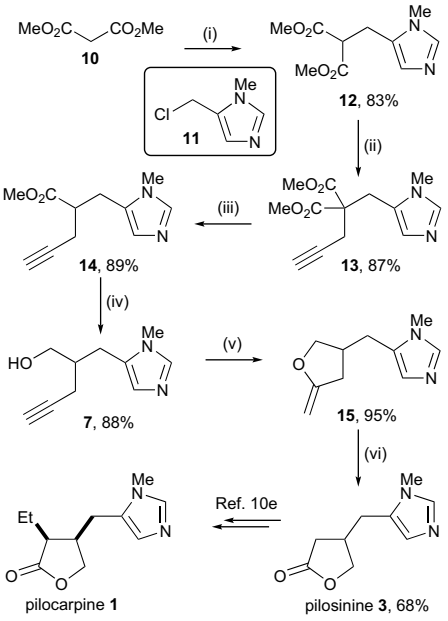
Figure 2. Retrosynthetic analysis of pilocarpine **1**.

dioxan-2-one **9** to give α-vinyl lactone **8** followed by double bond isomerisation to give the desired α-ethylidene lactone **5** (Fig. 2).

2.1. Synthesis of racemic pilocarpine

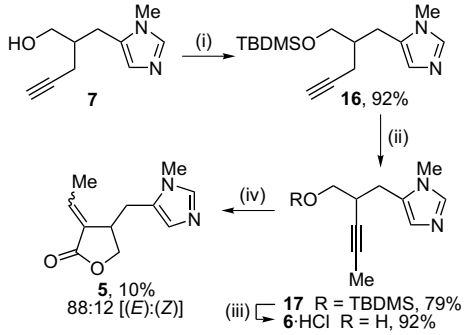
Following the first strategy for the synthesis of pilocarpine **1**, alkylation of dimethyl malonate **10** with *N*(1)-methyl-5-(chloromethyl)-1*H*-imidazole **11**[15] gave diester **12** in 83% isolated yield. Subsequent treatment of **12** with 1.0 equiv of NaOMe in MeOH was followed by the addition of propargyl bromide to give **13** in 87% isolated yield. Treatment of **13** with 3.0 equiv of imidazole in DMF at 150 °C for 4 h promoted demethoxycarbonylation to give **14** in 89% yield, and subsequent reduction of **14** with $LiAlH_4$ afforded bishomopropargylic alcohol **7** in 88% yield. Attempted base-catalysed isomerisation[16] of the triple bond within **7** with KO^{t}Bu in ^{t}BuOH at reflux for 3 h failed to give the desired homopropargylic alcohol **6**; instead vinyl ether **15** (arising from addition of the alcohol group across the triple bond) was isolated. Vinyl ether **15** proved to be unstable to either an acidic aqueous work-up or silica gel chromatography; however, chromatographic purification on alumina enabled isolation of **15** in 95% yield.[17] With a high yielding route to vinyl ether **15** available, the oxidation of **15** to pilosinine **3**, a known intermediate en route to pilocarpine **1**,[10e] was examined. Under optimised conditions, oxidation of **15** with *m*CPBA cleanly gave racemic pilosinine **3** in 68% isolated yield (37% overall yield in six steps from **10**), representing a formal synthesis of racemic pilocarpine **1** (Scheme 2).[10e]

Further studies towards the synthesis of pilocarpine **1** were directed towards the temporary protection of the hydroxyl group within **7** prior to triple bond isomerisation. Thus, treatment of *O*-TBDMS ether **16** with KO^{t}Bu in ^{t}BuOH at reflux for 24 h was found



Scheme 2. Reagents and conditions: (i) NaH, DMF then **11**; (ii) NaOMe, MeOH then propargyl bromide; (iii) DMF, NaCl, H_2O, imidazole (3.0 equiv), reflux, 4 h; (iv) $LiAlH_4$, Et_2O, rt; (v) KO^{t}Bu, ^{t}BuOH, reflux, 3 h; (vi) *m*CPBA, CH_2Cl_2, rt.

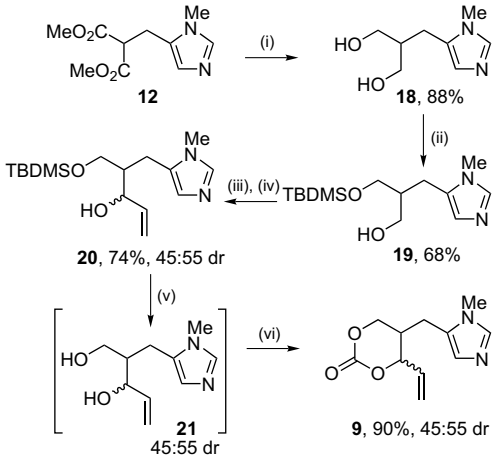
to give homopropargylic alcohol **17** in 79% isolated yield. Removal of the *O*-silyl protecting group within **17** was achieved with HF in MeCN to give alcohol **6** (isolated as the hydrochloride salt) in 92% yield. Palladium-catalysed carbonylation of **6**·HCl gave the desired α-ethylidene lactone **5** albeit in only 10% isolated yield, as an 88:12 mixture of (*E*):(*Z*) isomers (Scheme 3).



Scheme 3. Reagents and conditions: (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt; (ii) KO^{t}Bu, ^{t}BuOH, reflux, 24 h; (iii) HF, MeCN, rt then HCl; (iv) $PdCl_2(PPh_3)_2$ (7 mol %), $SnCl_2$, CO (1 atm), 110 °C, DMF, 5 h then $NaHCO_3$.

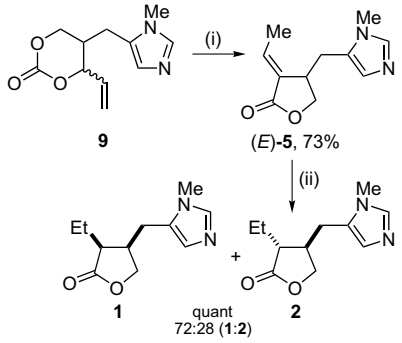
The second of our synthetic strategies was next explored in an effort to improve the overall yield of α-ethylidene lactone **5**, and therefore the overall yield of pilocarpine **1** obtained. 1,3-Dioxan-2-one **9** was synthesised from diester **12** via initial reduction with $LiAlH_4$ to give diol **18** in 88% yield. Conversion of **18** to monosilylated diol **19** followed by oxidation of the free hydroxyl group within **19** gave the corresponding aldehyde, which was immediately treated with vinylmagnesium bromide to give **20** as a 50:50 mixture of diastereoisomers in 50% yield over the three steps. Removal of the *O*-TBDMS protecting group was accomplished with HF in MeCN[18] to give diol **21**, which was used directly in the next step. Diol **21** was treated with 1,1′-carbonyldiimidazole (CDI) to give 1,3-dioxan-2-one **9** in 90% isolated yield (from **20**) as a 50:50 mixture of diastereoisomers (Scheme 4).

Addition of a solution of **9** in THF to a solution of 3 mol % $Pd(OAc)_2(PPh_3)_2$ in THF under an atmosphere of carbon monoxide[19]



Scheme 4. Reagents and conditions: (i) $LiAlH_4$, THF, reflux; (ii) NaH, DMF, rt then TBDMSCl, 0 °C to rt; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt; (iv) vinylmagnesium bromide, THF, rt; (v) HF, MeCN, rt; (vi) CDI, CH_2Cl_2, rt.

gave exclusively (*E*)-α-ethylidene lactone **5** in 73% isolated yield.[20] Subsequent hydrogenation of **5** gave a 72:28 mixture of the racemic alkaloids pilocarpine **1** and isopilocarpine **2** in quantitative yield (Scheme 5).[21] The two alkaloids are readily distinguishable by their ^{1}H NMR spectra, in particular the chemical shifts of the ABX systems from the lactone C(5)H_2 protons, and those of the triplet from the CH_3CH_2 side chain, which allow the composition of a mixture to be determined. The ^{1}H NMR spectrum of our synthetic material was identical in all respects to that of a sample (72:28 mixture) prepared from authentic samples of (+)-pilocarpine **1** and (+)-isopilocarpine **2**.[22]



Scheme 5. Reagents and conditions: (i) $Pd(OAc)_2(PPh_3)_2$ (3 mol %), THF, CO (1 atm), rt, 17 h; (ii) PtO_2, H_2 (50 atm), MeOH, rt.

With a high yielding route to racemic α-ethylidene lactone **5** established (24% overall yield in eight steps from commercially available starting materials) the application of this methodology to the synthesis of homochiral (+)-pilocarpine **1** was next pursued.

2.2. Synthesis of (+)-pilocarpine

Following the same strategy as the racemic series, we envisaged that synthesising a homochiral monoprotected diol **22** would facilitate the synthesis of (+)-pilocarpine **1** via the palladium-catalysed decarboxylation/carbonylation of homochiral 1,3-dioxan-2-one **9** (Fig. 3).

The synthesis of homochiral synthetic building blocks from prochiral precursors via enzyme-catalysed reactions has now

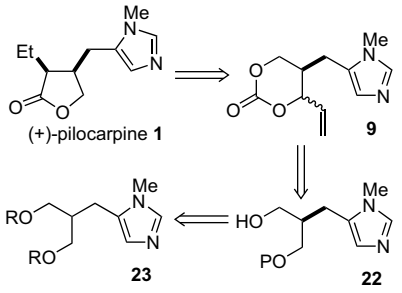
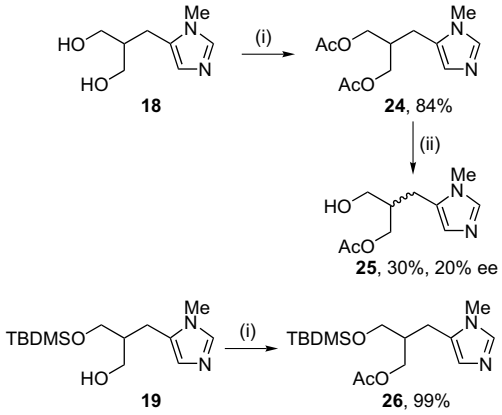


Figure 3. First retrosynthetic analysis of (+)-pilocarpine **1**. [R=H, Ac; P=protecting group (e.g., Ac)].

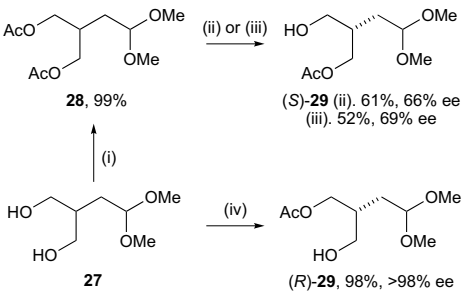
become an established synthetic method, with enzymes such as esterases and lipases being used to transform a wide range of substrates with good levels of enantioselectivity.[23] Perhaps the most widely used precursors to homochiral 2-monosubstituted-1,3-diols are the respective prochiral propane-1,3-diols or their corresponding diacetates. For example, a large number of these 1,3-diacetate substrates (containing a diverse range of functional groups) undergo enzyme-catalysed hydrolysis in the presence of an esterase or lipase, such as pig liver esterase (PLE) or pig pancreatic lipase (PPL), which are usually complementary since they show the opposite stereochemical preference as regards which of the acetoxy groups is hydrolysed.[24] The desymmetrisation of prochiral 1,3-diol **18** and the resolution of mono-silyl protected diol **19** were initially investigated as both **18** and **19** were identified as intermediates en route to racemic pilocarpine **1**. Unfortunately, attempted desymmetrisation of prochiral diol **18** via an enzyme-catalysed acetylation with PLE, PPL, *Candida cylindracea* lipase (CCL) or *Pseudomonas fluorescens* lipase (PFL), in a range of common solvents (e.g., hydrocarbons, chlorinated solvents, THF, ^{t}BuOMe and EtOAc, DMF or ^{t}BuOH), did not promote conversion to monoacetate **25**. Similarly, attempted desymmetrisation of the corresponding diacetate derivative **24** (prepared in 84% yield by treatment of diol **18** with Ac_2O, Et_3N and DMAP in CH_2Cl_2) via enzymatic hydrolysis with PLE gave poor conversion to monoacetate **25** in only 20% ee;[25] attempted hydrolysis with either PPL or PFL was unsuccessful. In addition, attempted enzyme-mediated kinetic resolution of racemic *O*-TBDMS protected monoacetate **26** (prepared in 99% yield by treatment of mono-*O*-TBDMS protected diol **19** with Ac_2O, Et_3N and DMAP in CH_2Cl_2) with either PPL or PFL in DME, ^{t}BuOH or ^{i}Pr$_2$O was not successful and only starting material was isolated (Scheme 6).

