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Syntheses of the racemic jaborandi alkaloids pilocarpine, isopilocarpine and pilosinine

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ABSTRACT

The synthesis of racemic pilocarpine has been achieved in high overall yield. Two alternative approaches for the formation of the γ-butyrolactone ring are described: the first involves a palladium-catalysed carbonylation reaction of a homopropargylic alcohol, whereas the second involves the palladium-catalysed decarboxylation/carbonylation of a 1,3-dioxan-2-one. Subsequent hydrogenation of an α-ethylidene lactone introduces the C(3)-stereochemistry to give a mixture of pilocarpine and isopilocarpine, its C(3)-epimer, which are readily separable by recrystallisation of their hydrochloride or nitrate salts. A concise synthesis of racemic pilosinine is also disclosed (37% overall yield in six steps); this also represents an alternative, formal synthesis of racemic pilocarpine.

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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 agent.[7] 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 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]

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 is yet to be reported. The facile epimerisation of either pilocarpine **1** or its precursors to the more stable C(3)-epimeric series makes 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** (Scheme 1).

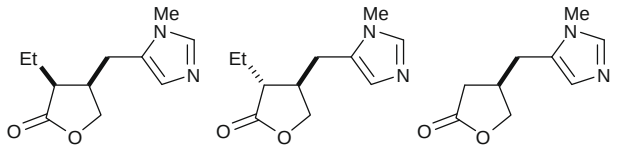

Figure 1. The jaborandi alkaloids (+)-pilocarpine **1**, (+)-isopilocarpine **2** and (+)-pilosinine **3**.

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 preliminary investigations within the racemic series.

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-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).

Following our first strategy for the synthesis of pilocarpine **1**, alkylation of dimethyl malonate **10** with *N*(1)-methyl-5-(chloromethyl)-1*H*-imidazole **11**[14] gave diester **12** in 83% isolated yield.

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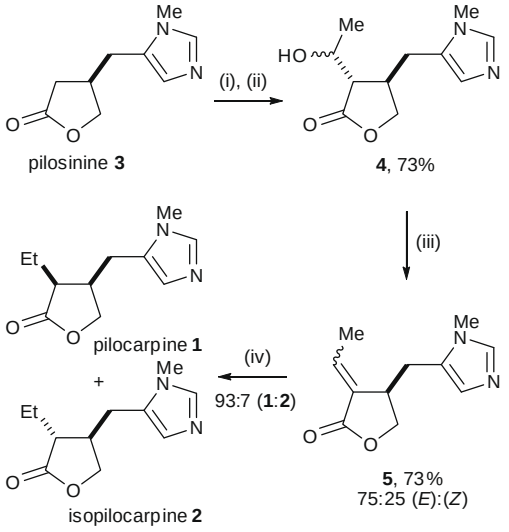
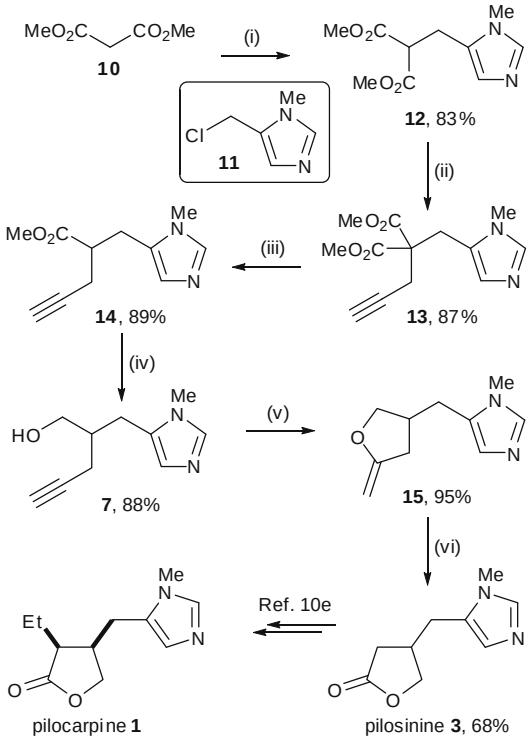


Scheme 1. Reagents and conditions: (i) KO^{t}Bu, EtOAc, ^{t}BuOH; (ii) PtO_2, H_2 (50 atm), MeOH, rt; (iii) Ac_2O, AcOH, 70–130 °C; (iv) PtO_2, H_2 (50 atm), MeOH, rt.



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.

