An Effective Chirospecific Synthesis of (+)-Pilocarpine from L-Aspartic Acid

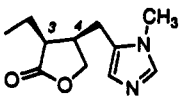
Jeffrey M. Dener, Lin-Hua Zhang, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

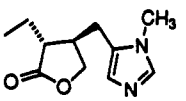
Received September 22, 1992

A short and efficient synthesis of (+)-pilocarpine (1) has been accomplished in 10 steps and 51% overall yield from L-aspartic acid. The synthesis features a diastereoselective alkylation of a protected aspartic acid diester derivative and a selective hydrolysis of the α-methyl ester to give the corresponding amino acid. Subsequent replacement of the amino group with bromo, esterification, and a modified Reformatsky reaction with 1-methylimidazole-5-carboxaldehyde (8) afforded imidazole-substituted lactone 28. Details concerning this novel lactone synthesis are also described. Finally, hydrogenolysis of the lactone carbon–oxygen bond and selective reduction of the resulting monoester afforded pure (+)-pilocarpine (1).

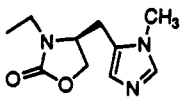
(+)-Pilocarpine (1) is the most prominent member of the Jaborandi alkaloids, a class of natural products that occur in South American plants of the Rutaceae family.[1] Both pilocarpine and its more stable C-3 isomer, isopilocarpine (2), were first isolated from assorted *Pilocarpus* species in 1875.[2] Since its isolation, pilocarpine has received constant attention for its diverse pharmacological properties.[3] Most utilized of these has been the application of 1 in the treatment of wide-angle glaucoma, the most common form of this ailment. When administered as an eye-drop solution, pilocarpine serves to control the elevated intraocular pressure associated with glaucoma.[3,4]



1



2



3

Due to this and other medicinal applications, pilocarpine (1) has been the target of several racemic[5] and enantioselective total syntheses.[6,7] Furthermore, some analogues of 1 have been prepared, such as carbamate 3, and their biological activity has been described.[8] A key consideration for all the reported syntheses of 1 is to preserve the crucial and thermodynamically less stable cis relationship between the α-ethyl group and the β-imidazole moiety. The facile epimerization of 1 to isopilocarpine (2) was recognized as early as 1880, and this fact must be one of concern to any synthetic effort since 2 is inactive as a miotic agent.[1,9] Most of the racemic syntheses focused on the initial construction of the lactone ring, followed by the formation of the imidazole nucleus. These approaches suffered from excessive length and a lack of regiospecificity in incorporating the *N*-methyl group of the imidazole, along with minimal stereoselectivity in establishing the key cis stereochemical relationship.

One notable earlier synthesis[10] utilized a preformed imidazole ring which was then incorporated into the lactone ring. Resolution of the lactone product and introduction of the ethyl group with reasonable cis selectivity gave (+)-1 in a 1% overall yield. Another approach to optically-active pilocarpine (1) utilized L-histidine as the chiral educt.[6] Early regiospecific synthesis of the imidazole ring, followed by an alkylation of this portion with an ethylated malonic diester, gave an intermediate which was decarboxylated and selectively reduced to 1. Unfortunately, the latter steps of this sequence proceeded with some racemization and little stereocontrol.

Our previous synthesis of 1 (Scheme I) hinged upon the alkylation of *tert*-butyl (*R*)-2-bromobutyrate (6), derived from either D-methionine (4) or D-2-amino-1-butanol (5), with the anion of a cyanophosphonate to initially construct the C-3, C-4 bond.[7] Introduction of the imidazole portion was then accomplished using phosphonate 7 and known imidazole aldehyde 8, giving the corresponding olefins 9. Selective reduction of the nitrile to the alcohol, followed by a stereocontrolled hydrogenation of the double bond, afforded hydroxy ester 10 which was then lactonized with trifluoroacetic acid to give (+)-isopilocarpine (2). Kinetic protonation of the enolate of 2 gave a 3/1 mixture of 1 and 2, which was separated by preparative HPLC. Although this route provided 1 in 46% overall yield, there was still a need for a shorter and more economical approach to this important alkaloid that avoided the tedious final HPLC separation and might be amenable to large-scale preparation. Our previous experience[11–13] with derivatives of L-aspartic acid, an inexpensive chiral educt, made this precursor our first choice for this objective.

(1) For a review on pilocarpine and other imidazole alkaloids, see: Maat, L.; Beyerman, H. C. The Imidazole Alkaloids. In *The Alkaloids*; New York: Academic Press, 1983; Vol. 23, Chapter 5.

(2) (a) Gerrard, A. W. *Pharm. J.* **1875**, *5*, 86. (b) Hardy, E. *Bull. Soc. Chim. Fr.* **1875**, *24*, 497.

(3) Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics*, 6th ed.; New York: MacMillan, 1980; p 97.

(4) Aboul-Enein, H. Y.; Al-Badr, A. A. *Meth. Find. Exptl. Clin. Pharm.* **1982**, *4*, 321.

(5) These syntheses have been summarized in ref 1.

(6) Noordam, A.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 441.

(7) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713.

(8) (a) Carbamate 3 was shown to be equipotent to pilocarpine (1) as a cholinergic muscarinic agent: Sauerberg, P.; Chem, J.; WoldeMussie, E.; Rapoport, H. *J. Med. Chem.* **1989**, *32*, 1322. (b) A review of structure–activity relationships of various analogues of 1 is presented in Shapiro, G.; Enz, A. *Drugs Future* **1992**, *17*, 489 and ref 4.

(9) Anderson, R. A.; Cowle, J. B. *Br. J. Ophthal.* **1958**, *52*, 607.

(10) Link, H.; Bernauer, K. *Helv. Chim. Acta* **1972**, *55*, 1053. Recently an asymmetric synthesis of an intermediate in this work was reported in a synthesis of (+)-pilosinine: Shapiro, G.; Chengzhi, C. *Tetrahedron Lett.* **1992**, *33*, 2447. Since pilosinine is only a β-substituted γ-lactone, the thermodynamically unstable cis configuration is not encountered in its synthesis.

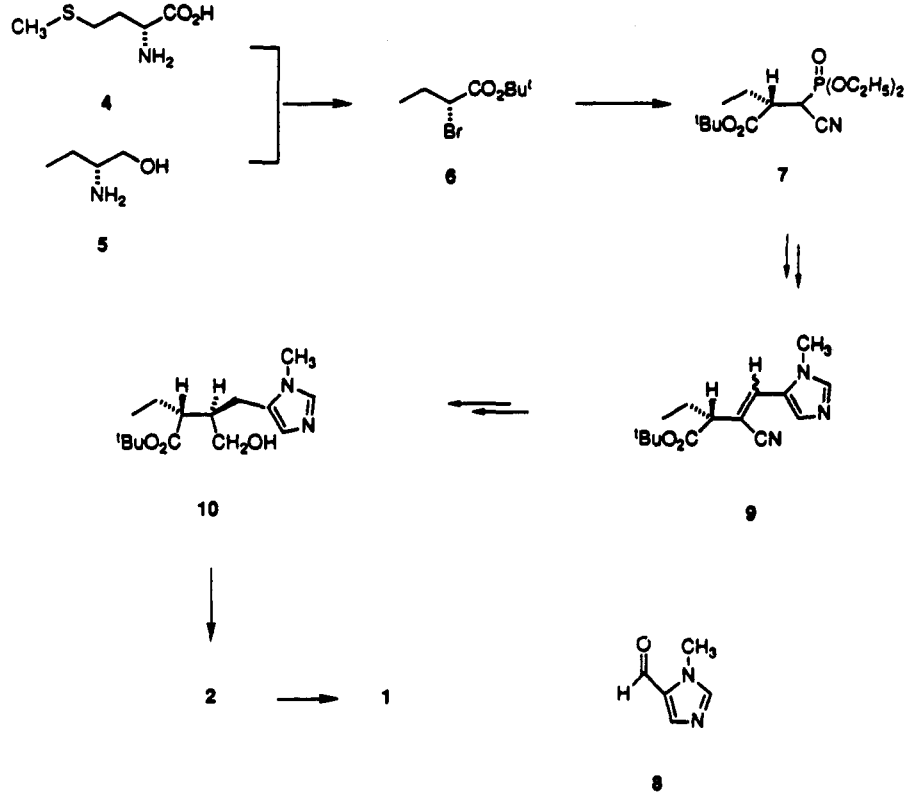
(11) Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164.