As the *N*-methylimidazole containing substrates were proving incompatible with the enzymatic protocols, it was envisaged that



Scheme 6. Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (ii) PLE, H_2O, pH 7.

this moiety could be installed at a later stage in the synthesis. The synthetic strategy adopted therefore relied upon the desymmetrisation of a masked aldehyde equivalent, such as a dimethyl acetal, with subsequent hydrolysis, formation of the corresponding *N*-methyl imine, and treatment with (*p*-toluenesulphonyl)methyl isocyanide (TsMIC)[26] facilitating installation of the *N*-methylimidazole ring.[27] Attempted desymmetrisation of diacetate **28** with PPL or PFL gave (*S*)-**29** in 61 and 52% yield, and 66 and 69% ee,[28] respectively. However, treatment of diol **27**[29] with PFL and 1.3 equiv of vinyl acetate in CH_2Cl_2 promoted full conversion to monoacetate (*R*)-**29**, which was isolated in 98% yield and >98% ee[28] {$[\alpha]_D^{20}$ +13.6 (*c* 1.0, $CHCl_3$)} after chromatographic purification; this protocol was found to be readily reproducible on >5 g scale (Scheme 7). The absolute configuration of **29** was assigned by analogy to the stereochemical preferences that have been previously observed for both PPL- and PFL-catalysed hydrolyses of 1,3-diacetates;[30] whilst it was not possible to unambiguously establish the absolute configuration of (*R*)-**29** a priori, it was subsequently assigned by chemical correlation with the C(4)-stereogenic centre within (+)-(3*S*,4*R*)-pilocarpine **1** (vide infra).



Scheme 7. Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (ii) PPL, H_2O, pH 7; (iii) PFL, H_2O, pH 7; (iv) PFL, vinyl acetate, CH_2Cl_2.

With enantiopure **29** in hand, further elaboration to (+)-pilocarpine **1** was examined. The susceptibility of the acetate group within **29** towards migration under both acidic and basic conditions (resulting in racemisation) made the direct conversion of the dimethyl acetal group within **29** into an *N*-methylimidazole ring unachievable at this stage.[31] Consequently, elaboration of monoacetate **29** into the corresponding γ-butyrolactone **31** was investigated prior to installation of the *N*-methylimidazole ring (Fig. 4).

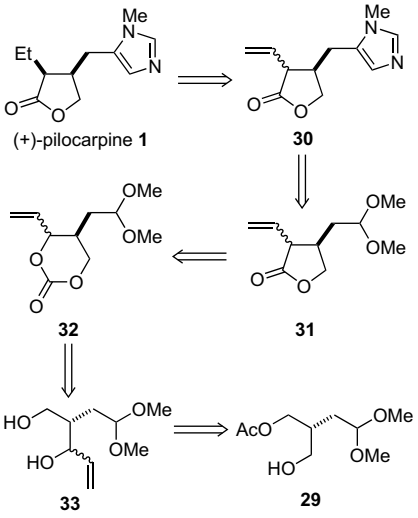
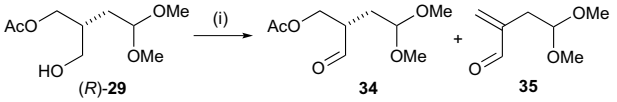


Figure 4. Second retrosynthetic analysis of (+)-pilocarpine **1** via homochiral γ-butyrolactone **31**.

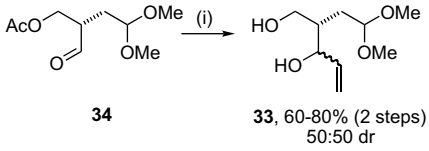
Swern oxidation of (*R*)-**29** gave a 75:25 ratio of the desired β-acetoxy aldehyde **34** and α,β-unsaturated ester **35**, respectively. However, attempted purification by flash chromatography resulted in complete conversion to α,β-unsaturated aldehyde **35**, which was isolated as the only product in 80% yield. Alternative oxidation protocols employing pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), silver carbonate, tetrapropylammonium perruthenate (TPAP), and Dess–Martin periodinane (DMP) were therefore screened and gave varying mixtures of **34**:**35**. Although oxidation with DMP gave a 90:10 ratio of the β-acetoxy aldehyde **34** and α,β-unsaturated aldehyde **35**, oxidation with DMP in the presence of 2 equiv of pyridine gave a crude reaction mixture containing exclusively **34** (Scheme 8).



Oxidant	Solvent	Temp (°C)	Product Ratio (34:35)
Swern	CH_2Cl_2	−78 to 20	75:25
PDC	CH_2Cl_2	20	78:22
PCC	CH_2Cl_2	20	0:100
Ag_2CO_3	C_6H_6	80	No Reaction
TPAP	CH_2Cl_2	20	73:27
TPAP	CH_2Cl_2	0	73:27
DMP	CH_2Cl_2	0 to 20	90:10
DMP[a]	CH_2Cl_2	0 to 20	100:0

Scheme 8. Reagents and conditions: (i) see table. [[a]Reaction carried out in the presence of 2.0 equiv of pyridine].

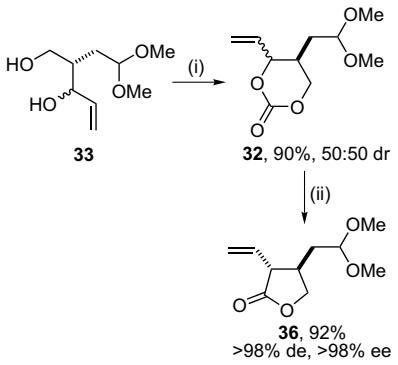
Aldehyde **34** was found to be unstable upon attempted purification and was therefore used directly in the next step. Thus, treatment of **34** with vinylmagnesium bromide (3.0 equiv) in THF at 0 °C gave quantitative conversion to alcohol **33** (50:50 mixture of diastereoisomers). Chromatographic purification of **33** resulted in variable yields, which were typically between 60 and 80% for the two-step oxidation/Grignard addition protocol (Scheme 9).



Scheme 9. Reagents and conditions: (i) vinylmagnesium bromide (3.0 equiv), THF, 0 °C.

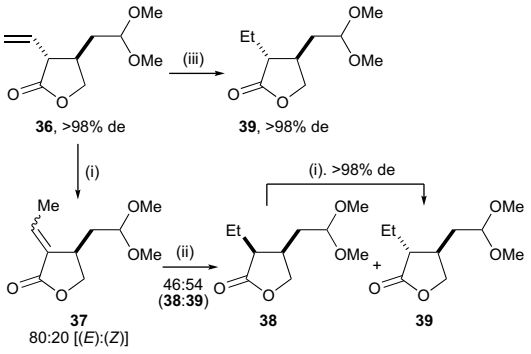
Attempted hydrolysis of the dimethyl acetal within **33** led to complex mixtures, therefore conversion of **33** into γ-butyrolactone **36** was next investigated as it was anticipated that this would be a more suitable substrate for hydrolysis of the dimethyl acetal and subsequent installation of the *N*-methylimidazole moiety. Thus, treatment of diol **33** with CDI gave a 50:50 diastereoisomeric mixture of 1,3-dioxan-2-ones **32**, isolated in 60% combined yield. However, slowly adding CDI (as a CH_2Cl_2 solution) over a period of 3 h was found to improve the conversion to 1,3-dioxan-2-one **32**, which was isolated in 90% yield (as a 50:50 mixture of diastereoisomers) after chromatographic purification. Treatment of a solution of **32** in THF with $Pd(OAc)_2(PPh_3)_2$ (3 mol %) under a carbon monoxide atmosphere gave clean conversion to γ-butyrolactone **36** via the palladium-catalysed decarboxylation/carbonylation procedure, with chromatographic purification giving **36** in 92% yield, >98% de[32] and >98% ee[33] (Scheme 10).

The relative configuration within **36** was initially assigned as *trans*, and was subsequently confirmed by chemical correlation. Isomerisation of **36** with KO^{t}Bu gave an 80:20 [(*E*):(*Z*)] mixture of α-ethylidene lactones **37**. Hydrogenation of this mixture afforded a 46:54 mixture of lactones *cis*-**38** and *trans*-**39**, respectively, and



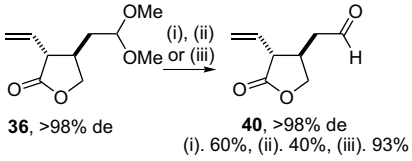
Scheme 10. Reagents and conditions: (i) CDI, CH_2Cl_2, rt, 3 h; (ii) $Pd(OAc)_2(PPh_3)_2$, CO (1 atm), THF, rt, 17 h.

treatment of this mixture with KO^{t}Bu resulted in complete conversion to the thermodynamically more stable *trans*-isomer **39**. Hydrogenation of lactone **36** gave exclusively *trans*-**39** thus confirming the trans-relative configuration within lactone **36** (Scheme 11).



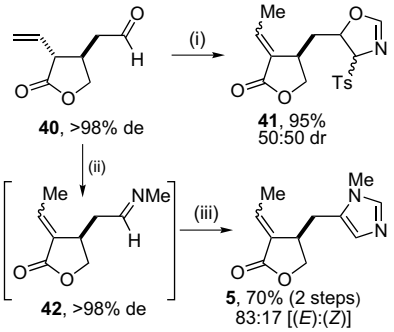
Scheme 11. Reagents and conditions: (i) KO^{t}Bu, ^{t}BuOH, rt; (ii) H_2 (50 atm), Pt_2O, MeOH, rt; (iii) H_2 (1 atm), Pt_2O, MeOH, rt.

With diastereo- and enantiomerically pure **36** in hand, attention turned towards hydrolysis of the dimethyl acetal moiety and installation of the *N*-methylimidazole functionality. Hydrolysis of the acetal was first attempted using a 3:1 mixture of THF/HCl (1.0 M, aq):[34] after 24 h at rt aldehyde **40** was obtained in 60% yield following purification by flash column chromatography. The exchange reaction between **36** and refluxing acetone in the presence of TsOH[35] gave **40** in only 40% isolated yield, although when pyridinium *p*-toluenesulphonate (PPTS)[36] was used as the acid catalyst aldehyde **40** was obtained in 93% isolated yield (Scheme 12).



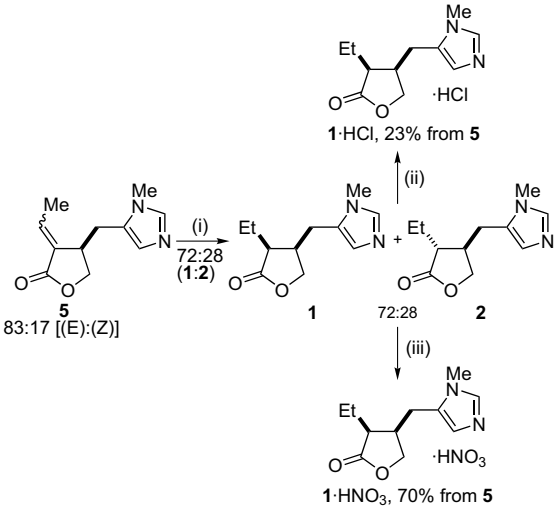
Scheme 12. Reagents and conditions: (i) THF/HCl (1.0 M, aq) (3:1), rt, 24 h; (ii) TsOH, acetone, reflux, 72 h; (iii) PPTS, acetone, reflux, 72 h.