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% yield after chromatographic purification. The demethoxycarbonylation of **13** in the presence of 3.0 equiv of imidazole in DMF at 150 °C for 4 hours gave **14** in 89% yield. Subsequent reduction of methyl ester **14** with $LiAlH_4$ afforded bishomopropargylic alcohol **7** in 88% yield. Attempted base-catalysed isomerisation[15] of the triple bond within **7** with KO^{t}Bu in ^{t}BuOH at reflux for 3 hours 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 acidic aqueous work-up or silica gel chromatography; however, chromatographic purification on alumina enabled isolation of **15** in 95% yield. The formation of vinyl ether **15** was not entirely unexpected as the base-catalysed cyclisation of simple acetylenic alcohols has been previously reported,[16] although more forcing conditions employing stronger bases (e.g. $NaNH_2$) are generally required for unactivated acetylenes.[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. Attempted oxidation of **15** with either PDC,[18] ozone[19] or RuO_4[20] resulted in the oxidative cleavage of the imidazole ring. Oxidation of **15** with *m*CPBA,[21] however, gave the desired alkaloid, racemic pilosinine **3**, in 68% yield (37% overall yield in six steps); this also represents a formal synthesis of pilocarpine **1** (Scheme 2).[10e]

As bishomopropargylic alcohol **7** was found to be prone to cyclisation, 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, conversion to the corresponding *O*-TBDMS ether **16** was achieved by treatment of **7** with TBDMSCl and Et_3N to give **16** in 92% yield. Treatment of **16** with KO^{t}Bu in ^{t}BuOH at reflux for 24 h gave the isomerised product **17** in 79% isolated yield, and removal of the *O*-silyl protecting group was achieved with HF in MeCN to afford alcohol **6**, isolated as the hydrochloride salt, in 92% yield. Attempted palladium-catalysed carbonylation of **6**·HCl gave the desired α-ethylidene lactone **5**, albeit in only 10% isolated yield

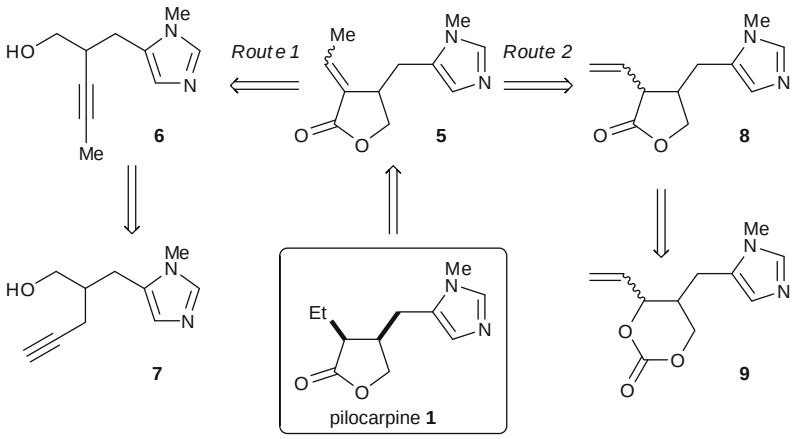
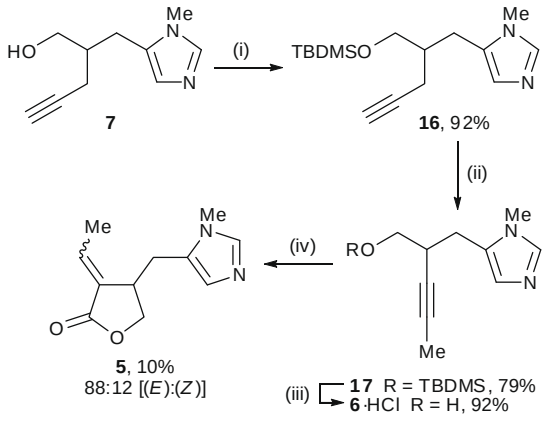
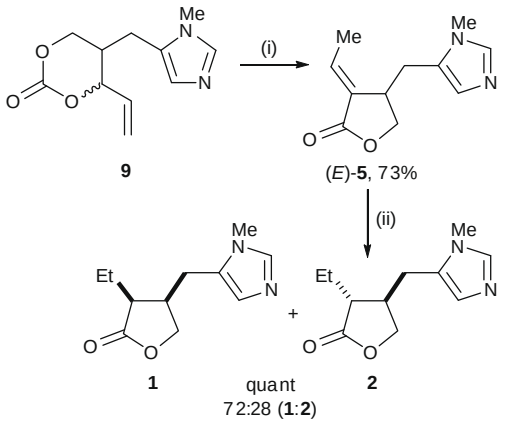


Figure 2. Retrosynthetic analysis of pilocarpine **1**.



