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ASYMMETRIC SYNTHESIS OF (+)-PILOSININE: A FORMAL SYNTHESIS OF (+)-PILOCARPINE

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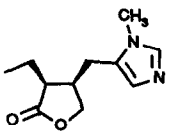
Summary: An efficient asymmetric synthesis of enantiomerically pure (+)-pilosinine 4 has been achieved in 6 steps from a known chiral bromoacyloxazolidinone.

The imidazole alkaloid (+)-pilocarpine 1 and analogs have been the subject of considerable study of late due to their therapeutic potential as muscarinic agonists for the symptomatic treatment of Alzheimer's Disease.[1] The thiolactone 2[2] and oxazolidinone 3[3] are particularly interesting pilocarpine isosteres.



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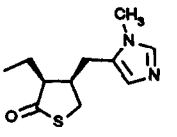

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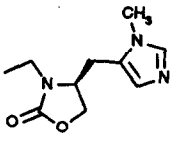

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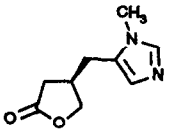

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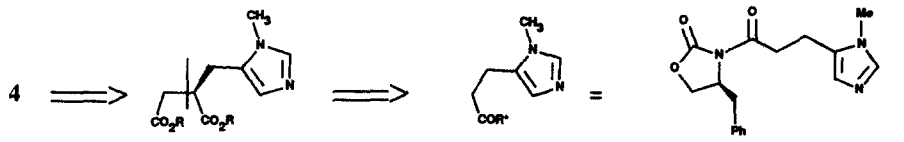
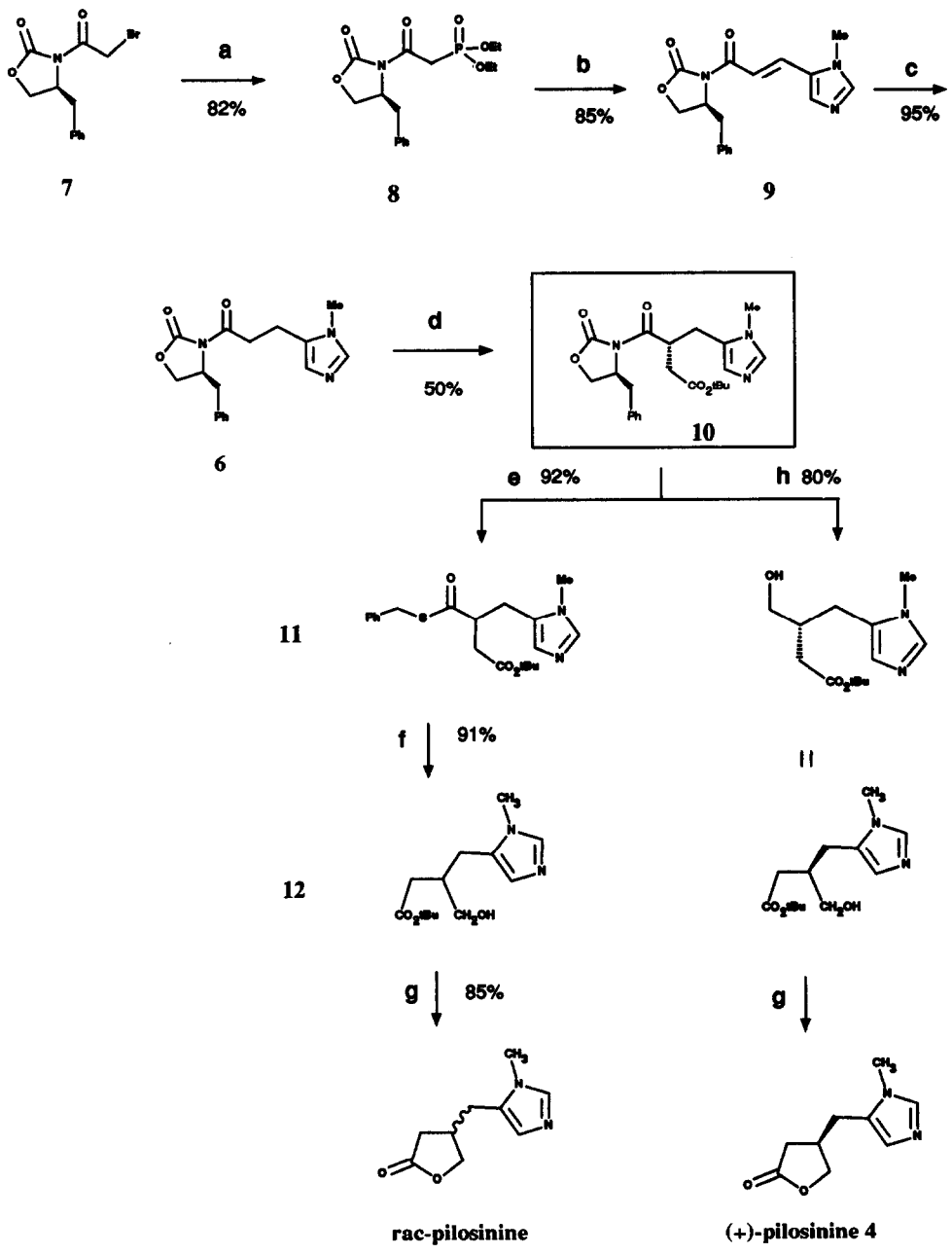
Several racemic syntheses[4] and two asymmetric syntheses[5ab] using chiral starting materials (L-histidine, D-2-aminobutyric acid) of pilocarpine have been reported. The first reported asymmetric synthesis[5a] gave a low optical yield and the later synthesis[5b] is somewhat tedious. We were interested in a practical asymmetric synthesis of natural (+)-pilocarpine and focussed on C4 as the important chiral center since the epimerizable center at C3 has been previously been a source of difficulty.[5ab] As a result our immediate target of interest was (+)-pilosinine 4 from which (+)-pilocarpine has been prepared via a simple four step sequence.[6] Simple retrosynthetic analysis (Scheme 1) of (+)-pilosinine leads to an imidazoylmethyl--2-substituted succinic ester[7] in which the ester functionalities must be differentiable. Further disconnection of acetate affords the key intermediate, imidazole-proprionate 5. A straightforward strategy results from this analysis: perform an asymmetric alkylation of acetate on a derivative of 5 bearing a suitable chiral auxiliary. The well established Evans chiral oxazolidinone auxiliary[8] was chosen. A report that acyloxazolidinones of the Evans type could be reduced with calcium borohydride[9] served as a pretext for the crucial ester differentiation mentioned above. To obtain the desired chirality in the alkylation based on precedent, an oxazolidinone auxiliary derived from an L-amino acid would be required. Since the phenylalanine derived oxazolidinone auxiliary was available to us in large quantities, 6 became the initial synthetic target.