Installation of the *N*-methylimidazole ring by treatment of *N*-methyl imine **42** (derived from aldehyde **40**) with TsMIC was next investigated. Since the reaction of lithiomethyl isocyanide with δ-lactones to give oxazoles has previously been reported,[37] it was important to establish whether this type of reaction would be competitive in this case. As a model reaction, a solution of **40** in MeOH was treated with 1 equiv of TsMIC and a catalytic quantity of K_2CO_3 (the usual conditions used for oxazole[38] and imidazole[26] synthesis). After stirring for 30 min at rt the reaction mixture was filtered and concentrated in vacuo to give **41** (as a 50:50 diastereoisomeric mixture), arising from attack of TsMIC at the aldehyde group. Isolation of *N*-methyl imine **42** was therefore deemed necessary prior to addition of TsMIC. Thus, *N*-methyl imine **42** was prepared from aldehyde **40** by bubbling dry $MeNH_2$ gas through a solution of aldehyde **40** in DME in the presence of 4 Å molecular sieves at 0 °C for 16 h. Imine **42** was then treated with TsMIC and K_2CO_3 (1.0 equiv) and anhydrous methylamine gas in MeOH at rt,[39] although under these conditions the lactone ring appeared to undergo ring-opening. With DME as solvent both the imine and TsMIC appeared to be indefinitely stable; after 6 h poor conversion to the desired product **5** was observed, however heating the reaction mixture to 80 °C for 24 h gave an 83:17 [(*E*):(*Z*)] mixture of α-ethylidene lactones **5**, which was isolated in 70% yield after purification by flash column chromatography (Scheme 13).



Scheme 13. Reagents and conditions: (i) TsMIC, K_2CO_3, MeOH, rt; (ii) $MeNH_2$, DME, 4 Å molecular sieves, 16 h; (iii) TsMIC, $MeNH_2$, DME, 80 °C, 12 h.

Under optimised conditions[40] hydrogenation of the 83:17 [(*E*):(*Z*)] mixture of α-ethylidene lactones **5** was carried out over PtO_2 at 50 atm pressure in MeOH[10e] to give a 72:28 mixture of (+)-pilocarpine **1** and (+)-isopilocarpine **2** with quantitative conversion. After purification by flash column chromatography the ^{1}H NMR spectrum of the mixture was identical to that of a 72:28 mixture of authentic (+)-pilocarpine **1** and (+)-isopilocarpine **2**.[22] Separation of the 72:28 mixture of the two alkaloids was achieved through recrystallisation of either their hydrochloride or nitrate salts: after four recrystallisations of the hydrochloride salt a sample of pure (+)-pilocarpine hydrochloride **1**·HCl (mp 201–202 °C; lit.[3a] mp 204–205 °C) was obtained, although the yield of the pure alkaloid was only 23% from **5**. However, recrystallisation of the mixture of nitrate salts from EtOH gave (+)-pilocarpine nitrate **1**·HNO_3 (mp 177–178 °C; lit.[41] mp 178 °C) in 70% isolated yield from **5** (Scheme 14).



Scheme 14. Reagents and conditions: (i) Pt_2O, H_2 (50 atm), MeOH, rt; (ii) HCl then recrystallisation; (iii) HNO_3 then recrystallisation.

The crystals of (+)-pilocarpine nitrate **1**·HNO_3 formed beautiful prisms and were subjected to X-ray crystallographic analysis enabling the *cis*-relative configuration of the C(3)- and C(4)-substituents within pilocarpine nitrate **1**·HNO_3 to be unambiguously determined (Fig. 5). The absolute (3*S*,4*R*)-configuration within (+)-pilocarpine **1** was established by comparison of the specific rotations for both the hydrochloride salt **1**·HCl and nitrate salt **1**·HNO_3 with those reported in the literature {for **1**·HCl $[\alpha]_D^{20}$ +90.1 (*c* 2.0, H_2O); lit.,[10j] $[\alpha]_D^{20}$ +88 (*c* 2.0, H_2O); for **1**·HNO_3 $[\alpha]_D^{20}$ +83.1 (*c* 1.0, H_2O); lit.[10b] $[\alpha]_D^{20}$ +81.3 (*c* 1.0, H_2O)}.

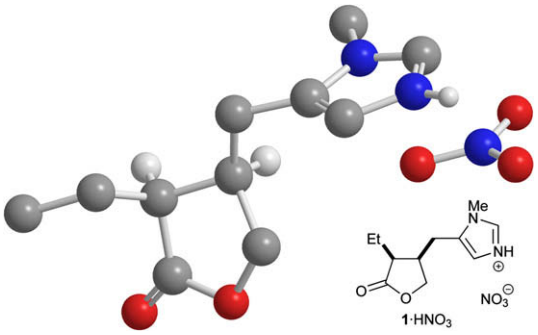


Figure 5. Chem3D representation of the single crystal X-ray structure of **1**·HNO_3 (some H atoms have been omitted for clarity).

3. Conclusion

The total synthesis of (+)-pilocarpine (as its nitrate salt) has been achieved in nine steps and 30% overall yield starting from 2-(2′,2′-dimethoxyethyl)propane-1,3-diol. The prochiral diol was desymmetrised via an enzymatic protocol and elaborated to give a key homochiral α-ethylidene lactone in good yield (42% over eight steps). Subsequent hydrogenation of the α-ethylidene lactone gave a 72:28 mixture of (+)-pilocarpine and (+)-isopilocarpine, which were readily separable via recrystallisation of the (+)-pilocarpine nitrate salt. This synthetic strategy is readily applicable to large scale synthesis and should be applicable to the generation of homologues of this natural product family.

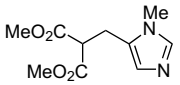
4. Experimental

4.1. General experimental

Water was purified by an Elix® UV-10 system. ^{t}BuOH was distilled at atmospheric pressure and stored over 4 Å molecular sieves. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere. DMF was heated to 100 °C for 4 h over $CaSO_4$ and then distilled under reduced pressure from fresh $CaSO_4$. DME and THF were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. DMSO was stored over 4 Å molecular sieves. EtOH and MeOH were distilled from Mg and I_2. 30–40 °C Petrol refers to the fraction of petroleum ether boiling between 30 °C and 40 °C, 40–60 °C petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. The following enzymes were used: PLE (immobilised), Fluka 46064; PPL, Sigma L3126; PFL, Fluka 62312; CCL, Sigma L1754; Lipase type XIII, Sigma L9518; and Lipoprotein lipase Fluka 62335 in conjunction with a Radiometer RTS822 recording titration system, which dispensed 1.0 M NaOH from an autoburette. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica, unless otherwise stated.

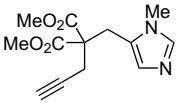
Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.1.1. *Dimethyl 2-[(N(1′)-methylimidazol-5′-yl)methyl]malonate* **12**



A solution of dimethyl malonate **10** (33.0 g, 0.25 mol) in THF (200 mL) was added dropwise over 1 h to a suspension of NaH (7.5 g of 60% dispersion in oil, 0.187 mol, 3 equiv) in THF (400 mL) at rt. *N*(1)-Methyl-5-(chloromethyl)imidazole **11** (9.31 g, 62.4 mmol) was then added portionwise and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo and the residue was cooled to 0 °C. Aq HCl (5%, 100 mL) was then added until pH 1 was achieved and the resultant mixture was extracted with Et_2O (3×50 mL). The aqueous layer was basified by the addition of $NaHCO_3$ until pH 8 was achieved and then extracted with $CHCl_3$ (4×100 mL). The combined organic extracts were then dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent $CHCl_3$) gave **12** as a pale brown oil (10.5 g, 83%); Found C, 53.05; H, 6.5; N, 12.2%; $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%; ν_{max} (film) 1755 (C=O), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 3.16 (2H, d, *J* 7.7, C(5′)CH_2), 3.58 (3H, s, NCH_3), 3.70 (1H, t, *J* 7.7, C(2)*H*), 3.73 (6H, s, 2×CO_2CH_3), 6.78 (1H, s, C(4′)*H*), 7.36 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 22.8 (C(5′)CH_2), 31.0 (NCH_3), 50.7 (*C*(2)H), 52.6 (2×CO_2CH_3), 126.9 (*C*(4′)H), 128.0 (*C*(5′)), 138.0 (*C*(2′)H), 168.8 (2×*C*O); *m*/*z* (CI^+) 227 ($[M+H]^+$, 100%).

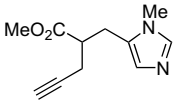
4.1.2. *Dimethyl 2-[(N(1′)-methylimidazol-5′-yl)methyl]-2-(prop-2″-ynyl)malonate* **13**



A solution of diester **12** (11.75 g, 51.9 mmol) in dry MeOH (30 mL) was added to a solution of NaOMe, prepared by dissolving sodium (1.31 g, 57.1 mmol, 1.1 equiv) in dry MeOH (70 mL). The resultant mixture was stirred at rt for 30 min, and then propargyl bromide (7.52 mL, 80% in toluene, 67.6 mmol, 1.3 equiv) was added via syringe. After 2 h the reaction mixture was concentrated in vacuo and the residue was redissolved in 5% aq HCl (until pH 1 was achieved) at 0 °C. The resultant solution was extracted with Et_2O (3×50 mL), basified with $NaHCO_3$ to pH 8 and extracted with $CHCl_3$ (4×100 mL). The combined organic extracts were

dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent $CHCl_3$) gave **13** as a yellow oil, which slowly crystallised upon standing (12.0 g, 87%); Found C, 59.1; H, 5.95; N, 10.5%; $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%; mp 77–79 °C; ν_{max} (film) 3300 (C≡C–H), 1750 (C=O); δ_H (400 MHz, $CDCl_3$) 2.11 (1H, t, *J* 2.7, C(3″)*H*), 2.79 (2H, d, *J* 2.7, C(1″)H_2), 3.38 (2H, s, C(5′)CH_2), 3.59 (3H, s, NCH_3), 3.76 (6H, s, 2×CO_2CH_3), 6.76 (1H, s, C(4′)*H*), 7.36 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (*C*(1″)H_2), 25.6 (C(5′)CH_2), 31.2 (NCH_3), 52.9 (2×CO_2CH_3), 57.2 (*C*(2)), 72.2 (*C*(3″)H), 78.7 (*C*(2″)), 125.8 (*C*(4′)H), 128.6 (*C*(5′)), 138.3 (*C*(2′)H), 169.8 (2×*C*O); *m*/*z* (CI^+) 265 ($[M+H]^+$, 100%).

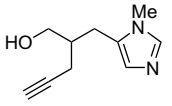
4.1.3. Methyl (RS)-2-[(N(1′)-methylimidazol-5′-yl)methyl]pent-4-ynoate ***14***



Method A. Diester **13** (1.00 g, 3.78 mmol), NaCl (265 mg, 1.28 mmol, 1.2 equiv) and water (0.14 mL, 7.77 mmol, 2.0 equiv) were mixed in DMF (15 mL) and heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt, and water (15 mL) was added. The resultant solution was extracted with EtOAc (5×20 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent $CHCl_3$) gave **14** as a pale brown oil (336 mg, 42%); Found C, 64.0; H, 7.0; N, 13.25%; $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%; ν_{max} (film) 3310 (C≡C–H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 2.06 (1H, t, *J* 2.6, C(5)*H*), 2.50–2.57 (2H, m, C(3)H_2), 2.83–3.02 (3H, m, C(5′)CH_2, C(2)*H*), 3.59 (3H, s, NCH_3), 3.69 (3H, s, CO_2CH_3), 6.81 (1H, s, C(4′)*H*), 7.37 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 20.4 (*C*(3)H_2), 24.2 (C(5′)CH_2), 30.9 (NCH_3), 43.4 (*C*(2)H), 51.8 (CO_2CH_3), 70.6 (*C*(5)H), 80.2 (*C*(4)), 127.2 (*C*(4′)H), 128.4 (*C*(5′)), 137.8 (*C*(2′)H), 173.5 (*C*O); *m*/*z* (CI^+) 207 ($[M+H]^+$, 100%).