(12) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017.

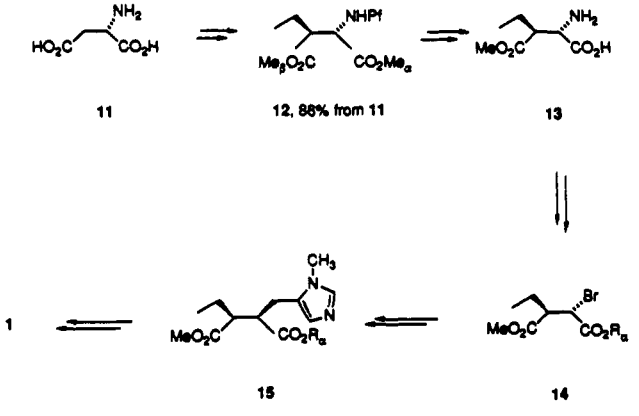
(13) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.

0022-3263/93/1958-1159$04.00/0

Scheme I. Synthesis of (+)-Pilocarpine (1) from *tert*-Butyl (*R*)-2-Bromobutyrate (6)



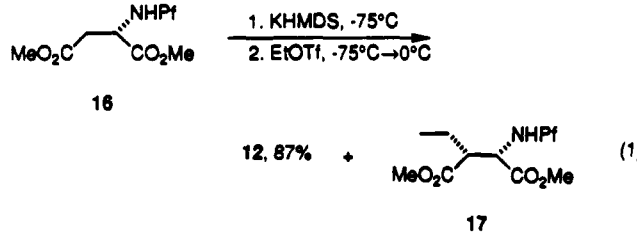
Scheme II. Plan for Synthesis of (+)-Pilocarpine from L-Aspartic Acid (11)



The synthetic plan is outlined in Scheme II. Our previous work[11] demonstrated that L-aspartic acid (11) can be converted to 3-ethyl aspartate 12 in three steps, with the C-3 stereocenter possessing the absolute stereochemistry found in pilocarpine (1). Next, selective differentiation of the α-methyl ester was projected, to be followed by conversion of amino acid 13 to bromo acid 14 (R_α = H). Esterification of the acid, followed by introduction of the imidazole portion of the molecule, would lead to an intermediate α,β-disubstituted succinate, e.g., 15. Our plan was to use a Reformatsky reaction between this bromo ester and an aldehyde similar to 8 to accomplish this goal. Finally, selective reduction of the α-carboxyl group of 15 and lactonization would then afford 1.

Results and Discussion

Alkylation of the anion of the known[13] dimethyl *N*-(9-phenylfluoren-9-yl)- (Pf) aspartate (16) with ethyl triflate gave a mixture of 12 and its diastereomer 17 (eq 1). While the previously described conditions could be used to prepare 12, the low diastereomeric ratio (2/1 to 3/1) required tedious chromatographic separations for the isolation of pure 12 in large quantities. Furthermore, the conversion of 16 to alkylated products was often low, and

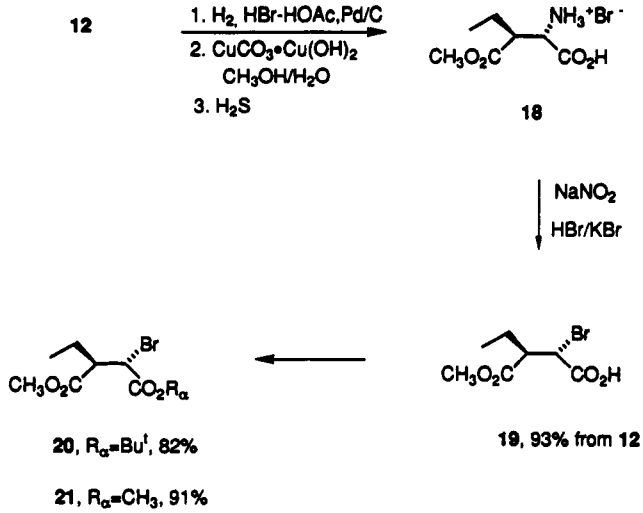


(1)

significant amounts of byproducts were isolated. For these reasons we investigated conditions to improve the conversion and diastereoselectivity of this transformation.

After many experiments, the major factors controlling this alkylation were found to be the stoichiometry of the base, potassium bis(trimethylsilyl)amide, and electrophile relative to the substrate. Optimum results were obtained when 95–105 mol % of base and 110–120 mol % of ethyl triflate were employed. These conditions afforded a mixture of 12 and 17 in an 18/1 ratio with less than 20% starting material remaining. Another factor contributing to losses was the use of 230–400-mesh, TLC-grade silica gel in the initial chromatographic purification since some of the product was not being eluted from this adsorbant. This problem was minimized by chromatography on gravity (70–230-mesh) silica gel. One last modification was to add the base to higher concentrations of the diester than previously employed, allowing for alkylation reactions on 60-g batches of material. This change still afforded an efficient conversion to 12 and 17 with excellent diastereoselectivity. Fortunately, the desired diester was crystalline, a fact which simplified the purification process. The high diastereoselectivity allowed simple crystallization

Scheme III. Conversion of Aspartate 12 to Bromosuccinate 19



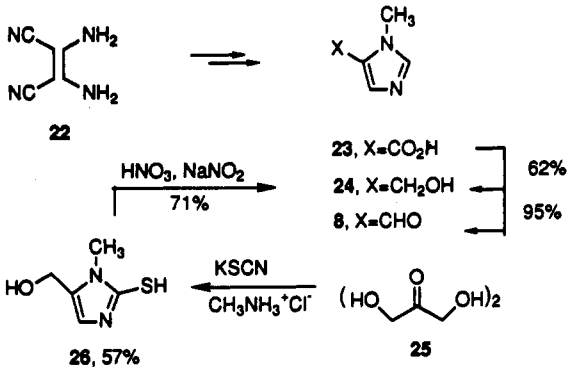
of the crude alkylation mixture from methanol to give the desired 3(*S*)-ethylaspartate **12** in 87% yield with only traces (less than 2%) of the other diastereomer and starting dimethyl aspartate **16** present.

With an ample supply of the alkylated aspartate **12** secured, this material was then converted to bromo acid **19** using essentially a one-pot reaction sequence (Scheme III). The key feature of this sequence was the selective hydrolysis of the α-methyl ester with basic copper(II) carbonate[13,14] under essentially neutral conditions. First, hydrogenolytic removal of the phenylfluorenyl nitrogen protecting group of **12** was effected using Pd/C in methanol in the presence of hydrobromic acid. The crude material was treated with a suspension of basic copper(II) carbonate in aqueous methanol, followed by destruction of the intermediate copper complex of the amino acid with gaseous hydrogen sulfide. Amino acid **18**, obtained directly as the hydrobromide salt from this catalyzed hydrolytic process, was converted to the desired bromo acid **19** using sodium nitrite and potassium bromide in hydrobromic acid.[7] Racemization due to excess bromide ion was avoided by strict temperature control. This sequence, which involved no purification steps, proceeded in excellent overall yield (93%) and could be performed on large amounts of **12** (25 g) without difficulty.

Although bromo acid **19** was usually obtained from this sequence in 90–95% chemical purity and purification of this product was possible at this stage, it was more convenient to purify the corresponding diesters. Our initial approach to **1** required differentiated esters, and for this reason bromo acid **19** was converted to the 4-methyl 1-*tert*-butyl diester **20** in 82% yield using a modification of standard conditions for *tert*-butyl ester preparation.[15] The dimethyl ester **21** of **19** was also prepared, using sulfuric acid in refluxing methanol in 91% yield. Although the differentiation of the two methyl esters of **21** was anticipated to be difficult, later observations would make this material the substrate of choice for the preparation of pilocarpine (**1**).