Scheme 1

Typically, Evans acyloxazolidinones are prepared by coupling the lithium salt of the auxiliary oxazolidinone to an acid chloride. This methodology is not suitable for the preparation of **6** since the imidazole and acid chloride functionalities are not compatible. To solve this problem we prepared the phosphonate **8** (Scheme 2) which greatly expands the substrates for which acyloxazolidinones can be prepared. Arbusov reaction of the known bromo-acetyloxazolidinone **7**[10] with triethylphosphite afforded **8** in 85% yield ($[\alpha]_D^{20}$= +55.2 c= 1.2 in CH_2Cl_2). Wadsworth-Emmons reaction of **8** with 1-methylimidazole-5--carboxaldehyde[11] gave the E-olefin **9** which was converted by catalytic hydrogenation to **6** (hydrogen fumarate: mp 149-151°C, $[\alpha]_D^{20}$= +75.3 c= 0.52 in H_2O) in 81% overall yield. Having **6**, available in large quantities by this facile route, in hand, the stage was set for the key alkylation reaction. Deprotonation of **6** was performed under carefully controlled conditions[12] by adding 1.1 equivalents of sodium hexamethyldisilazide to a 0.025M THF solution of **6** at -78°C over 3 hours. Bromoacetic acid t-butyl-ester (1.0 Eq.) was added and the mixture was kept at -60°C for 3h and then allowed to warm slowly to 0°C. Under these conditions **10** (mp 152-155°C, $[\alpha]_D^{20}$= +96.5, c= 1.1 in CH_2Cl_2) was received as the exclusive alkylation product in 50% yield after chromatographic purification. It remained to convert **10** to (+)-pilosinine **1** and verify that the absolute chirality was as postulated. A selective reduction of the acyloxazoldinone function of **10** in the presence of the t-butyl ester function was required, and it was also clear that a mild or carefully controlled reduction condition would be necessary. Many reduction conditions were tested on **10** which resulted in more or less complicated reaction mixtures in which the hydroxy t-butyl ester **12** and/or pilosinine were formed in small amounts at best.[13] The aforementioned reduction protocol[11] using calcium borohydride in a THF-ethanol mixture which has been effective in the reduction of Evans acyloxazolidinones appeared very attractive but gave consistently poor results with substrate **10**. An alternative two step protocol has been described for the reduction of highly hindered Evans acyloxazolidinones which tend to pose problems under standard reduction conditions.[14] First the acyloxazolidinone function is converted to a thiobenzyl ester by treatment with lithium benzylmercaptide; the resulting thioester can then be reduced either *in situ* or after isolation. Conversion of **10** to the thiobenzyl ester **11** proceeded cleanly very, and reduction of the thioester of **11** with sodium borohydride[15] in ethanol to give the hydroxy-t-butyl ester **12** was also unproblematic. Compound **12** showed no tendency to lactonize spontaneously and lactonized only slowly in 2N HCl-THF. In 95:5 trifluoroacetic acid-water the high yield lactonization of **12** to pilosinine was rapid. Somewhat to our surprise the pilosinine prepared via this route was of very low optical purity. Since the optical rotation of **11** was also extremely small, we assume that epimerization occurs during the preparation of this thioester.