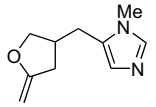
Method B. Diester **13** (1.00 g, 3.78 mmol), NaCl (265 mg, 4.53 mmol, 1.2 equiv), imidazole (773 mg, 11.4 mmol, 3.0 equiv) and water (0.20 mL, 11.1 mmol, 3.0 equiv) were mixed in DMF (15 mL) and the resultant mixture was heated at reflux for 4 h. The reaction mixture was then allowed to cool to rt, water (15 mL) was added and the resultant solution was extracted with EtOAc (5×20 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent 5% MeOH in $CHCl_3$) gave **14** as a pale brown oil (694 mg, 89%).

4.1.4. (RS)-2-[(N(1′)-Methylimidazol-5′-yl)methyl]pent-4-yn-1-ol ***7***



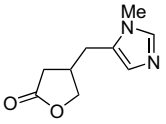
A solution of methyl ester **14** (1.07 g, 5.18 mmol) in anhydrous Et_2O (10 mL) was added dropwise to a suspension of $LiAlH_4$ (200 mg, 5.27 mmol) in anhydrous Et_2O (20 mL) and the resultant mixture was stirred for 1 h at rt. The reaction mixture was then cooled to 0 °C and water (5 mL) was carefully added. The mixture was then filtered, and the solid residue was washed with $CHCl_3$ (2×30 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:9) gave a pale yellow solid, which was recrystallised from MeOH/Et_2O to give **7** as a white solid (813 mg, 88%); Found C, 67.3; H, 8.2; N, 15.6%; $C_{10}H_{14}N_2O$ requires C, 67.4; H, 7.9; N, 15.7%; mp 118–119 °C; ν_{max} (KBr) 3310 (C≡C–H); δ_H (400 MHz, MeOH-d_4) 1.90–1.95 (1H, m, C(2)*H*), 2.24–2.28 (2H, m, C(3)H_2), 2.32 (1H, t, *J* 2.6, C(5)*H*), 2.70 (2H, dd, *J* 7.1, 3.5, C(5′)CH_2), 3.57 (2H, d, *J* 5.8, C(1)H_2), 3.63 (3H, s, NCH_3), 6.75 (1H, s, C(4′)*H*), 7.52 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(3)H_2), 23.7 (C(5′)CH_2), 30.6 (NCH_3), 39.9 (*C*(2)H), 63.0 (*C*(1)H_2), 70.4 (*C*(5)H), 81.7 (*C*(4)), 126.2 (*C*(4′)H), 130.7 (*C*(5′)), 138.1 (*C*(2′)H); *m*/*z* (CI^+) 178 ($[M]^+$, 100%).

4.1.5. (RS)-2-Methylene-4-[(N(1′)-methylimidazol-5′-yl)methyl]tetrahydrofuran ***15***



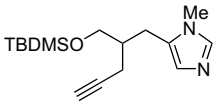
KO^{t}Bu (240 mg, 0.1 equiv) was added to a solution of alcohol **7** (3.45 g, 19.4 mmol) in ^{t}BuOH (70 mL), and the resultant solution was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt before being concentrated in vacuo. The residue was dissolved in water (20 mL) at 0 °C, and this solution was extracted with $CHCl_3$ (4×50 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (alumina, eluent $CHCl_3$) gave vinyl ether **15** as a pale yellow oil (475 mg, 95%); Found C, 67.3; H, 8.3; N, 15.5%; $C_{10}H_{14}N_2O$ requires C, 67.4; H, 7.9; N, 15.7%; ν_{max} (film) 1680 (C=C); δ_H (400 MHz, $CDCl_3$) 2.74–2.30 (5H, m, C(5′)CH_2, C(3)H_2, C(4)*H*), 3.54 (3H, s, NCH_3), 3.80–3.89 (2H, m, C(2)=C$H_A$$H_B$, C(5)$H_A$), 4.15–4.19 (1H, m, C(5)H_B), 4.20–4.26 (1H, m, C(2)=C$H_A$$H_B$), 6.78 (1H, s, C(4′)*H*), 7.37 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 26.3 (C(5′)CH_2), 31.0 (NCH_3), 34.9 (*C*(3)H_2), 36.8 (*C*(4)H), 74.5 (*C*(5)H_2), 80.1 (C(2)=*C*H_2), 126.8 (*C*(4′)H), 129.8 (*C*(5′)), 137.8 (*C*(2′)H), 161.9 (*C*(2)); *m*/*z* (CI^+) 178 ($[M]^+$, 100%).

4.1.6. (RS)-4-[(N(1′)-Methylimidazol-5′-yl)methyl]tetrahydrofuran-2-one ***3*** *[(±)-pilosinine* ***3****]*



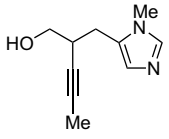
A solution of enol ether **15** (388 mg, 2.18 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of *m*CPBA (85%, 1.13 g, 5.55 mmol, 2.55 equiv) in CH_2Cl_2 (30 mL) and the resultant mixture was stirred at rt for 30 min. Aq Na_2SO_3 (10%, 5 mL) and satd aq $NaHCO_3$ (10 mL) were then sequentially added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were dried, filtered and concentrated in vacuo, the residue was then redissolved in 1.0 M aq HCl (3 mL) and the resultant solution was extracted with Et_2O (3×5 mL). The aqueous layer was basified with solid $NaHCO_3$ until pH 8 was achieved and the mixture was then extracted with $CHCl_3$ (4×10 mL). The combined organic extracts were then dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:9) gave (±)-pilosinine **3** as a pale yellow oil (267 mg, 68%);[10e] δ_H (400 MHz, $CDCl_3$) 2.29–2.80 (4H, m, C(5′)CH_2, C(3)H_2), 2.87–2.92 (1H, m, C(4)*H*), 3.57 (3H, s, NCH_3), 4.07 (1H, dd, *J* 9.3, 6.9, C(5)H_A), 4.46 (1H, dd, *J* 9.3, 5.3, C(5)H_B), 6.80 (1H, s, C(4′)*H*), 7.43 (1H, s, C(2′)*H*).

4.1.7. (RS)-1-(tert-Butyldimethylsilyloxy)-2-[(N(1′)-methylimidazol-5′-yl)methyl]pent-4-yne ***16***



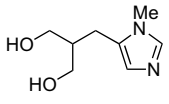
TBDMSCl (186 mg, 1.23 mmol, 1.1 equiv) was added to a suspension of alcohol **7** (200 g, 1.12 mmol), Et_3N (187 μL, 1.34 mmol, 1.2 equiv) and DMAP (5 mg) in CH_2Cl_2 (20 mL). The resultant solution was stirred for 16 h at rt then water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue via distillation (Kugelrohr, 1 mmHg, 150 °C) gave silyl ether **16** as a colourless oil (300 mg, 92%); ν_{max} (KBr) 3312 (C≡C–H); δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, Si(C*H*$_3$)$_2$), 0.90 (9H, s, C(C*H*$_3$)$_3$), 1.89–1.93 (1H, m, C(2)*H*), 1.99 (1H, t, *J* 2.6, C(5)*H*), 2.27 (2H, dd, *J* 6.2, 2.6, C(3)*H*$_2$), 2.66 (1H, dd, *J* 15.2, 7.2, C(5′)C*H*$_A$), 2.76 (1H, dd, *J* 15.2, 7.1, C(5′)C*H*$_B$), 3.57 (3H, s, NC*H*$_3$), 3.60 (2H, app d, *J* 5.3, C(1)*H*$_2$), 6.81 (1H, s, C(4′)*H*), 7.38 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) −5.8 (Si(*C*H$_3$)$_2$), 18.0 (*C*(CH$_3$)$_3$), 19.6 (*C*(3)H$_2$), 23.7 (C(5′)*C*H$_2$), 25.7 (C(*C*H$_3$)$_3$), 31.1 (NCH$_3$), 39.8 (*C*(2)H), 63.6 (*C*(1)H$_2$), 69.8 (*C*(5)H), 82.2 (*C*(4)), 127.6 (*C*(4′)H), 129.9 (*C*(5′)), 137.7 (*C*(2′)H); *m*/*z* (CI$^+$) 293 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{15}N_2O^+$ ([M+H]$^+$) requires 179.1179; found 179.1182.

4.1.8. (RS)-2-[(N(1′)-Methylimidazol-5′-yl)methyl]pent-3-yn-1-ol ***6***



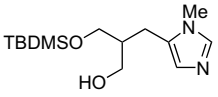
O-TBDMS protected alcohol **16** (200 mg, 0.68 mmol) was added to a solution of 5% KO^{t}Bu in ^{t}BuOH (10 mL) and the resultant solution was heated at reflux for 24 h. The reaction mixture was then concentrated in vacuo and water (5 mL) was added. The resultant solution was extracted with $CHCl_3$ (4×10 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. The residue was then dissolved in a 5% solution of 40% aq HF in MeCN (10 mL) and the mixture was stirred at rt for 16 h. K_2CO_3 (excess) was then added and the solution was stirred until the pH 8 was achieved. The mixture was then filtered and the solid residue was washed with MeCN. The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **6** as a pale yellow oil (112 mg, 92%); Found C, 67.3; H, 8.0; N, 15.9%. $C_{10}H_{14}N_2O$ requires C, 67.4; H, 7.9; N, 15.7%; δ_H (400 MHz, $CDCl_3$) 1.78 (3H, d, *J* 2.1, C(5)*H*$_3$), 2.76–2.80 (3H, m, C(5′)C*H*$_2$, C(2)*H*), 3.17 (1H, br s, O*H*), 3.59 (3H, s, NC*H*$_3$), 3.61 (2H, d, *J* 5.3, C(1)*H*$_2$), 6.86 (1H, s, C(4′)*H*), 7.35 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 3.2 (*C*(5)H$_3$), 25.3 (C(5′)*C*H$_2$), 31.2 (NCH$_3$), 34.9 (*C*(2)H), 64.0 (*C*(1)H$_2$), 78.8, 77.2 (*C*(3), *C*(4)), 127.2 (*C*(4′)H), 129.8 (*C*(5′)), 137.3 (*C*(2′)H); *m*/*z* (CI$^+$) 179 ([M+H]$^+$, 100%). Treatment of the residue with HCl(g) gave **6**·HCl as a white solid (107 mg, quant).

4.1.9. 2-[(N(1′)-Methylimidazol-5′-yl)methyl]propane-1,3-diol ***18***



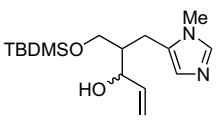
A solution of dimethyl ester **12** (16.7 g, 65.5 mmol) in THF (50 mL) was added dropwise to a solution of $LiAlH_4$ (3.73 g, 98.3 mmol, 1.5 equiv) in THF (300 mL) at such a rate as to maintain a gentle reflux. After 6 h, the careful addition of water (3.7 mL), 15% NaOH (3.7 mL) and water (11.1 mL) at 0 °C gave a granular precipitate of aluminium salts, which was removed by filtration. The solid residue was suspended in hot MeOH (100 mL) and stirred vigorously, then filtered; this extraction process was then repeated twice. The combined extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent $CHCl_3$/MeOH, 3:1) gave **18** as a pale yellow oil, which slowly crystallised upon standing (9.81 g, 88%); Found C, 56.3; H, 8.3; N, 16.4%; $C_8H_{14}N_2O_2$ requires C, 56.45; H, 8.3; N, 16.5%; bp 110 °C (1 mmHg, sub); mp 46–48 °C; δ_H (400 MHz, D_2O) 1.79–1.83 (1H, m, C(2)*H*), 2.46 (2H, d, *J* 7.3, C(5′)C*H*$_2$), 3.43 (4H, d, *J* 5.5, C(1)*H*$_2$, C(3)*H*$_2$), 3.44 (3H, s, NC*H*$_3$), 6.64 (1H, s, C(4′)*H*), 7.42 (1H, s, C(2′)*H*); δ_C (400 MHz, D_2O) 22.1 (C(5′)CH$_2$), 31.8 (NCH$_3$), 42.4 (*C*(2)H), 62.2 (*C*(1)H$_2$, C(3)*H*$_2$), 126.1 (*C*(4′)H), 132.0 (*C*(5′)), 139.4 (*C*(2′)H); *m*/*z* (CI$^+$) 171 ([M+H]$^+$, 100%).