Preparation of the Imidazole Fragment. Utilization of bromosuccinates **20** and **21** in the Reformatsky reaction

Scheme IV. Preparation of 1-Methylimidazole-5-carboxaldehyde (8)

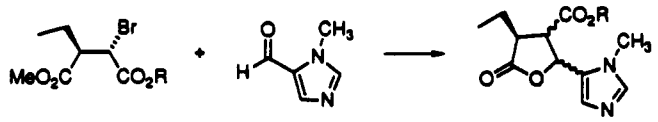


required preparation of the imidazole portion of pilocarpine. Our choice for this fragment was imidazole aldehyde **8** whose preparation is well-known.[10,16,17] Most of our early samples of **8** were derived from imidazolecarboxylic acid **23** which originated from diaminomaleonitrile (**22**).[17] Alternatively (Scheme IV), a simple two-step process to alcohol **24**, the direct precursor to aldehyde **8**, was devised. Starting from 1,3-dihydroxyacetone dimer (**25**), methylamine hydrochloride, and potassium thiocyanate, 5-(hydroxymethyl)-2-mercapto-1-methylimidazole (**26**) was obtained in 57% yield.[18] Removal of the thiol group was accomplished with aqueous nitric acid and a catalytic amount of sodium nitrite[19] to give known alcohol **24** after basification and extraction of the aqueous solution. Yields for this process were 71%. Oxidation of the crude imidazole alcohol **24** with manganese dioxide in refluxing chloroform afforded the pivotal aldehyde **8** after sublimation. This new sequence gave **8** in three steps, in essentially the same overall yield as that starting from diaminomaleonitrile (**22**). More importantly, this approach is amenable to large-scale work and avoids the use of dimethyl sulfate and lithium aluminum hydride.

Coupling the Key Fragments: Investigation of a New Lactone Synthesis. With the key pieces for our pilocarpine synthesis in hand, the stage was set to explore the Reformatsky reaction conditions to couple them.[20] This aspect of the synthesis turned out to be more difficult than had been anticipated. Exposure of either bromosuccinate **20** or **21** and aldehyde **8** to traditional Reformatsky reaction conditions only resulted in decomposition of the ester component, mostly via elimination. The use of additives or highly reactive forms of zinc also met with failure.[21] Attempts to couple bromosuccinate *tert*-butyl methyl ester **20** or dimethyl ester **21** with aldehyde **8** with zinc dust and tri-*n*-butylphosphine, with or without solvent, were performed (Table I). While these conditions were reported to give olefins from aldehydes and methyl bromoacetate,[22] we observed highly variable product

(14) Prestidge, R. L.; Harding, D. R. K.; Battersby, J. E.; Hancock, W. S. *J. Org. Chem.* **1975**, *40*, 3287.
(15) (a) Roesky, R. *J. Org. Chem.* **1963**, *28*, 1251. (b) Pavlov, S.; Bogavac, M.; Arsenijevic, V. *Bull. Soc. Chim. Fr.* **1974**, 2985.
(16) (a) Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, *33*, 3758. (b) Jones, R. G.; McLaughlin, K. C. *J. Am. Chem. Soc.* **1949**, *71*, 2444.
(17) O'Connell, J. F.; Parquette, J.; Yelle, W. E.; Wang, W.; Rapoport, H. *Synthesis* **1988**, 767.
(18) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312. See also: Marckwald, W. *Chem. Ber.* **1892**, *25*, 2354.
(19) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 644.
(20) The Reformatsky reaction has been reviewed recently: Fürstner, A. *Synthesis* **1989**, 571.
(21) Activation methods for zinc-mediated reactions have been reviewed: Erdik, E. *Tetrahedron* **1987**, *43*, 2203.
(22) Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* **1988**, *29*, 6119.

Table I. Lactone Formation from Bromosuccinates 20 and 21 and 1-Methylimidazole-5-carboxaldehyde (8) with Various Reformatsky Reagents



20, R=Bu^t **8** **27**, R=Bu^t
21, R=Me **28**, R=CH$_3$

diester	reagent	temp, °C	time, h	product	yield, %
20	Zn, Br(CH$_2$)$_2$Br *n*-Bu$_3$P/dioxane	90–95	2	27	49
20	Zn, Br(CH$_2$)$_2$Br *n*-Bu$_3$P	105–110	1.5	27	25
21	Zn, Br(CH$_2$)$_2$Br *n*-Bu$_3$P/dioxane	90–95	2	28	35
20	Zn(Ag), Et$_2$AlCl THF/hexane	25	1.5	27	97
21	Zn(Ag), Et$_2$AlCl THF/hexane	25	1.5	28	94

formation, along with substantial bromo ester decomposition and some reductive dimerization of the aldehyde. Purification of these products was hampered by the presence of tri-*n*-butylphosphine residues which proved to be difficult to remove.

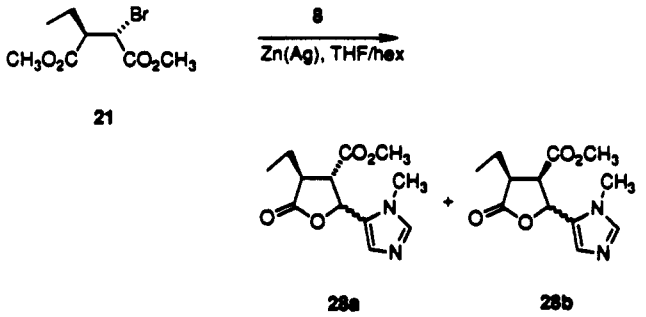
The problem of coupling aldehyde 8 with either **20** or **21** was best solved by employing a zinc/silver couple and diethylaluminum chloride[23] as shown in Table I. Addition of a solution of bromosuccinate *tert*-butyl methyl ester **20** and aldehyde 8 in dry tetrahydrofuran to a premixed suspension of a zinc/silver couple, copper(I) bromide, and diethylaluminum chloride in dry tetrahydrofuran and hexane, followed by quenching and chromatographing, gave *tert*-butyl ester lactone **27** in 97% yield. A similar result was obtained with bromosuccinate dimethyl ester **21**, giving methyl ester lactone **28** in 94% yield. Only trace amounts of bromo diester decomposition could be detected, and less than 5% of unreacted aldehyde 8 was present, as indicated by the proton NMR spectrum of the crude reaction mixture. Each of these bromo esters gave a mixture of lactone isomers in roughly a 78/22 ratio at C-4 of the lactone ring.

We also studied the use of other dialkylaluminum chlorides (Table II). Using dimethylaluminum chloride in this reaction improved the ratio of **28a/28b** to 91/9 without affecting the yield. However, diisobutylaluminum chloride produced a poorer diastereomer ratio at C-4 (63/37), as well as a reduction in yield. These results imply a steric factor in the reaction of the aluminum enolate, produced from the bromosuccinate, with aldehyde 8. Enolate geometry may also play a role, with bulkier Lewis acids generating a greater mixture of two enolates and hence more of the undesired lactone isomer. Other Lewis acids were less effective. While di-*n*-butylboron triflate did afford a modest yield of lactone products after a substantial reaction time, no reaction took place with *tert*-butyldimethylsilyl triflate.

Lastly, variation of the solvent composition used in the reaction was also examined. Replacing THF with diethyl ether suppressed lactone formation after 1.5 h at −10 °C, while a mixture of THF and toluene only afforded a 20% conversion to the lactone mixture. The use of either pure THF, or a 4.5/1 mixture of THF and hexane, gave virtually

(23) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3301.

Table II. Effect of Lewis Acid on the Diastereoselectivity in the Reformatsky Reaction



21 **28a** **28b**

Lewis acid	temp, °C	time, h	yield, %	ratio 28a/28b
Et$_2$AlCl	22	1.5	96	78/22
(*i*-Bu)$_2$AlCl	22	1.5	70	63/37
Me$_2$AlCl	22	1.0	94	91/9
(*n*-Bu)$_2$BOTf	0	16	30	75/25
t-BuMe$_2$SiOTf	22	8	0	

identical results, providing a 91/9 mixture of lactones **28a/28b** in 95% yields at reasonable reaction times. The application of the latter mixture is preferred due to the commercial availability of the dialkylaluminum chloride as a hexane solution.