Scheme 2

a. $P(OEt)_3$ toluene reflux b. NaH THF 0°C, 1-methyl-imidazole-5-carboxaldehyde c. H_2 10% Pd/C MeOH d. $NaN(SiMe_3)_2$ THF -78°C, $BrCH_2CO_2tBu$ e. 2.0 Eq. $PhCH_2SH$/1.5 Eq. BuLi, THF -10°C f. $NaBH_4$-EtOH g. CF_3CO_2H-H_2O 95:5 0°C h. excess $Zn(BH_4)_2$ Et_2O room temperature 5 days

At this point with **12** in hand as a reference material, our efforts were redirected toward simple one step reduction of **10**. A mild chelating reducing agent was anticipated to hold the most promise. Indeed, the reduction of **10** with an excess of zinc borohydride in ether at room temperature proceeded slowly (5 days), but very cleanly to give **12** and the starting chiral auxiliary in excellent yield. Direct conversion of **12** to (+)-pilosinine was performed with trifluoroacetic acid as described above. The optical rotation of the (+)-pilosinine ($[\alpha]_D^{20}$= +25.5, c= 1.6 in CH_2Cl_2)[16] prepared by this method indicated it to be of high enantiomeric purity. For a more exact determination an ^{1}H-NMR experiment was performed using a chiral shift reagent.[17] None of the (-)-antipode of pilosinine could be detected indicating an optical purity of >99.5%. Since (+)-pilocarpine has been prepared from (+)-pilosinine this work constitutes a formal synthesis of (+)-pilocarpine. Finally, the zinc borohydride reduction and the phosphonate reagent **8** expand the scope and utility of asymmetric synthesis via Evans oxazolidinones.

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7. This type of intermediate was used in the synthesis of racemic pilosinine[6] but was prepared by a Stobbe condensation of ethyl succinate with 1-methyl-imidazole-5-carboxaldehyde.
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11. This material was prepared using a described method[6] starting from 1-methyl--5-carbomethoxy-imidazole which was synthesized according to: Koehler, H.; Dockner, T. and Karn, H. European Patent Application 306868.
12. Formation of the sodium enolate of **6** with sodium hexamethyldisilazide at -78°C was slow, and the enolate formed was very poorly soluble in the THF solvent.
13. $LiBH_4$-THF, sodium bis(2-methoxyethoxy)aluminum hydride -70°C-THF, Bu_4NBH_4-CH_2Cl_2, $Ca(BH_4)_2$-THF, Dibal-magnesiumbromide-etherate.
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16. We found the optical rotation of our (+)-pilosinine standard which we prepared from (+)-pilosine to be significantly higher (ca. 10°) in dichloromethane solvent than in the previously described protic solvents.
17. The N-methyl group for the two enantiomers was well resolved in the ^{1}H-NMR (360MHz, $CDCl_3$) spectrum using (R)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol as a chiral shift reagent (detection limit ca. 0.5%)

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