4.1.10. (RS)-2-[(N(1′)-Methylimidazol-5′-yl)methyl]-3-(tert-butyldimethylsilyloxy)propan-1-ol ***19***



A solution of diol **18** (1.00 g, 5.88 mmol) in anhydrous DMF (5.0 mL) was added to a suspension of NaH (235 mg of 60% dispersion in oil, 5.88 mmol) in anhydrous DMF (5 mL) and the resultant solution was stirred at rt for 2 h. The reaction mixture was then cooled to 0 °C and TBDMSCl (886 mg, 5.88 mmol) was added. The resultant mixture was allowed to warm to rt and was stirred for 16 h before being concentrated in vacuo. The residue was dissolved in satd aq $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent $CHCl_3$/MeOH, 3:1) gave mono-*O*-TBDMS ether **19** as a colourless oil (1.14 g, 68%); Found C, 59.0; H, 10.2; N, 9.6%; $C_{14}H_{28}N_2O_2Si$ requires C, 59.1; H, 9.9; N, 9.85%; mp 74–75 °C; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, Si(C*H*$_3$)$_2$), 0.91 (9H, s, C(C*H*$_3$)$_3$), 1.92–1.95 (1H, m, C(2)*H*), 2.47 (1H, br s, O*H*), 2.62 (2H, d, *J* 7.2, C(5′)C*H*$_2$), 3.58 (3H, s, NC*H*$_3$), 3.65 (1H, dd, *J* 10.8, 4.9, C(1)*H*$_A$), 3.67 (1H, dd, *J* 10.8, 3.9, C(1)*H*$_B$), 3.69 (1H, dd, *J* 10.0, 4.5, C(3)*H*$_A$), 3.77 (1H, dd, *J* 10.0, 4.6, C(3)*H*$_B$), 6.79 (1H, s, C(4′)*H*), 7.38 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) −5.9 (Si(*C*H$_3$)$_2$), 17.9 (*C*(CH$_3$)$_3$), 21.5 (C(5′)CH$_2$), 25.6 (C(*C*H$_3$)$_3$), 31.0 (NCH$_3$), 42.4 (*C*(2)H), 63.4, 64.4 (*C*(1)H$_2$, *C*(3)H$_2$), 126.9 (*C*(4′)H), 130.4 (*C*(5′)), 137.5 (*C*(2′)H); *m*/*z* (CI$^+$) 285 ([M+H]$^+$, 100%).

4.1.11. (2RS,3RS)- and (2RS,3SR)-1-(tert-Butyldimethylsilyloxy)-2-[(N(1′)-methylimidazol-5′-yl)methyl]pent-4-en-3-ol ***20***



Dry DMSO (1.7 mL, 22 mmol) was added dropwise to a solution of oxalyl chloride (1.0 mL, 11 mmol) in anhydrous CH_2Cl_2 (25 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 2 min then a solution of alcohol **19** (2.85 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 2 min and stirring was continued for a further 15 min. Et_3N (7.0 mL, 50 mmol) was then added, and the reaction mixture was stirred at −78 °C for a further 5 min, then allowed to warm to rt. Water (50 mL) was then added and the

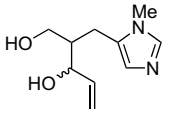
organic layer was separated; the aqueous layer was then extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo to give (*RS*)-3-(*tert*-butyldimethylsilyloxy)-2-[(*N*(1′)-methylimidazol-5′-yl)methyl]-propanal; δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, Si(CH_3)$_2$), 0.88 (9H, s, C(CH_3)$_3$), 2.65–3.05 (3H, m, C(2)*H*, C(5′)CH_2), 3.59 (3H, s, NCH_3), 3.84 (1H, dd, *J* 10.4, 4.1, C(3)H_A), 4.02 (1H, dd, *J* 10.4, 4.6, C(3)H_B), 6.84 (1H, s, C(4′)*H*), 7.47 (1H, s, C(2′)*H*), 9.79 (1H, s, C(1)*H*). The aldehyde was immediately dissolved in THF (50 mL) and the resultant solution was filtered and cooled to 0 °C. Vinylmagnesium bromide (30 mL, 30 mmol, 1.0 M solution in THF) was then added dropwise via syringe. The reaction mixture was allowed to warm to rt and stirring was continued for 30 min before satd aq NH_4Cl (20 mL) and water (5 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **20** (45:55 mixture of diastereoisomers) as a colourless oil, which slowly crystallised upon standing (2.28 g, 74%).

Data for mixture of **20A** and **20B**. Found C, 61.85; H, 10.0; N, 9.0%; $C_{16}H_{30}N_2O_2Si$ requires C, 61.9; H, 9.7; N, 9.0%; *m*/*z* (CI^+) 311 ($[M+H]^+$, 100%).

Data for **20A**. δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, Si(CH_3)$_2$), 0.86 (9H, s, C(CH_3)$_3$), 1.81–1.85 (1H, m, C(2)*H*), 2.61–2.75 (2H, m, C(5′)CH_2), 3.53 (3H, s, NCH_3), 3.58–3.84 (2H, m, C(1)H_2), 4.00 (1H, br s, O*H*), 4.32–4.39 (1H, m, C(3)*H*), 5.13–5.34 (2H, m, C(5)H_2), 5.80–5.93 (1H, m, C(4)*H*), 6.72 (1H, s, C(4′)*H*), 7.31 (1H, s, C(2′)*H*).

Data for **20B**. δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, Si(CH_3)$_2$), 0.86 (9H, s, C(CH_3)$_3$), 1.72–1.76 (1H, m, C(2)*H*), 2.61–2.75 (2H, m, C(5′)CH_2), 3.50 (3H, s, NCH_3), 3.58–3.84 (2H, m, C(1)H_2), 4.00 (1H, br s, O*H*), 4.13–4.18 (1H, m, C(3)*H*), 5.13–5.34 (2H, m, C(5)H_2), 5.80–5.93 (1H, m, C(4)*H*), 6.70 (1H, s, C(4′)*H*), 7.31 (1H, s, C(2′)*H*).

4.1.12. (2RS,3RS)- and (2RS,3SR)-2-[(N(1′)-Methylimidazol-5′-yl)methyl]pent-4-en-1,3-diol **21**



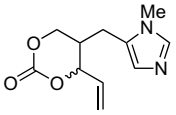
A solution of *O*-TBDMS protected diol **20** (500 mg, 1.61 mmol) in 40% HF/MeCN 95:5 (5 mL) was stirred at rt for 4 h. K_2CO_3 (excess) was then added and stirring was continued until pH 8 was achieved. The mixture was then filtered and the solid residue was washed with MeCN. The combined organics were dried, filtered and concentrated in vacuo. The residue was purified via distillation (Kugelrohr, 1 mmHg, 190 °C) to give **21** (45:55 mixture of diastereoisomers) as a colourless oil (307 mg, 97%).

Data for mixture of **21A** and **21B**. Found C, 61.3; H, 8.4; N, 14.2%. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.2; N, 14.3%; *m*/*z* (CI^+) 223 ($[M+NH_4]^+$, 100%).

Data for **21A**. δ_H (400 MHz, $CDCl_3$) 1.76–1.83 (1H, m, C(2)*H*), 2.59–2.84 (2H, m, C(5′)CH_2), 3.31 (2H, br s, O*H*), 3.57 (3H, s, NCH_3), 3.58–3.95 (2H, m, C(1)H_2), 4.21–4.27 (1H, m, C(3)*H*), 5.21–5.39 (2H, m, C(5)H_2), 5.88–6.01 (1H, m, C(4)*H*), 6.72 (1H, s, C(4′)*H*), 7.36 (1H, s, C(2′)*H*).

Data for **21B**. δ_H (400 MHz, $CDCl_3$) 1.91–1.96 (1H, m, C(2)*H*), 2.59–2.84 (2H, m, C(5′)CH_2), 3.31 (2H, br s, O*H*), 3.54 (3H, s, NCH_3), 3.58–3.95 (2H, m, C(1)H_2), 4.48–4.52 (1H, m, C(3)*H*), 5.21–5.39 (2H, m, C(5)H_2), 5.88–6.01 (1H, m, C(4)*H*), 6.68 (1H, s, C(4′)*H*), 7.34 (1H, s, C(2′)*H*).

4.1.13. (4RS,5RS)- and (4RS,5SR)-4-Vinyl-5-[(N(1′)-methylimidazol-5′-yl)methyl]-1,3-dioxan-2-one **9**



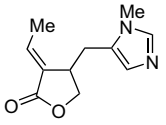
A solution of CDI (226 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of diol **21** (249 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) under a nitrogen atmosphere. The resultant mixture was stirred at rt for 4 h before being concentrated in vacuo. Purification of the residue by flash column chromatography (eluent ^{i}PrOH/CH_2Cl_2, 1:19) gave **9** (45:55 mixture of diastereoisomers) as a colourless oil (254 mg, 90% from **20**).

Data for mixture of **9A** and **9B**. ν_{max} (film) 1740 (C=O); *m*/*z* (CI^+) 223 ($[M+NH_4]^+$, 100%).

Data for **9A**. δ_H (400 MHz, $CDCl_3$) 2.22–2.27 (1H, m, C(5)*H*), 2.53–2.84 (2H, m, C(5′)CH_2), 3.58 (3H, s, NCH_3), 4.26 (1H, dd, *J* 11.2, 4.0, C(6)H_A), 4.44 (1H, dd, *J* 11.2, 5.0, C(6)H_B), 4.73–4.78 (1H, m, C(4)*H*), 5.46–5.58 (2H, m, C(4)CHCH_2), 5.82–5.91 (1H, m, C(4)C*H*CH_2), 6.85 (1H, s, C(4′)*H*), 7.43 (1H, s, C(2′)*H*).

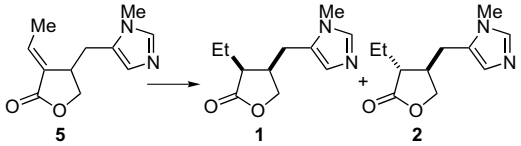
Data for **9B**. δ_H (400 MHz, $CDCl_3$) 2.53–2.84 (3H, m, C(5′)CH_2, C(5)*H*), 3.57 (3H, s, NCH_3), 4.16 (1H, dd, *J* 6.5, 6.0, C(6)H_A), 4.43 (1H, dd, *J* 6.5, 3.7, C(6)H_B), 5.11–5.15 (1H, m, C(4)*H*), 5.46–5.58 (2H, m, C(4)CHCH_2), 5.82–5.91 (1H, m, C(4)C*H*CH_2), 6.84 (1H, s, C(4′)*H*), 7.43 (1H, s, C(2′)*H*).