The formation of lactone products was not surprising for these substrates,[24,25] although our original objective was to prepare an olefinic product from this reaction similar to that obtained in our first pilocarpine synthesis (Scheme I). Lactone formation, on the other hand, serves as a functional method to differentiate between the two esters of the bromosuccinate. For this reason and for its simplicity of preparation, dimethyl bromosuccinate **21** was now the substrate of choice. We then set out to convert either of the lactones to pilocarpine (**1**).

Conversion of the Lactone Products to (+)-Pilocarpine. As was the case for the coupling of the aldehyde and bromosuccinates, this objective initially proved to be quite elusive. Our attempts to utilize lactones **27** and **28** for this purpose centered upon the cleavage of the carbon–oxygen bond of the lactone ring. We had anticipated that this reaction would afford a product which could be reduced to the succinate **15** (Scheme II) or converted to an olefinic system similar to **9** shown in Scheme I. Unfortunately, treatment of either *tert*-butyl ester lactone **27** or methyl ester **28** with acidic reagents known to cleave simple lactone ring systems met with complete failure.[26] One possible explanation for this lack of reactivity might be steric factors at C-5 which prevent nucleophiles from attacking this center in an S_N2 fashion. Alternatively, protonation or complexation of the imidazole ring under the reaction conditions may be inhibiting the formation

(24) One example of a Reformatsky reaction between diethyl bromosuccinate and several carbonyl compounds has been described: Blanc, J., Gastambide, B. *Bull. Soc. Chim. Fr.* **1962**, 2055. The reaction products were also lactones.

(25) This reaction is a reliable method to generate the monoenolate of succinic acid diesters, an intermediate difficult to prepare by other methods. For an example of this problem, see: Long, N. R.; Rathke, M. W. *Synth. Commun.* **1981**, *11*, 687.

(26) Several of the methods that were tried included: Gaseous hydrogen bromide: (a) Knobler, Y.; Frankel, M. *J. Chem. Soc.* **1958**, 1629. (b) Jošt, K.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2485. (c) Miyoshi, M.; Sugano, H.; Fujii, T.; Ishihara, T.; Yoneda, N. *Chem. Lett.* **1973**, 5. Lewis acids and nucleophiles: (d) Ochiai, M.; Nishide, K.; Node, M.; Fujita, E. *Chem. Lett.* **1981**, 283. (e) Node, M.; Nishide, K.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 5163. (f) Olah, G. A.; Karpeles, R.; Narang, S. C. *Synthesis* **1982**, 963. Trimethylsilyl iodide: (g) Olah, G. A.; Hussain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

Scheme V. Conversion of Lactone Products to (+)-Pilocarpine (1)

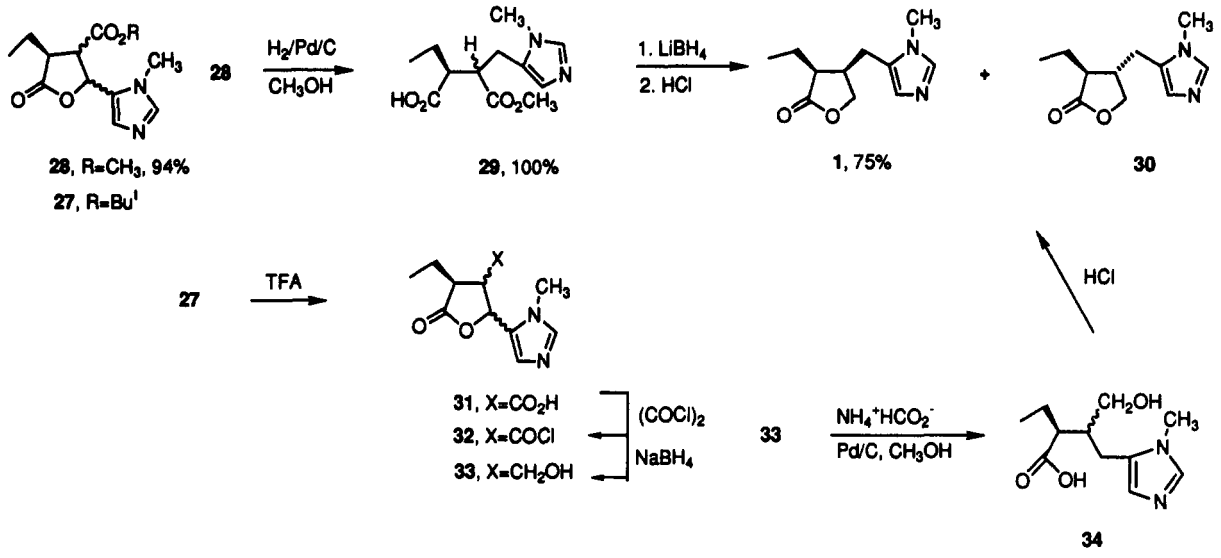
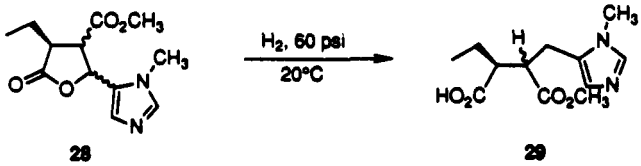


Table III. Hydrogenolysis of Lactone 28



catalyst	solvent	time, h	yield, %
10% Pd/C	HOAc/CH_3OH	24	30
20% $Pd(OH)_2$/C	CH_3OH	24	40
10% Pd/C	HOAc/CH_3OH/HCl	24	0
10% Pd/C	CH_3OH	48	100
5% Pd/C	CH_3OH	72	100

of a carbocation at C-5 via an S_N1 process and thus preventing ring cleavage.

Alternatively, cleavage of the carbon–oxygen bond was accomplished in a simple and direct manner using hydrogenolysis conditions[27] (Scheme V). Reaction of lactone methyl ester **28**, derived from the sequence using dimethylaluminum chloride, with hydrogen at 60 psi in the presence of 5% palladium-on-charcoal in methanol for 60 h afforded a quantitative yield of monomethyl ester **29**. Proton NMR analysis of this hydrogenolysis product indicated a 91/9 ratio of diastereomers, implying that the two major diastereomers in methyl ester lactone **28** possessed different configurations at C-4, each in turn being a mixture of diastereomers at C-5. Table III shows that this simple hydrogenolysis is highly sensitive to the solvent and catalyst employed. Acids seem to retard or inhibit the hydrogenolysis, perhaps for reasons similar to those affecting the acid-catalyzed ring cleavage. Pearlman's catalyst also seems to retard the hydrogenolytic cleavage of the lactone ring. Replacement of 5% palladium-on-carbon with 10% catalyst also gave excellent results and at shorter reaction times.

The final and crucial assessment of lactone stereochemistry, particularly that of the C-3, C-4 relative stereochemistry, could best be determined at the final product stage. Since the hydrochloride salt of monomethyl ester **29** had already been converted to pilocarpine,[6] treatment of our material under the reported conditions afforded a 91/9 mixture of **1** and (−)-isopilocarpine (**30**), the mirror image of **2**, in 88% yield (Scheme V). Therefore, the Reformatsky reaction gives as the major products the lactone in which the C-3 ethyl group is trans to the C-4 carboxyl, as one might anticipate based on steric arguments. Although the separation of (+)-pilocarpine (**1**) and (+)-isopilocarpine (**2**) has already been described by other methods, we found that the hydrochlorides of this mixture of **1** and (−)-isopilocarpine (**30**) could be readily recrystallized from a mixture of ethanol and acetone to afford pure **1** hydrochloride, identical by direct comparison (mp, $[\alpha]$, NMR) with a twice-recrystallized commercial sample of the natural product. This synthesis of (+)-pilocarpine (**1**) proceeds in 10 steps from L-aspartic acid (**11**) through **12**, **19**, **21**, **28**, and **29** in an overall yield of 51%.