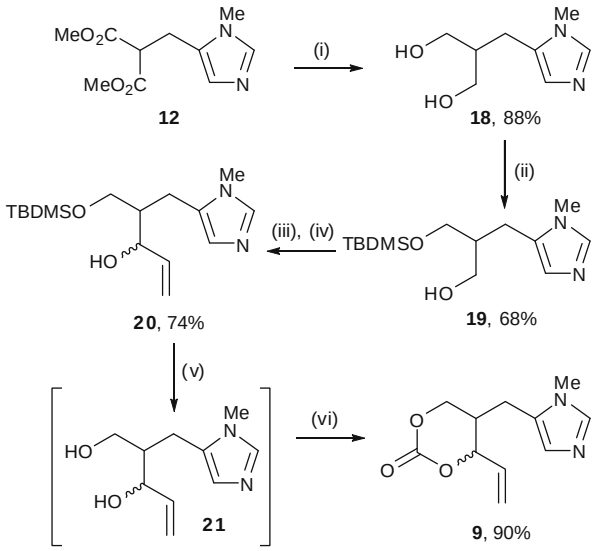
Scheme 3. Reagents and conditions: (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt; (ii) KO^{t}Bu, ^{t}BuOH, reflux, 24 h; (iii) HF, MeCN, rt then HCl; (iv) $PdCl_2(PPh_3)_2$ (7 mol %), $SnCl_2$, CO (1 atm), 110 °C, DMF, 5 h then $NaHCO_3$.



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.

after flash column chromatography, as an 88:12 ratio of (*E*):(*Z*) isomers (Scheme 3).

The requirement for protecting group manipulation and the low yield of the subsequent carbonylation step in our first generation synthesis resulted in an unacceptably low overall yield of α-ethylidene lactone **5**. Thus, the second of our synthetic strategies was 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. Monosilylation of **18** was achieved via deprotonation with 1.0 equiv of NaH followed by the addition of TBDMSCl to give monosiylated diol **19** in 68% yield. Monosilylation of **18** was achieved via deprotonation with 1.0 equiv of NaH followed by the addition of TBDMSCl to give monosilylated diol **19** in 68% yield. Oxidation of the free hydroxy group within **19** under Swern conditions[22] gave the corresponding aldehyde which was found to be unstable upon attempted purification by either column chromatography or distillation, and was therefore treated immediately with vinylmagnesium bromide to give **20** as a 50:50 mixture of diastereoisomers in 74% yield over the two steps. Removal of the *O*-TBDMS protecting group was accomplished with HF in MeCN[23] 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**, which was found to be susceptible to ring-opening upon aqueous work-up or chromatographic purification with unhindered alcohols as eluent. However, column chromatography employing 5% ^{i}PrOH in CH_2Cl_2 as the eluent enabled isolation of **9** in 90% yield as a 50:50 mixture of diastereoisomers (Scheme 4).



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.

With 1,3-dioxan-2-one **9** in hand the palladium-catalysed decarboxylation/carbonylation protocol for formation of the γ-butyrolactone ring was attempted. 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[24] gave exclusively (*E*)-α-ethylidene lactone **5** in 73% isolated yield.[25] Subsequent hydrogenation of **5** gave a 72:28 mixture of pilocarpine **1** and isopilocarpine **2** in quantitative yield (Scheme 5).[26] The two alkaloids are readily distinguishable from their ^{1}H NMR spectra,[27] 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 the synthetic material prepared above was identical in all respects to that of a sample (72:28 mixture) prepared from authentic samples of (+)-pilocarpine **1** and (+)-isopilocarpine **2**.[28] (+)-Pilocarpine **1** and (+)-isopilocarpine **2** are readily separated via recrystallisation of either their hydrochloride or nitrate salts.

In conclusion, the total synthesis of the racemic jaborandi alkaloid pilosinine was achieved in 37% overall yield in six steps from commercially available dimethyl malonate and *N*(1)-methyl-5-(chloromethyl)-1*H*-imidazole. In addition, and from the same starting materials, a high yielding synthesis of racemic pilocarpine has been developed in which Link and Bernauer's α-ethylidene lactone intermediate was obtained in 24% overall yield in eight steps. Hydrogenation of the α-ethylidene lactone readily gives access to mixtures of pilocarpine and isopilocarpine which can be separated via recrystallisation of their hydrochloride or nitrate salts. This synthetic strategy is practical, high yielding and potentially applicable to other members of the jaborandi alkaloid family and their derivatives. The total synthesis of enantio- and diastereoisomerically pure pilocarpine will be reported in due course.

Acknowledgement

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24. 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.
25. 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.
26. 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 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.
27. 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*).
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*).
28. 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**.