4.1.14. (RS,E)-3-Ethylidene-4-[(N(1′)-methylimidazol-5′-yl)methyl]tetrahydrofuran-2-one **5**



$Pd(OAc)_2$ (5.2 mg, 23 μmol, 0.03 equiv) and PPh_3 (12.0 mg, 46 μmol, 0.06 equiv) were stirred in THF (3.0 mL) for 5 min. A solution of carbonate **9** (170 mg, 0.765 mmol) in THF (10 mL) was then added and the mixture was stirred under an atmosphere of CO (1 atm). The dark red solution became yellow in colour and a yellow precipitate was formed. After 16 h the solution was filtered, the solid residue was washed with CH_2Cl_2 (2×10 mL), and the combined organics were concentrated in vacuo. The residue was purified by flash column chromatography (eluent MeOH/$CHCl_3$, 3:97) to give **5** as a colourless oil (115 mg, 73%);[10e] ν_{max} (film) 1755 (C=O), 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 1.72 (3H, d, *J* 7.2, CHCH_3), 2.76 (2H, d, *J* 7.9, C(5′)CH_2), 3.32–3.38 (1H, m, C(4)*H*), 3.56 (3H, s, NCH_3), 4.18 (1H, dd, *J* 9.4, 6.8, C(5)H_A), 4.33 (1H, dd, *J* 9.4, 1.6, C(5)H_B), 6.81 (1H, s, C(4′)*H*), 6.87 (1H, app qd, *J* 7.2, 1.8, *CH*CH_3), 7.42 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CHCH_3), 27.6 (C(5′)CH_2), 31.0 (NCH_3), 36.1 (*C*(4)H), 70.0 (*C*(5)H_2), 127.3 (*C*(4′)H), 128.3 (*C*(3)), 129.7 (*C*(5′)), 137.6 (*C*(2′)H), 138.1 (*C*HCH_3), 170.6 (*C*(2)).

4.1.15. Hydrogenation of (RS,E)-3-ethylidene-4-[(N(1′)-methylimidazol-5′-yl)methyl]tetrahydrofuran-2-one **5**

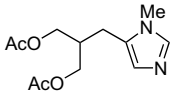


A solution of α-ethylidene lactone (*E*)-**5** (60 mg, 0.29 mmol) and PtO_2 (5 mg) in degassed MeOH (10 mL) was stirred under 50 atm of hydrogen at rt for 24 h. The solution was then filtered through Celite (eluent MeOH) and concentrated in vacuo to give a 72:28 mixture of (±)-pilocarpine **1** and (±)-isopilocarpine **2** (61 mg, quant).

Data for (±)-pilocarpine **1**. δ_H (400 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.4, CH_3CH_2), 1.56–1.63 (1H, m, CH_3CH_A), 1.87–1.93 (1H, m, CH_3CH_B), 2.36–2.84 (4H, m, C(3)*H*, C(4)*H*, C(5′)CH_2), 3.56 (3H, s, NCH_3), 4.08 (1H, dd, *J* 9.4, 2.4, C(5)H_A), 4.19 (1H, dd, *J* 9.4, 5.5, C(5)H_B), 6.79 (1H, s, C(4′)*H*), 7.41 (1H, s, C(2′)*H*).

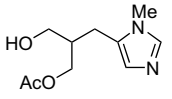
Data for (±)-isopilocarpine **2**. δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.4, CH_3CH_2), 1.71–1.76 (2H, m, CH_3CH_2), 2.26–2.31 (1H, m, C(3)*H*), 2.58–2.88 (3H, m, C(5′)CH_2, C(4)*H*), 3.58 (3H, s, NCH_3), 3.92 (1H, dd, *J* 9.3, 7.1, C(5)H_A), 4.41 (1H, dd, *J* 9.3, 6.6, C(5)H_B), 6.81 (1H, s, C(4′)*H*), 7.42 (1H, s, C(2′)*H*).

4.1.16. 1,3-Diacetoxy-2-[(N(1′)-methylimidazol-5′-yl)-methyl]propane **24**



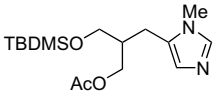
Et_3N (4.9 mL, 35.3 mmol, 3.0 equiv) and Ac_2O (3.3 mL, 35.3 mmol, 3 equiv) were added to a suspension of diol **18** (2.00 g, 11.8 mmol) in anhydrous CH_2Cl_2 (100 mL). A catalytic quantity of DMAP (10 mg) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was then washed with satd aq $NaHCO_3$ (20 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **24** as a pale yellow oil (2.50 g, 84%); Found C, 56.4; H, 7.3; N, 11.0%; $C_{12}H_{18}N_2O_4$ requires C, 56.7; H, 7.1; N, 11.0%; ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 2.07 (6H, s, 2×$COCH_3$), 2.28–2.34 (1H, m, C(2)*H*), 2.66 (2H, d, *J* 7.3, C(5′)CH_2), 3.57 (3H, s, NCH_3), 4.06 (2H, dd, *J* 11.2, 5.3, C(1)H_A, C(3)H_A), 4.13 (2H, dd, *J* 11.2, 5.9, C(1)H_B, C(3)H_B), 6.84 (1H, s, C(4′)*H*), 7.44 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 20.3 (2×$COCH_3$), 22.2 (C(5′)CH_2), 30.8 (NCH_3), 36.5 (*C*(2)H), 63.2 (*C*(1)H_2, *C*(3)H_2), 127.5 (*C*(4′)H), 128.3 (*C*(5′)), 137.9 (*C*(2′)H), 170.7 (2×*C*OCH_3); *m*/*z* (CI^+) 255 ($[M+H]^+$, 100%).

4.1.17. 2-[(N(1′)-Methylimidazol-5′-yl)methyl]-3-acetoxy-propan-1-ol **25**



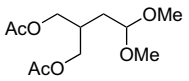
PLE (immobilised on Eupergit C®) (20 mg, 50 units) was added to a solution of diacetate **24** (0.3 g, 1.18 mmol) in pH 7 phosphate buffer (20 mL). The pH of the solution was maintained at its original value (pH 7.5) by the addition of 1.0 M NaOH from an autoburette in a pH stat apparatus. After 6 h, 1.2 mL of the solution had been added (1.05 equiv, 52.5% conversion) and the reaction mixture was filtered. The aqueous solution was extracted with $CHCl_3$ (5×20 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **25** as a pale yellow oil (75 mg, 30%, 20% ee); $[\alpha]_D^{20}$ +1.2 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3300 (O–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 2.09 (3H, s, $COCH_3$), 2.07–2.12 (1H, m, C(2)*H*), 2.58 (1H, dd, *J* 15.4, 6.9, C(5′)CH_A), 2.67 (1H, dd, *J* 15.4, 7.7, C(5′)CH_B), 3.58 (3H, s, NCH_3), 3.55 (1H, dd, *J* 15.4, 5.6, C(1)H_A), 3.64 (1H, dd, *J* 15.4, 4.6, C(1)H_B), 4.15 (1H, dd, *J* 11.3, 6.3, C(3)H_A), 4.20 (1H, dd, *J* 11.3, 5.3, C(3)H_B), 6.81 (1H, s, C(4′)*H*), 7.38 (1H, s, C(2′)*H*).

4.1.18. (RS)-1-Acetoxy-2-[(N(1′)methylimidazol-5′-yl)methyl]-3-(tert-butyldimethylsilyloxy)propane **26**



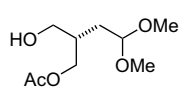
Et_3N (2.2 mL, 15.9 mmol, 1.2 equiv) and Ac_2O (1.5 mL, 15.9 mmol, 1.2 equiv) were added to a solution of *O*-TBDMS ether **19** (3.72 g, 13.1 mmol) in anhydrous CH_2Cl_2 (30 mL). A catalytic quantity of DMAP (5 mg) was added and the reaction mixture was stirred at rt for 16 h. The solution was washed with satd aq $NaHCO_3$ solution (10 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **26** as a colourless oil (4.25 g, 99%); Found C, 58.55; H, 9.3; N, 8.3%. $C_{16}H_{30}N_2O_3Si$ requires C, 58.9; H, 9.3; N, 8.6%; ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, C(CH_3)$_3$), 2.04 (3H, s, $COCH_3$), 2.05–2.09 (1H, m, C(2)*H*), 2.54 (1H, dd, *J* 15.3, 7.8, C(5′)CH_A), 2.70 (1H, dd, *J* 15.3, 6.7, C(5′)CH_B), 3.56 (3H, s, NCH_3), 3.59 (2H, app dd, *J* 4.8, 1.5, C(3)H_2), 4.08 (2H, d, *J* 6.1, C(1)H_2), 6.80 (1H, s, C(4′)*H*), 7.38 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) −5.9 (Si(*C*H_3)$_2$), 18.0 (*C*(CH_3)$_3$), 20.6 (CO*C*H_3), 21.7 (C(5′)CH_2), 25.6 (C(*C*H_3)$_3$), 31.0 (NCH_3), 39.8 (*C*(2)H), 61.5 (*C*(3)H_2), 64.1 (*C*(1)H_2), 127.3 (*C*(4′)H), 129.5 (*C*(5′)), 137.7 (*C*(2′)H), 171.1 (*C*O); *m*/*z* (CI^+) 327 ($[M+H]^+$, 100%).

4.1.19. 1,3-Diacetoxy-2-(2′,2′-dimethoxyethyl)propane **28**



Et_3N (0.56 mL, 4.02 mmol, 2.2 equiv) and DMAP (2 mg) were added to a solution of diol **27** (300 mg, 1.83 mmol) in CH_2Cl_2 (10 mL). Ac_2O (0.38 mL, 4.02 mmol, 2.2 equiv) was then added dropwise via syringe and the reaction mixture was stirred at rt for 1 h. Satd aq $NaHCO_3$ was then added (10 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) gave **28** as a colourless oil (454 mg, 99%); Found C, 53.3; H, 8.4%; $C_{11}H_{20}O_6$ requires C, 53.2; H, 8.12%; ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.66 (2H, dd, *J* 6.5, 6.0, C(1′)H_2), 2.05 (6H, s, 2×$COCH_3$), 2.13–2.20 (1H, m, C(2)*H*), 3.32 (6H, s, CH(OCH_3)$_2$), 4.04 (2H, dd, *J* 11.1, 5.0, C(1)H_A, C(3)H_A), 4.09 (2H, dd, *J* 11.1, 5.3, C(1)H_B, C(3)H_B), 4.48 (1H, t, *J* 5.8, C(2′)*H*)); δ_C (100 MHz, $CDCl_3$) 20.5 ($COCH_3$), 30.9 (*C*(1′)H_2), 33.4 (*C*(2)H), 52.7 (CH(OCH_3)$_2$), 64.0 (C(1)H_2, *C*(3)H_2), 102.6 (*C*(2′)H), 171.1 (2×*C*OCH_3); *m*/*z* (CI^+) 266 ($[M+NH_4]^+$, 100%).

4.1.20. (S)-2-(2′,2′-Dimethoxyethyl)-3-acetoxy-propan-1-ol (S)-**29**

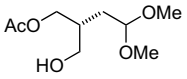


Method A. Diacetate **28** (400 mg, 1.61 mmol) and PPL (40 mg, 532 units, 13.3 units/mg) were sequentially added to pH 7

phosphate buffer (5 mL). The pH of the solution was maintained at its original value (pH 7) by the addition of 1.0 M aq NaOH. After 24 h 1.42 mL of the solution had been added (44% conversion) and the reaction mixture was filtered. The aqueous solution was repeatedly extracted with $CHCl_3$ (10×20 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) gave (*S*)-**29** as a colourless oil (203 mg, 61%, 66% ee); Found C, 52.6; H, 9.0%. $C_9H_{18}O_5$ requires C, 52.4; H, 8.8%; $[\alpha]_D^{20}$ −8.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.68 (2H, t, *J* 5.7, C(1′)H_2), 1.98–2.04 (1H, m, C(2)*H*), 2.07 (3H, s, COCH_3), 2.47 (1H, t, *J* 6.3, O*H*), 3.34 (3H, s, (OCH_3)$_A$), 3.35 (3H, s, (OCH_3)$_B$), 3.58 (2H, t, *J* 5.7, C(1)H_2), 4.08 (1H, dd, *J* 11.2, 6.6, C(3)H_A), 4.15 (1H, dd, *J* 11.2, 5.2, C(3)H_B), 4.50 (1H, t, *J* 5.5, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (COCH_3), 31.0 (*C*(1′)H_2), 36.6 (*C*(2)H), 53.1, 52.6 (2×OCH_3), 62.3 (*C*(1)H_2), 64.6 (*C*(3)H_2), 103.1 (*C*(2′)H), 171.7 (*C*O); *m*/*z* (CI^+) 224 ($[M+NH_4]^+$, 100%).