The conversion of lactone *tert*-butyl ester **27** to pilocarpine was also possible through a slightly longer reaction sequence (Scheme V). Removal of the ester moiety of this lactone with trifluoracetic acid in dichloromethane gave the lactone acid **31** as its trifluoroacetate salt. The acid functionality of **31** was reduced to the alcohol **33** in 59% yield using a two-step procedure which proceeded through acid chloride **32**.[28,29] Lactone alcohol **33** was initially prepared as an alternative substrate for the previously described lactone ring-cleavage experiments which failed; however, hydrogenolysis of this material under catalytic transfer hydrogenation conditions[30] gave hydroxy acid **34** which lactonized after exposure to aqueous hydrochloric acid. Subsequent basification and extraction also gave pilocarpine (**1**) and its C-4 isomer **30** as a 6/1 mixture in 56% yield.

(27) Several examples of hydrogenolysis of benzylic lactones are known: (a) Chakraborti, A. K.; Ray, J. K.; Kundu, K. K.; Chakrabarty, S.; Mukherjee, D.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 261. (b) Jurewicz, A. T.; Forney, L. S. U.S. Patent 3 651 126, 1972. (c) Ghatak, U. R.; Chatterjee, N. R.; Banerjee, A. K.; Chakravarty, J.; Moore, R. E. *J. Org. Chem.* **1969**, *34*, 3739.

(28) For a similar method, see: Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* **1983**, 853. These authors were able to selectively reduce an acid in the presence of an ester.

(29) Diborane has been shown to reduce acids in the presence of lactones: (a) Corey, E. J.; Sachdev, H. S. *J. Org. Chem.* **1975**, *40*, 579. (b) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919. Reduction of acid **31** with borane in tetrahydrofuran did give alcohol **33**, but the yields were inconsistent due to the difficulty in destroying the intermediate boron complex.

(30) Reviewed in Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. Treatment of lactone **33** under the same conditions which successfully hydrogenolyzed lactone **28** only resulted in a 30% conversion of **33** to acid **34** after a reaction time of 3 days.

Experimental Section

General. All melting points are uncorrected as are boiling points. The ^{1}H- and ^{13}C-NMR spectra are reported in $CDCl_3$ (except where noted) and coupling constants, J, in hertz. Mass spectra and elemental analysis were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. Solvents and reagents were dried and purified before use. Organic layers from aqueous extractions were dried over anhydrous $MgSO_4$ unless otherwise indicated and evaporated using water aspirator vacuum. The zinc/silver couple was prepared as described, except that zinc dust was substituted for the "coarse zinc powder".[31] Solutions of potassium bis(trimethylsilyl)amide in toluene were obtained from the Callery Chemical Co., Callery, PA, and were titrated before use; the dialkylaluminum chlorides were obtained from the Aldrich Chemical Co. as 1 M solutions in hexane, and the MnO_2 was obtained from the Kerr-McGee Chem. Corp.

Dimethyl 3(*S*)-Ethyl-*N*-(9-phenylfluoren-9-yl)-L-aspartate (12). To a stirred solution of 63.5 g (157 mmol) of diester 16[13] in 700 mL of dry tetrahydrofuran, cooled to −74 °C in a dry ice–2-propanol bath, was added 270 mL of a 0.6 M solution of potassium bis(trimethylsilyl)amide in toluene over a 45-min period. The resulting green solution was stirred for 45 min at −74 °C, then 24.0 mL (32.9 g, 185 mmol) of freshly distilled ethyl trifluoromethanesulfonate was added in one portion, and the reaction mixture was stirred for 10 min at −74 °C and then allowed to warm up to rt. The reaction mixture was quenched with 1 M aqueous phosphoric acid solution (250 mL), the aqueous solution was extracted with diethyl ether (3 × 300 mL), the combined organic layers were washed with saturated aqueous sodium chloride (2 × 200 mL), dried ($MgSO_4$), and evaporated, and the residue was crystallized from 200 mL of methanol to provide 58.3 g (87%) of **12**, containing less than 2% of the minor diasteromer **17**: mp 138–139 °C; $[\alpha]^{22}_D$ −302° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.77 (t, J = 7.4, 3 H, CH_3), 1.61–1.70 (m, 1 H, CH_2), 1.76–1.84 (m, 1 H, CH_2), 2.37 (ddd, J = 10.9, 6.6, 4.3, 1 H, CCH), 2.80 (dd, J = 10.1, 6.7, 1 H, NCH), 3.04 (d, J = 10.1, 1 H, NH), 3.24 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 7.16–7.42 (m, 11 H, ArH), 7.64–7.69 (m, 2 H, ArH); ^{13}C NMR δ 11.8 (q), 20.9 (t), 51.5 (q), 51.5 (q), 52.2 (d), 56.7 (d), 72.7 (s), 119.8 (d), 119.9 (d), 125.5 (d), 126.0 (d), 126.3 (d), 127.2 (d), 127.2 (d), 127.7 (d), 128.2 (d), 128.3 (d), 128.3 (d), 139.8 (s), 141.1 (s), 144.4 (s), 148.0 (s), 148.4 (s), 173.1 (s), 174.8 (s).

Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.5; H, 6.3; N, 3.3. Found: C, 75.6; H, 6.4; N, 3.2.

3(*S*)-Ethyl-L-aspartic Acid Hydrobromide 4-Methyl Ester (18). Nitrogen was bubbled through a suspension of 25.1 g (58 mmol) of 3-ethylaspartate **12** in 450 mL of methanol for 10 min, then 5.20 g of 10% palladium-on-carbon, and 36 mL of a solution consisting of 12 mL of 48% aqueous hydrobromic acid and 24 mL of acetic acid were added. This mixture was hydrogenated at 55 psi for 4.5 h using a Parr hydrogenator and then filtered through Celite. After the filter cake was washed with 300 mL of methanol, 200 mL of methanol containing 20 mL of hydrobromic acid in acetic acid (1/2), and then with 200 mL of methanol, the combined filtrate and washings were evaporated to give 27.2 g of the deprotected amine hydrobromide as an orange-brown semisolid residue. This residue was suspended in 200 mL of water and filtered, the filter cake was washed with 300 mL of water, and the combined filtrate and washings were diluted with 500 mL of methanol. To this solution was added 76.4 g (345 mmol) of copper(II) carbonate–copper(II) hydroxide, and the resulting turquoise-green suspension was mechanically stirred in a 2-L, three-neck Morton flask for 120 h. Hydrogen sulfide was bubbled through the suspension for 1 h, the resulting black suspension was filtered through Celite, the filter cake was washed with a methanol/water solution (2/1, 1800 mL), and the combined filtrate and washings were evaporated to give 19.6 g of crude amino acid hydrobromide salt **18** as an orange oil: ^{1}H NMR (D_2O) δ 0.76 (t, J = 7.4, 3 H, CH_3), 1.38–1.48 (m, 1 H, CH_2), 1.54–1.65 (m, 1 H, CH_2), 2.78 (dt, J = 9.8, 5.1, 1 H, CCH), 3.56 (s, 3 H, OCH_3), 3.92 (d, J = 4.8, 1 H, NCH).

This material was used in the subsequent reaction without further purification.

(31) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649.

(2*S*,3*S*)-2-Bromo-3-ethylbutane-1,4-dioic Acid 4-Methyl Ester (19). To a stirred suspension of 19.6 g of the crude amino acid salt **18** in 450 mL of 2.5 N aqueous hydrobromic acid, cooled to −9 °C was added 20.9 g (175.6 mmol) of solid potassium bromide in one portion followed by 10.0 g (145 mmol) of solid sodium nitrite in small portions over a 1.5-h period, keeping the internal temperature between −9 and −7 °C. The reaction mixture was stirred for 2 h in the cooling bath after the addition was complete, it was extracted with ethyl acetate (2 × 500 mL), and the combined organic layers were washed with saturated aqueous sodium chloride (2 × 250 mL), dried, and evaporated to give 13.0 g (93% overall from **12**) of bromo acid **19** as a pale yellow, waxy solid: ^{1}H NMR δ 0.93 (t, J = 7.5, 3 H, CH_3), 1.83–1.90 (m, 1 H, CH_2), 1.98–2.04 (m, 1 H, CH_2), 3.07 (ddd, J = 10.6, 6.5, 3.2, 1 H, CCH), 3.74 (s, 3 H, OCH_3), 4.47 (d, J = 10.2, 1 H, BrCH); ^{13}C NMR δ 9.8 (q), 22.8 (t), 44.1 (d), 49.0 (d), 52.3 (q), 172.9 (s), 174.6 (s). Anal. Calcd for $C_7H_{11}BrO_4$: C, 35.2; H, 4.6. Found: C, 35.6; H, 4.7.