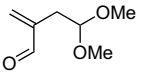
Method B. Diacetate **28** (400 mg, 1.61 mmol) and PFL (10 mg, 415 units) were sequentially added to pH 7 phosphate buffer (5 mL). The pH of the solution was maintained at its original value (pH 7) by the addition of 1.0 M aq NaOH. After 42 h, 1.83 mL of the solution had been added (57% conversion) and the reaction mixture was filtered. The aqueous solution was repeatedly extracted with $CHCl_3$ (10×20 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) gave (*S*)-**29** as a colourless oil (173 mg, 52%, 69% ee); $[\alpha]_D^{20}$ −9.2 (*c* 1.0, $CHCl_3$).

4.1.21. (R)-2-(2′,2′-Dimethoxyethyl)-3-acetoxy-propan-1-ol (R)-29



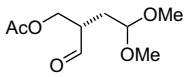
Vinyl acetate (1.73 mL, 18.8 mmol, 1.3 equiv) and PFL (10 mg, 415 units) were sequentially added to a solution of diol **27** (2.38 g, 14.5 mmol) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred for 48 h ar rt. The reaction mixture was then filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) gave (*R*)-**29** as a colourless oil (3.52 g, 98%, >98% ee); $[\alpha]_D^{20}$ +13.6 (*c* 1.0, $CHCl_3$).

4.1.22. 2-Methylene-4,4-dimethoxybutyraldehyde 35



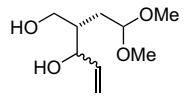
Dry DMSO (0.42 mL, 5.92 mmol) was added dropwise to a solution of oxalyl chloride (0.25 mL, 2.75 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred for 2 min then a solution of monoacetate (*R*)-**29** (515 mg, 2.5 mmol) in CH_2Cl_2 (5 mL) was added and the resultant mixture was stirred for a further 15 min. Et_3N (1.05 mL, 7.53 mmol) was then added and stirring was continued for 5 min and the mixture was allowed to warm to rt. Water (10 mL) was then added and the organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (10 mL), and the combined organic extracts were dried, filtered and concentrated in vacuo to give a 75:25 mixture of **34**:**35**, respectively. Purification of the residue by flash column chromatography (eluent Et_2O) gave **35** as a colourless oil (408 mg, 80%); ν_{max} (film) 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 2.59 (2H, d, *J* 5.7, C(3)H_2), 3.34 (6H, s, CH(OCH_3)$_2$), 4.54 (1H, t, *J* 5.7, C(4)*H*), 6.12 (1H, app s, C(2)CH_A), 6.42 (1H, app s, C(2)CH_B), 9.54 (1H, s, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 31.2 (*C*(3)H_2), 53.0 (CH(OCH_3)$_2$), 102.4 (*C*(4)H), 137.0 (C(2)CH_2), 145.1 (*C*(2)), 194.7 (*C*(1)H); *m*/*z* (CI^+) 143 ($[M+H]^+$, 100%).

4.1.23. (S)-2-(2′,2′-Dimethoxyethyl)-3-acetoxy-propanal 34



Pyridine (1.02 g, 12.6 mmol, 2.6 equiv) was added to a suspension of DMP (2.68 g, 6.30 mmol, 1.3 equiv) in CH_2Cl_2 (25 mL). The resultant solution was stirred at 0 °C for 30 min before a solution of monoacetate (*R*)-**29** (1.00 g, 4.85 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was allowed to warm to rt and stirred for 1 h. Et_2O (50 mL), sodium thiosulphate (11.0 g) and satd aq $NaHCO_3$ (40 mL) were then added sequentially. The resultant mixture was stirred for 5 min then the organic layer was separated. The aqueous layer was extracted with Et_2O (2×40 mL), and the combined organic extracts were washed with satd aq $NaHCO_3$ (40 mL) and satd aq $CuSO_4$ (4×20 mL), then dried, filtered and concentrated in vacuo to give **34** as an unstable colourless oil, which was used directly in the next step (950 mg, 96%); δ_H (400 MHz, $CDCl_3$) 1.77–1.81 (1H, m, C(3)H_A), 2.05 (3H, s, COCH_3), 2.00–2.09 (1H, m, C(3)H_B), 2.73–2.81 (1H, m, C(2)*H*), 3.33 (3H, s, CH(OCH_3)$_A$), 3.34 (3H, s, CH(OCH_3)$_B$), 4.33 (2H, d, *J* 5.7, C(1′)H_2), 4.46 (1H, t, *J* 5.5, C(2′)*H*), 9.68 (1H, d, *J* 1.6, C*H*O).

4.1.24. (2S,3R)- and (2S,3S)-1-Acetoxy-2-(2′,2′-dimethoxyethyl)pent-4-en-3-ol 33



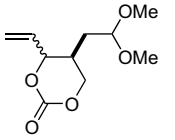
A solution of vinylmagnesium bromide (1.0 M in THF, 14.5 mL, 3.0 equiv) was added dropwise via syringe to a solution of aldehyde **34** (950 mg, 4.65 mmol) in THF (20 mL) at 0 °C. The resultant mixture was then allowed to warm to rt and was stirred for 10 min. Satd aq NH_4Cl (15 mL) and water (5 mL) were then sequentially added. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4×40 mL), then the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) afforded diol **33** (50:50 mixture of diastereoisomers) as a colourless oil (738 mg, 80% from (*R*)-**29**).

Data for mixture of **33A** and **33B**. Found C, 56.5; H, 9.8%; $C_9H_{18}O_4$ requires C, 56.8; H, 9.5%; *m*/*z* (CI^+) 144 ($[M-46]^+$, 100%).

Data for **33A**. δ_H (400 MHz, $CDCl_3$) 1.69–1.91 (3H, m, C(2)*H*, C(1′)H_2), 2.66–2.78 (2H, m, O*H*), 3.35 (3H, s, (OCH_3)$_A$), 3.37 (3H, s, (OCH_3)$_B$), 3.90–3.62 (2H, m, C(1)H_2), 4.20–4.25 (1H, m, C(3)*H*), 4.55–4.49 (1H, m, C(2′)*H*), 5.37–5.20 (2H, m, C(5)H_2), 5.97–5.84 (1H, m, C(4)*H*).

Data for **33B**. δ_H (400 MHz, $CDCl_3$) 1.69–1.91 (3H, m, C(2)*H*, C(1′)H_2), 2.66–2.78 (2H, m, O*H*), 3.36 (3H, s, (OCH_3)$_A$), 3.34 (3H, s, (OCH_3)$_B$), 3.90–3.62 (2H, m, C(1)H_2), 4.32–4.39 (1H, m, C(3)*H*), 4.55–4.49 (1H, m, C(2′)*H*), 5.37–5.20 (2H, m, C(5)H_2), 5.97–5.84 (1H, m, C(4)*H*).

4.1.25. (4R,5S)- and (4S,5S)-4-Vinyl-5-(2′,2′-dimethoxyethyl)-1,3-dioxan-2-one 32



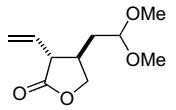
A solution of CDI (1.02 g, 6.31 mmol, 1.2 equiv) in CH_2Cl_2 (30 mL) was added dropwise over the course of 3 h to a solution of diol **33** (1.00 g, 5.26 mmol) in CH_2Cl_2 (30 mL) at rt. The resultant solution was stirred for 1 h at rt then water (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O) gave **32** (50:50 mixture of diastereoisomers) as a colourless oil (1.14 g, 90%).

Data for mixture of **32A** and **32B**. Found C, 55.4; H, 7.8%; $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.5%; $[\alpha]_D^{20}$ −2.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O); *m*/*z* (CI^+) 234 ($[M+NH_4]^+$, 100%).

Data for **32A**. δ_H (400 MHz, $CDCl_3$) 1.54–1.85 (2H, m, C(1′)H_2), 2.11–2.19 (1H, m, C(5)*H*), 3.35 (6H, s, (OCH_3)$_2$), 4.09–4.55 (3H, m, C(6)H_2, C(2′)*H*), 4.63 (1H, m, C(4)*H*), 5.41–5.50 (2H, m, C(4)CH=CH_2), 5.76–5.88 (1H, m, C(4)C*H*=CH_2).

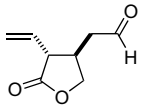
Data for **32B**. δ_H (400 MHz, $CDCl_3$) 1.54–1.85 (2H, m, C(1′)H_2), 2.44–2.49 (1H, m, C(5)*H*), 3.33 (3H, s, (OCH_3)$_A$), 3.34 (3H, s, (OCH_3)$_B$), 4.09–4.55 (3H, m, C(6)H_2, C(2′)*H*), 4.83 (1H, m, C(4)*H*), 5.41–5.50 (2H, m, C(4)CH=CH_2), 5.76–5.88 (1H, m, C(4)C*H*=CH_2).

4.1.26. (2R,3R)-3-Vinyl-4-(2′,2′-dimethoxyethyl)tetrahydrofuran-2-one ***36***



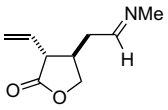
A solution of carbonate **32** (1.50 g, 6.94 mmol) in degassed THF (15 mL) was added to a solution of $Pd(OAc)_2$ (46 mg, 205 μmol, 3 mol %) and PPh_3 (109 mg, 416 μmol, 6 mol %) in degassed THF (20 mL) at rt. The resultant mixture was stirred under CO (1 atm), the yellow mixture rapidly turned dark red, and after 16 h the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography (eluent 30–40 petrol/Et_2O, 1:3) gave **36** as a colourless oil (1.28 g, 92%, >98% de, >98% ee); Found C, 60.1; H, 8.4%; $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%; $[\alpha]_D^{20}$ +24.3 (*c* 1.0, $CHCl_3$); ν_{max} 1760 (C=O); δ_H (400 MHz, $CDCl_3$) 1.70 (1H, ddd, *J* 14.1, 9.7, 6.0, C(1′)H_A), 1.96 (1H, ddd, *J* 14.1, 4.4, 4.4, C(1′)H_B), 2.51–2.56 (1H, m, C(4)*H*), 2.82–2.89 (1H, m, C(3)*H*), 3.33 (3H, s, CH(OCH_3)$_A$), 3.35 (3H, s, CH(OCH_3)$_B$), 3.91 (1H, dd, *J* 9.5, 9.5, C(5)H_A), 4.40 (1H, dd, *J* 6.0, 4.4, C(2′)*H*), 4.50 (1H, dd, *J* 9.5, 7.6, C(5)H_B), 5.30 (1H, app d, *J* 17.2, C(3)CH=C$H_A$$H_B$), 5.36 (1H, d, *J* 10.3, C(3)CH=C$H_A$$H_B$), 5.83–5.72 (1H, ddd, *J* 17.2, 10.3, 7.7, C(3)C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 34.5 (*C*(1′)H_2), 38.1 (*C*(4)H), 49.9 (*C*(3)H), 53.9, 53.0 (CH(OCH_3)$_2$), 72.1 (*C*(5)H_2), 103.1 (*C*H(OMe)$_2$), 120.4 (C(3)CH=CH_2), 132.0 (C(3)CH=CH_2), 176.7 (*C*(2)); *m*/*z* (CI^+) 218 ($[M+NH_4]^+$, 100%).