(2*S*,3*S*)-2-Bromo-3-ethylbutane-1,4-dioic Acid 1-*tert*-Butyl 4-Methyl Diester (20). To a solution of 2.81 g (11.8 mmol) of bromo acid **19**, 4 mL of dry *tert*-butyl alcohol, and 4 mL of dry dioxane in a Fisher-Porter pressure bottle, cooled in a dry ice–2-propanol bath, were added 40 mL of liquid isobutylene and 2 mL of sulfuric acid. The reaction vessel was sealed and shaken mechanically for 18 h, cooled in a dry ice–2-propanol bath, and opened carefully. The reaction mixture was partitioned between 200 mL of diethyl ether and 100 mL of water, the aqueous phase was extracted with 200 mL of ether, and the combined ether layers were washed with 150 mL of saturated sodium chloride, dried, and evaporated to afford 4.58 g of a pale yellow liquid. Chromatography over 200 g of silica gel (ethyl acetate/hexane, 1/19) gave 2.86 g (82%) of the mixed diester **20** as a colorless liquid: $[\alpha]^{22}_D$ −66.4° (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 0.91 (t, J = 7.5, 3 H, CH_3), 1.47 (s, 9 H, CH_3), 1.75–1.86 (m, 1 H, CH_2), 1.94–2.05 (m, 1 H, CH_2), 3.00 (ddd, J = 10.8, 7.7, 3.7, 1 H, CCH), 3.70 (s, 3 H, OCH_3) 4.31 (d, J = 10.7, 1 H, BrCH); ^{13}C NMR δ 10.0 (q), 23.0 (t), 27.6 (q), 46.6 (d), 49.6 (d), 51.9 (q), 82.4 (s), 168.2 (s), 172.7 (s). Anal. Calcd for $C_{11}H_{19}BrO_4$: C, 44.8; H, 6.8. Found: C, 44.4; H, 6.9.

Dimethyl (2*S*,3*S*)-2-Bromo-3-ethyl-1,4-butanedioate (21). To a stirred solution of 11.0 g (46.0 mmol) of bromo acid **19** in 200 mL of methanol was added 5.0 mL of sulfuric acid, and the resulting solution was heated under reflux for 6 h. The reaction mixture was cooled to room temperature and evaporated, the residue was partitioned between 300 mL of diethyl ether and 100 mL of water, the aqueous phase was extracted with ether (2 × 200 mL), and the combined organic layers were washed with cold, 10% aqueous sodium carbonate (2 × 30 mL) and saturated aqueous sodium chloride (2 × 50 mL). To the organic phase was added activated charcoal, it was filtered, dried, and evaporated to afford 10.6 g (91%) of dimethyl bromosuccinate **21** as a colorless oil. An analytical sample was obtained by chromatography on silica gel (ethyl acetate/hexane, 1/12): $[\alpha]^{22}_D$ −72.4° (*c* 3.0, $CHCl_3$); ^{1}H NMR δ 0.87 (t, J = 7.5, 3 H, CH_3), 1.76–1.85 (m, 1 H, CH_2), 1.93–2.01 (m, 1 H, CH_2), 3.04 (ddd, J = 10.9, 7.5, 3.8, 1 H, COCH), 3.66 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.40 (d, J = 10.7, 1 H, BrCH); ^{13} C NMR δ 9.8 (q), 22.8 (t), 44.4 (d), 49.2 (d), 52.1 (q), 53.0 (q), 169.9 (s), 172.7 (s). Anal. Calcd for $C_8H_{13}BrO_4$: C, 38.0; H, 5.2. Found: C, 38.1; H, 5.3.

5-(Hydroxymethyl)-2-mercapto-1-methylimidazole (26). A mixture of 128 g (1.4 mol, based on the monomer) of dihydroxyacetone dimer (**25**), 207 g (2.1 mol) of potassium thiocyanate, and 124 g (1.8 mol) of methylamine hydrochloride was added to a solution of 160 mL of acetic acid and 1000 mL of 1-butanol in a 2-L, three-neck Morton flask equipped with a mechanical stirrer. The resulting white suspension was stirred for 70 h after which it was suspended in 200 mL of water and filtered. The filter cake was washed with 600 mL of water and then with 600 mL of diethyl ether, and the off-white solid was dried in vacuo at 50-60 °C to give 117.5 g (57%) of imidazole **26** as a white powder: mp 203–206 °C dec: ^{1}H NMR (DMSO-d_6) δ 3.43 (s, 3 H, NCH_3), 4.31 (s, 2 H, CH_2), 5.1 (br s, 1 H, OH), 6.80 (s, 1 H, =CH), 9.48 (s, 1 H, SH); ^{13}C NMR (DMSO-d_6) δ 30.6 (q), 53.0 (t), 112.2 (d), 130.5 (s), 161.7 (s). Anal. Calcd for $C_5H_8N_2OS$: C, 41.7; H, 5.6; N, 19.4. Found: C, 41.7; H, 5.5; N, 19.5.

5-(Hydroxymethyl)-1-methylimidazole (24): A. From 1-Methylimidazole-5-carboxylic Acid (23). To 220 mL of dry tetrahydrofuran, cooled in an ice water bath, was added 4.0 g (105 mmol) of $LiAlH_4$, followed by 8.90 g (70.6 mmol) of imidazole acid **23**. The resulting suspension was heated under reflux for 4 h, cooled in an ice bath, and then sequentially 4 mL of water, 4 mL of 15% aqueous sodium hydroxide, and 12 mL of water were added. The mixture was filtered through Celite, the filter cake was washed with tetrahydrofuran/methanol (1/1) and then with three portions of hot tetrahydrofuran/methanol (1/1), and the combined filtrate and washings were evaporated to give 8.2 g of a brown semisolid. This material was absorbed onto 55 g of silica gel and chromatographed over 170 g of silica gel (acetone/methanol, 9/1) to give 4.88 g (62%) of imidazole alcohol **24** as a light yellow solid: mp 105–108 °C. Recrystallization from 100 mL of acetone gave 3.83 g (48%) of pure alcohol **24** as tan crystals: mp 112.5–114 °C (lit.[16] mp 113–114 °C); ^{1}H NMR δ 3.68 (s, 3 H, NCH_3), 4.59 (s, 2 H, OCH_2), 6.83 (s, 1 H, CH), 7.35 (s, 1 H, CH); ^{13}C NMR (CD_3OD) δ 31.8 (q), 54.0 (t), 128.1 (d), 132.9 (s), 139.9 (d).

B. From Mercaptoimidazole 26. To a stirred solution of 10 mg (0.145 mmol) of sodium nitrite in 2.7 mL of 5.6 M aqueous nitric acid was added 510 mg (3.54 mmol) of mercaptoimidazole **26** in small portions over a 20-min period, applying occasional ice bath cooling to keep the internal temperature below 35 °C. After the addition was complete, the solution was stirred for an additional 45 min, 15 mL of water was added, the pH was adjusted to 8 with solid sodium carbonate, and the solution was then saturated with solid sodium chloride. The solution was extracted with chloroform/2-propanol (3/1, 3 × 50 mL), and the combined organic extracts were dried and evaporated to give 281 mg (71%) of imidazole alcohol **24** as a bright yellow solid: mp 109–112 °C.

1-Methylimidazole-5-carboxaldehyde (8). A suspension of 3.0 g (26.8 mmol) of imidazole alcohol **24** and 15.0 g (172.5 mmol) of MnO_2 in 90 mL of chloroform was heated under reflux with mechanical stirring in a Morton flask for 23 h. The reaction mixture was cooled to rt and filtered through Celite, and the filter cake was washed with chloroform/2-propanol (1/1, 3 × 60 mL). The combined filtrate and washings were evaporated to a residue which was purified by sublimation (65–70 °C; 0.2 mmHg) to give 2.8 g (95%) of aldehyde **8** as a white solid: mp 54–55 °C (lit.[10] mp 54–56 °C); ^{1}H NMR δ 3.96 (s, 3 H, NCH_3), 7.64 (s, 1 H, CH), 7.79 (d, J = 0.8, 1 H, CH), 9.77 (d, J = 0.9 Hz, 1 H, CHO); ^{13}C NMR δ 34.0 (q), 131.5 (s), 143.2 (d), 144.0 (d), 179.3 (d).

(3*S*,4*RS*,5*RS*)-3-Ethyl-4-(*tert*-butoxycarbonyl)-5-(1-methyl-1*H*-imidazol-5-yl)dihydro-2(3*H*)-furanone (27). To a stirred solution of 540 mg (8.26 mmol) of the zinc/silver couple and 110 mg (0.77 mmol) of copper(I) bromide in 13 mL of dry tetrahydrofuran was added 7 mL (7.00 mmol) of a 1.0 M solution of Et_2AlCl in hexane. The resulting suspension was stirred for 1 h, and then a solution of 610 mg (5.55 mmol) of aldehyde **8** and 1.60 g (5.42 mmol) of bromosuccinate **20** in 14 mL of tetrahydrofuran was added dropwise via syringe pump over 75 min. After the addition was complete, the resulting solution was stirred for 1.5 h at rt and then cooled in an ice water bath, and 5 mL of 50% aqueous methanol and 10 mL of ethyl acetate were added. After being stirred for 5 min, the resulting gelatinous suspension was filtered through Celite, the filter cake was washed with 200 mL of ethyl acetate and 150 mL of chloroform, and the combined filtrate and washings were evaporated to give 2.49 g of a white foam. This residue was dissolved in 75 mL of chloroform, and the solution was extracted with 1 M aqueous phosphoric acid (3 × 75 mL). The combined acid layers were washed with 200 mL of ethyl acetate, and then the aqueous phase was vigorously stirred with 250 mL of ethyl acetate while solid potassium carbonate was added in small portions until gas evolution ceased, after which the aqueous phase was saturated with solid sodium chloride and the layers were separated. The aqueous phase was extracted with 250 mL of ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride (2 × 125 mL) and evaporated to give 1.54 g (97%) of essentially pure lactone **27** as a light yellow oil. This oil was chromatographed over 100 g of silica gel (chloroform/2-propanol, 9/1) to give 1.42 g (89%) of lactone **27** as a pale yellow oil which was shown to be a 3/3/1 mixture of isomers by ^{1}H NMR analysis. Anal. Calcd for $C_{15}H_{22}O_4N_2$: C, 61.2; H, 7.5; N, 9.5. Found: C, 61.6; H, 7.6; N, 9.3.

Continued elution afforded 78 mg (5%) of a minor isomer of **27** in pure form: ^{1}H NMR δ 1.07 (t, J = 7.6, 3 H, CCH_3), 1.29 (s, 9 H, CCH_3), 1.55–1.67 (m, 1 H, CCH_2), 1.99–2.07 (m, 1 H, CCH_2), 2.81–2.86 (m, 1 H, COCH), 3.32 (dd, J = 8.6, 5.8, 1 H, COCH), 3.68 (s, 3 H, NCH_3), 5.51 (d, J = 5.2, 1 H, ArCH), 7.09 (s, 1 H, NCH), 7.43 (s, 1 H, NCH); ^{13}C NMR δ 12.1 (q), 19.1 (t), 27.6 (q), 32.2 (q), 46.1 (d), 50.1 (d), 72.9 (d), 83.0 (s), 125.7 (s), 128.3 (d), 139.2 (d), 167.9 (s), 175.5 (s).

(3*S*,4*RS*,5*RS*)-3-Ethyl-4-(methoxycarbonyl)-5-(1-methyl-1*H*-imidazol-5-yl)dihydro-2(3*H*)-furanone (28). To a stirred solution of 1.38 g (21.1 mmol) of the zinc/silver couple and 276 mg (1.9 mmol) of copper(I) bromide in 30 mL of dry tetrahydrofuran was added 16.7 mL (16.7 mmol) of a 1.0 M solution of Me_2AlCl in hexane, and the resulting suspension was stirred for 20 min then cooled in −8 °C. Next a solution of 1.53 g (13.9 mmol) of aldehyde **8** and 3.52 g (13.9 mmol) of bromosuccinate **21** in 30 mL of tetrahydrofuran was added dropwise over a 20-min period. After the addition was complete, the resulting solution was stirred for 2 h at −8 °C and then for 30 min at rt. The reaction mixture was cooled to −8 °C, 20 mL of 50% aqueous methanol was slowly added, the mixture was stirred for 20 min at rt and then filtered through Celite, and the filter cake was washed with 500 mL of methanol, followed by 20 mL of methanol/aqueous concd hydrochloric acid (10/1). The combined filtrate and washings were evaporated to give 5.04 g of a pale yellow foam. This residue was dissolved in 100 mL of 1.0 M aqueous phosphoric acid, and this solution was washed with diethyl ether (2 × 50 mL) and then vigorously stirred with 300 mL of ethyl acetate while solid sodium carbonate was added in small portions until gas evolution ceased. Following saturation of the aqueous layer with solid sodium chloride, the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 150 mL), and the combined organic layers were washed with saturated aqueous sodium chloride (2 × 50 mL). The organic phase was dried and evaporated to give 3.29 g (94%) of an oil. An analytical sample (ratio **28a**/**28b**, 91/9; the same ratio was found in the initially isolated oil) was obtained by chromatography on silica gel (chloroform/2-propanol, 10/1). Anal. Calcd for $C_{12}H_{16}O_4N_2$: C, 57.1; H, 6.4; N, 11.1. Found: C, 56.9; H, 6.3; N, 10.9.

28a (C-5 isomer x): ^{1}H NMR δ 0.95 (t, J = 7.5, 3 H, CH_3), 1.66–1.74 (m, 1 H, CH_2), 1.78–1.94 (m, 1 H, CH_2), 2.97 (ddd, J = 11.1, 7.4, 5.2, 1 H, CH), 3.33 (dd, J = 11.1, 9.8, 1 H, CH), 3.60 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3), 5.39 (d, J = 9.8, 1 H, CH), 7.06 (s, 1 H, CH), 7.43 (s, 1 H, CH). **28a** (C-5 isomer y): ^{1}H NMR δ 0.95 (t, J = 7.5, 3 H, CH_3), 1.66–1.74 (m, 1 H, CH_2), 1.78–1.94 (m, 1 H, CH_2), 3.13 (dt, J = 10.1, 6.2, 1 H, CH), 3.47 (s, 3 H, CH_3), 3.49 (t, J = 10.1, 8.9, 1 H, CH), 3.58 (s, 3 H, CH_3), 5.68 (d, J = 8.9, 1 H, CH), 6.91 (s, 1 H, CH), 7.34 (s, 1 H, CH). **28b**: ^{1}H NMR δ 1.01 (t, J = 7.5, 3 H, CH_3), 3.62 (s, 3 H, CH_3), 3.68 (s, 3 H, CH_3), 5.60 (d, J = 6.3, 1 H, CH). Other signals due to **28b** were buried in the signals of **28a** and could not be distinguished.

(2*S*,3*RS*)-2-Ethyl-3-(1-methyl-1*H*-imidazol-5-yl)butane-1,4-dioic Acid 4-Methyl Ester (29). Nitrogen was bubbled through a solution of 1.00 g (4.0 mmol) of lactone methyl ester **28** in 20 mL of methanol for 5 min, 2.00 g of 5% Pd/C was added, and the resulting suspension was shaken under 60 psi of hydrogen on a Parr hydrogenation apparatus for 60 h. The reaction mixture was filtered through Celite, the filter cake was washed with 300 mL of methanol, and the combined filtrate and washings were evaporated to give 1.08 g (100%) of monoester **29** as a colorless oil. Based on the NMR analysis (integration of both OCH_3 and NCH_3 absorptions), the diastereomeric ratio (91/9) remained unchanged, as expected: ^{1}H NMR (CD_3OD) δ 0.95 (t, J = 7.5, 3 H, CCH_3), 1.54–1.68 (m, 2 H, CH_2), 2.62–2.66 (m, 1 H, COCH), 2.87–2.95 (m, 1 H, COCH), 2.99–3.11 (m, 2 H, CH_2), 3.64 (s, 3 H, NCH_3), 3.84 (s, 3 H, OCH_3), 7.25 (s, 1 H, NCH), 8.69 (s, 1 H, NCH); ^{13}C NMR (CD_3OD) δ 13.5 (q), 26.0 (t), 26.5 (t), 35.5 (q), 49.7 (d), 54.9 (q), 119.4 (d), 134.4 (s), 137.6 (d), 178.2 (s), 182.2 (s). Anal. Calcd for $C_{12}H_{18}O_4N_2$: C, 56.7; H, 7.1; N, 11.0. Found: C, 56.5; H, 7.3; N, 10.8.