4.1.27. (2R,3R)-3-Vinyl-4-(2′-oxoethyl)tetrahydrofuran-2-one ***40***



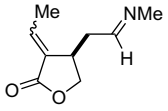
A solution of lactone **36** (500 mg, 2.50 mmol) in acetone (30 mL) containing a catalytic quantity of PPTS was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and was concentrated in vacuo. The residue was redissolved in acetone (30 mL) and heated at reflux for a further 24 h. The reaction mixture was then allowed to cool to rt and was concentrated in vacuo. Purification of the residue by flash column chromatography (eluent Et_2O/CH_2Cl_2, 1:1) gave **40** as a colourless oil, which was used immediately in the next step (358 mg, 93%, >98% de); ν_{max} (film) 1765 (C=O), 1715 (C=O); δ_H (400 MHz, $CDCl_3$) 2.55–2.96 (4H, m, C(3)*H*, C(4)*H*, C(1′)H_2), 3.85 (1H, dd, *J* 9.1, 8.9, C(5)H_A), 4.66 (1H, dd, *J* 9.1, 6.9, C(5)H_B), 5.28 (1H, d, *J* 17.1, C(3)CH=C$H_A$$H_B$), 5.36 (1H, d, *J* 10.3, C(3)CH=C$H_A$$H_B$), 5.71–5.83 (1H, m, C(3)HC*H*=CH_2), 9.85 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 35.8 (*C*(4)H), 45.1 (C(1′)H_2), 49.0 (*C*(3)H), 71.0 (*C*(5)H_2), 120.7 (C(3)CH=*C*H_2), 131.3 (C(3)*C*H=CH_2), 176.2 (*C*(2)), 199.7 (CHO); *m*/*z* (CI^+) 172 ($[M+NH_4]^+$, 100%).

4.1.28. (2R,3R)-3-Vinyl-4-[2′-(N-methylimino)ethyl]-tetrahydrofuran-2-one



Dry methylamine gas was bubbled into a solution of aldehyde **40** (100 mg, 0.65 mmol) in DME (10 mL) at 0 °C in the presence of 4 Å molecular sieves for 2 min. The reaction mixture was stirred for 5 min then filtered and concentrated in vacuo to give (2*R*,3*R*)-3-vinyl-4-[2′-(*N*-methylimino)ethyl]tetrahydrofuran-2-one as a pale yellow oil (108 mg, quant, >98% de); δ_H (400 MHz, $CDCl_3$) 2.33–2.98 (4H, m, C(3)*H*, C(4)*H*, C(1′)H_2), 3.28 (3H, d, *J* 1.5, NCH_3), 3.91 (1H, app t, *J* 9.1, C(5)H_A), 4.59 (1H, dd, *J* 7.5, 9.2, C(5)H_B), 5.28–5.35 (2H, m, C(3)CH=CH_2), 5.74–5.83 (1H, m, C(3)C*H*=CH_2), 7.66–7.72 (1H, m, C(2′)*H*).

4.1.29. (R,E)-3-Ethylidene-4-[2′-(N-methylimino)ethyl]-tetrahydrofuran-2-one ***42***

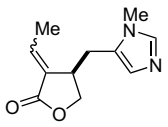


Dry methylamine gas was bubbled into a solution of aldehyde **40** (100 mg, 0.65 mmol) in DME (10 mL) at 0 °C in the presence of 4 Å molecular sieves for 2 min. The resultant mixture was stirred for 16 h then filtered and concentrated in vacuo to give **42** (variable mixtures of diastereoisomers) as a pale yellow oil (108 mg, quant).

Data for **42A**. δ_H (400 MHz, $CDCl_3$) 1.91 (3H, dd, *J* 7.3, 1.1, C(3)=CHCH_3), 2.42–2.52 (2H, m, C(1′)H_2), 3.30 (3H, d, *J* 1.6, NCH_3), 3.51–3.58 (1H, m, C(4)*H*), 4.15 (1H, dd, *J* 9.5, 7.4, C(5)H_A), 4.41 (1H, dd, *J* 9.5, 2.4, C(5)H_B), 6.84 (1H, qd, *J* 7.3, 2.1, C(3)C*H*), 7.70–7.74 (1H, m, C(2′)*H*).

Data for **42B**. δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.21 (3H, dd, *J* 7.3, 2.2, C(3)=CHCH_3), 3.36 (3H, d, *J* 2.2, NCH_3), 6.31 (1H, m, C*H*CH_3), 7.71 (1H, m, C*H*NMe).

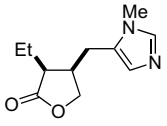
4.1.30. (R,E)- and (R,Z)-3-Ethylidene-4-[(N(1′)-methylimidazol-5′-yl)methyl]tetrahydrofuran-2-one ***5***



Dry methylamine gas was bubbled into a solution of imine **42** (200 mg, 1.30 mmol) in DME (20 mL) at 0 °C in the presence of 4 Å molecular sieves for 2 min, the reaction mixture was then allowed to stir for 30 min at rt. TsMIC (380 mg, 1.5 equiv) was added and the solution was slowly warmed to 80 °C and stirred for 24 h. The solution was decanted from the molecular sieves (which were washed with further DME) and concentrated in vacuo. Satd aq

$NaHCO_3$ (5 mL) was added and the mixture was extracted with $CHCl_3$ (4×20 mL), the combined organic extracts were dried, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 1:19) gave **5** [83:17 mixture of (*E*):(*Z*) isomers] as a pale brown oil (186 mg, 70%).

*4.1.31. (3S,4R)-3-Ethyl-4-[(N(1′)-methylimidazol-5′-yl)methyl]-γ-butyrolactone **1** [(+)-pilocarpine **1**]*



Hydrogenation. A mixture of α-ethylidene lactone **5** (150 mg, 0.73 mmol, 83:17 (*E*):(*Z*) mixture) and PtO_2 (10 mg) in degassed MeOH (5 mL) was stirred under hydrogen (3 atm) for 24 h. The reaction mixture was then filtered through Celite (eluent MeOH) and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography (eluent MeOH/$CHCl_3$, 3:97) gave a 72:28 mixture of (+)-pilocarpine **1** and (+)-isopilocarpine **1** as a colourless oil (150 mg, quant).

Recrystallisation of hydrochloride salt. A 72:28 mixture of (+)-pilocarpine **1** and (+)-isopilocarpine **1** (450 mg, 2.16 mmol) was dissolved in EtOH (1.0 mL) and the solution was cooled to 0 °C. 12 M aq HCl (0.18 μL, 1.0 equiv) in EtOH (0.5 mL) was then added dropwise and the resultant mixture was refrigerated for 16 h. The crystals of pilocarpine hydrochloride **1**·HCl were removed by filtration and twice recrystallised from EtOH to give pure (+)-pilocarpine hydrochloride **1**·HCl as a white crystalline solid (122 mg, 23%); mp 201–202 °C (lit.[3a] mp 204–205 °C); $[\alpha]_D^{20}$ +90.1 (*c* 2.0, H_2O) {lit.,[10j] $[\alpha]_D^{20}$ +88 (*c* 2.0, H_2O)}.

Recrystallisation of nitrate salt. A 72:28 mixture of (+)-pilocarpine **1** and (+)-isopilocarpine **1** (450 mg, 2.16 mmol) was dissolved in EtOH (1.0 mL) and the solution was cooled to 0 °C. Aq HNO_3 (6 M, 0.36 mL, 1.0 equiv) in EtOH (0.5 mL) was then added dropwise and the resultant mixture was refrigerated for 16 h. The crystals of pilocarpine nitrate **1**·HNO_3 were removed by filtration and twice recrystallised from EtOH to give pure (+)-pilocarpine nitrate **1**·HNO_3 as a white crystalline solid (410 mg, 70%); mp 177–178 °C (lit.[41] mp 178 °C); $[\alpha]_D^{20}$ +83.1 (*c* 1.0, H_2O) {lit.[10b] $[\alpha]_D^{20}$ +81.3 (*c* 1.0, H_2O)}.

*4.1.31.1. X-ray crystal structure determination for **1**·HNO_3*. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[42]

X-ray crystal structure data for **1**·HNO_3 [$C_{11}H_{17}N_3O_5$]: M=271.27, monoclinic, space group $P\ 2_1$, a=6.0473(2) Å, b=9.5320(4) Å, c=11.2321(5) Å, β=92.1417(19)°, V=647.00(5) Å^3, Z=2, μ=0.111 mm^{-1}, colourless plate, crystal dimensions=0.05×0.05×0.2 mm^3. A total of 1561 unique reflections were measured for $5<\theta<27$ and 1561 reflections were used in the refinement. The final parameters were wR_2=0.089 and R_1=0.063 [$I>-3.0\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 722773. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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19. Treatment of **9** under these conditions resulted in a change of colour of the solution from deep red to yellow, followed by the formation of a light brown precipitate.

20. The formation of (*E*)-α-ethylidene lactone **5** presumably arises from the isomerisation of the initially formed α-vinyl lactone **8**, under the influence of the basic imidazole ring.
21. Since hydrogenation of exclusively (*E*)-**5** gave a 72:28 mixture of pilocarpine **1** and isopilocarpine **2** in quantitative yield, and hydrogenation of an 88:12 mixture of (*E*)- and (*Z*)-α-ethylidene lactones **5** (obtained from our first generation racemic synthesis) produced a 70:30 mixture of pilocarpine **1** and isopilocarpine **2** in quantitative yield; this indicates that the double bond geometry within **5** does not have a major impact on the product distributions obtained.
22. An authentic sample of (+)-pilocarpine **1** was kindly supplied by Macfarlan Smith Ltd., Edinburgh; base-catalysed epimerisation of this sample also provided a diastereoisomerically pure sample of (+)-isopilocarpine **2**.
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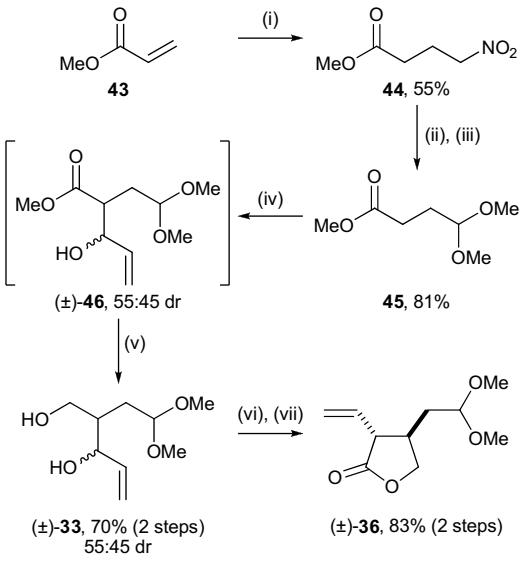
31. Monoacetate **29** was found to slowly racemise upon standing at room temperature, for example, after four months the ee of a sample had dropped to 92%. However, upon treatment with Et_3N complete racemisation of monoacetate **29** was observed after only 48 h.
32. The diastereoisomeric purity of **36** was determined by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture and pure product.
33. The ee of lactone **36** was determined by ^{1}H NMR spectroscopic analysis in the presence of (−)-(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol and comparison with an authentic racemic sample, prepared according to the following procedure.



Reagents and conditions: (i) $MeNO_2$, NaOH, CH_2Cl_2, H_2O, rt; (ii) NaOMe, MeOH; (iii) H_2SO_4, MeOH; (iv) LDA, THF, −78 °C then acrolein; (v) $LiAlH_4$, THF, rt; (vi) CDI, CH_2Cl_2, rt; (vii) $Pd(OAc)_2(PPh_3)_2$, CO (1 atm), 20 °C, 17 h.

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40. A range of alternative heterogeneous and homogeneous catalysts (e.g., Pd/C, $Pd(OH)_2$/C, Rh/C, Ru/C, Ni_2B, Wilkinson's catalyst [$Rh(PPh_3)_3Cl$], $RuCl_2(PPh_3)_3$ and Crabtree's iridium catalyst), were screened in different solvents (e.g., MeOH, MeOH/AcOH or EtOAc) at various temperatures. The optimum ratio of pilocarpine **1** to isopilocarpine **2** was obtained with PtO_2 at 50 atm pressure in MeOH, giving a 72:28 mixture of **1**:**2**, respectively. Interestingly Pearlman's catalyst showed a small preference for formation of isopilocarpine **2** (56:44 mixture).
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