Lactone Acid (31) Trifluoroacetate Salt. To a stirred solution of 1.79 g (6.1 mmol) of lactone *tert*-butyl ester **27** in 20 mL of dichloromethane was added 10 mL (14.8 g, 130 mmol) of

trifluoroacetic acid. The resulting solution was stirred for 18 h at rt and then evaporated, and the residual oil was coevaporated several times with a mixture of ethyl acetate and benzene to give 2.09 g (96%) of the lactone acid salt **31** as a white solid: mp 112–140 °C. Analysis of this mixture by 500-MHz NMR indicates that this material is a 5/4/1 mixture of isomers. Anal. Calcd for $C_{13}H_{15}F_3N_2O_6$: C, 44.3; H, 4.3; N, 7.9. Found: C, 44.3; H, 4.4; N, 7.6.

(3*S*,4*RS*,5*RS*)-3-Ethyl-4-(hydroxymethyl)-5-(1-methyl-1*H*-imidazol-5-yl)dihydro-2(3*H*)-furanone (33). To a stirred suspension of 2.01 g (5.71 mmol) of lactone acid **31** in 50 mL of dry dichloromethane was added 7 drops of dry DMF. The suspension was cooled in an ice water bath, 12 mL (17.5 g, 138 mmol) of oxalyl chloride was added in one portion, and the reaction mixture was stirred for 10 min in an ice bath and then for 4 h at rt. Solvent and excess oxalyl chloride were evaporated, and the residue was dried by coevaporation with benzene. The residue of crude acid chloride was dissolved in 25 mL of dry DMF and cooled in a dry ice–2-propanol bath. To this solution was added a solution of 900 mg (23.8 mmol) of sodium borohydride in 12 mL of dry DMF, the dry ice–2-propanol bath was replaced with a dry ice–carbon tetrachloride bath, and the resulting semisolid mixture was stirred for 30 min in this bath and then for 1.5 h in an ice–salt–acetone bath. The reaction mixture was partitioned between 100 mL of ethyl acetate and 100 mL of 1 M aqueous phosphoric acid, the layers were separated, and the aqueous phase was washed with 100 mL of ethyl acetate, followed by chloroform/2-propanol (9/1, 2 × 100 mL). The aqueous layer was vigorously stirred with 100 mL of chloroform/2-propanol (9/1) while solid potassium carbonate was added in small portions until gas evolution ceased. The aqueous phase was saturated with solid sodium chloride, the layers were separated, the aqueous phase was extracted with chloroform/2-propanol (9/1, 2 × 150 mL), and the combined organic extracts were dried and evaporated to a residue which was chromatographed over 100 g of silica gel (chloroform/2-propanol, 1/1) to give 750 mg (59%) of hydroxymethyl lactone **33** as a pale yellow oil: ^{1}H NMR (characteristic signals) δ 1.08 (t, J = 7.5, 3 H, CCH_3), 1.77–1.90 (m, 2 H, CCH_2), 3.68 (s, 3 H, NCH_3), 3.70 (s, 3 H, NCH_3), 3.81–3.82 (m, 2 H, CH_2O), 5.35 (d, J = 9.2, 1 H, ArCH), 5.67 (d, J = 7.7, 1 H, ArCH), 6.93 (s, 1 H, NCH), 6.96 (s, 1 H, NCH), 7.41 (s, 1 H, NCH), 7.47 (s, 1 H, NCH). The doublets at 5.35 and 5.67 ppm correspond to the major isomers of a 4/3/1 mixture of lactone isomers. Anal. Calcd for $C_{11}H_{16}O_3N_2$: C, 58.9; H, 7.2; N, 12.5. Found: C, 58.8; H, 7.0; N, 12.2.

Hydrochloride of (+)-Pilocarpine (1) from Monoester 29. To a stirred solution of 1.00 g (3.9 mmol) of monoester **29** in 25 mL of 2-propanol, cooled to −5 °C, was added 436 mg (20.0 mmol) of lithium borohydride over a 10-min period. The solution was stirred for 1 h at −5 °C and then for 21 h at rt, and then it was diluted with 8.0 mL of methanol and stirred for 30 min. Next, 1.0 mL of water was added, and the solution was acidified to pH 1 with concentrated hydrochloric acid. After being stirred for 2 h the solution was evaporated at a bath temperature of 60 °C, and the residue was dissolved in 10 mL of 1 M aqueous hydrochloric acid and stirred for 30 min. The solution was cooled to 0 °C, solid sodium bicarbonate was added to pH 8, and then it was extracted with chloroform (3 × 100 mL). The combined organic extracts were dried, acidified with concentrated hydrochloric acid, and then evaporated to give 850 mg (88%) of a residue of essentially pure hydrochloride. Recrystallization of this material from ethanol/acetone afforded 715 mg (75%) of the hydrochloride of (+)-pilocarpine (**1**), identical with a twice-recrystallized sample of the natural product: mp 200–201 °C (lit.[32] mp 204–205 °C); $[\alpha]^{22}_D$ +88° (c 2.0, H_2O) (lit.[32] $[\alpha]^{22}_D$ +91°); ^{1}H NMR (D_2O) δ 0.90 (t, J = 7.5, 3 H, CH_3), 1.45 (m, 1 H, CH_2), 1.65 (m, 1 H, CH_2), 2.52 (dd, J = 16.1, 11.4, 1 H, CH_2), 2.73–2.80 (m, 2 H, CH and CH_2), 2.96 (m, 1 H, COCH), 3.66 (s, 3 H, CH_3), 4.01 (dd, J = 9.6, 3.2, 1 H, OCH_2), 4.24 (dd, J = 9.6, 5.8, 1 H, OCH_2), 7.16 (s, 1 H, CH), 8.48 (s, 1 H, CH); ^{13}C NMR (free base of (+)-1; $CDCl_3$) δ 12.1 (q), 18.2 (t), 21.2 (t), 31.3 (q), 37.2 (d), 44.8 (d), 69.8 (t), 126.9 (d), 128.5 (s), 138.2 (d), 177.8 (s).

(+)-Pilocarpine (1) from Hydroxymethyl Lactone 33. Nitrogen was bubbled through a solution of 449 mg (2.00 mmol) of lactone **33** in 25 mL of methanol for 15 min. To this solution was added 2.25 g of 10% palladium-on-charcoal, followed by 2.56 g (40.6 mmol) of ammonium formate. The black suspension was stirred at room temperature for 10 min, and then it was slowly heated to a bath temperature of 60–70 °C over a 30-min period, kept at this temperature for 21 h, cooled to rt, and filtered through Celite. The filter cake was washed with 100 mL of methanol and then with 90 mL of a 1/1 mixture of 2 N hydrochloric acid/methanol. The combined filtrate and washings were evaporated to give an orange solid which was dissolved in 45 mL of water, solid sodium bicarbonate was added to pH 8, and then the solution was extracted with chloroform (3 × 50 mL). The combined organic layers were dried and evaporated to give 234 mg (56%) of a mixture of **1** and **30**. The ^{1}H NMR spectrum of this material indicated a 6/1 ratio of **1** to **30**, based on comparison with the spectra of (+)-pilocarpine (**1**, above) and a sample of (−)-isopilocarpine (**30**) prepared previously.[7]

Acknowledgment. We are indebted to Undergraduate Research Participants Vu-Ahn Vuong and Jill Abramson for assistance in the preparation of intermediates.

(32) *Merck Index*, 10th ed.; Merck and Co., Inc.: Rahway, NJ, 1983; p 1070, no. 7301.