Chirospecific Synthesis of (+)-Pilocarpine

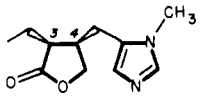
Reinaldo S. Compagnone[1] and Henry Rapoport*

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

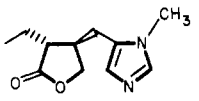
Received November 26, 1985

An efficient chirospecific synthesis for (+)-pilocarpine (**1a**) using D-methionine or D-2-aminobutanol as chiral educt is described. Formation of the C3–C4 carbon bond at an early stage gave the key intermediate diethyl [cyano((1-*tert*-butoxycarbonyl)propyl)methyl]phosphonate. Wittig coupling of this phosphonate with 1-methyl-5-imidazolecarboxaldehyde introduced the imidazole moiety of the pilocarpine skeleton. Selective reduction of an α,β-unsaturated nitrile to the corresponding allylic alcohol, stereocontrolled hydrogenation of the olefin, and epimerization of (+)-isopilocarpine to (+)-pilocarpine via kinetic protonation led to formation of the natural alkaloid. This methodology allows chirospecific syntheses of the four possible stereoisomers of pilocarpine. A short and convenient route to (±)-pilocarpine based on the key intermediate phosphonate is also described.

(+)-Pilocarpine (**1a**),[2] the most important imidazole alkaloid, has been for many years the focus of much attention because of its extensive pharmacological properties.[3] These include diaphoretic effects,[4] stimulation of the parasympathetic system,[4,5] miotic action,[6] and particularly applications in ophthalmology.[6] Pilocarpine is currently the drug of choice for treatment of narrow and wide angle glaucoma because it decreases the intraocular pressure and can be administered for long periods without side effects.[7] Pilocarpine along with its epimer isopilocarpine (**1b**) was first isolated in 1875[8] from various species



1a, (+)-pilocarpine



1b, (+)-isopilocarpine

of Pilocarpus plants belonging to the Rutaceae family. The structure of this alkaloid, proposed in 1900,[9] was later confirmed by degradation studies,[3b,10] X-ray analysis,[11] and several syntheses.[12-14]

Earlier syntheses[13-15] of (±)-**1a** were based on the formation of the lactone ring at an early stage followed by various group transformation and construction of the imidazole ring in the final stages. These syntheses suffered from the burden of many steps, low yields, lack of stereoselectivity, and mixtures of *N*-methylimidazole regiosiomers. A later approach to (+)-**1a** was based on using a preformed imidazole nucleus and building the lactone at a subsequent stage. However, the reported yield was less than 1%.[16] More recently a synthesis of (+)-**1a** starting with L-histidine was reported.[17] This synthesis is based on regioselective methylation of L-histidine, alkylation at the α-carbon with an ethyl malonate, and decarboxylation and formation of the lactone. In this last route the alkylation and decarboxylation steps occurred with limited stereochemical control, resulting in a mixture of diastereoisomeric products.

The strategy we adopted involved making the C3–C4 bond at an early stage to give diethyl [cyano(1-(*tert*-butoxycarbonyl)propyl)methyl]phosphonate (**10**), followed by coupling of the imidazole moiety to **10** and subsequent stereocontrolled formation of the lactone ring. Use of the cyano phosphonate ester **10** as the key intermediate allows linkage of the imidazole moeity via the phosphonate group. The construction of the lactone ring is carried out by selective reduction of the cyano functionality in the presence of a *tert*-butyl ester. Finally, asymmetric induction during reduction of the double bond of allylic alcohol **15** gives the natural product with the desired absolute stereochemistry.

Results and Discussion

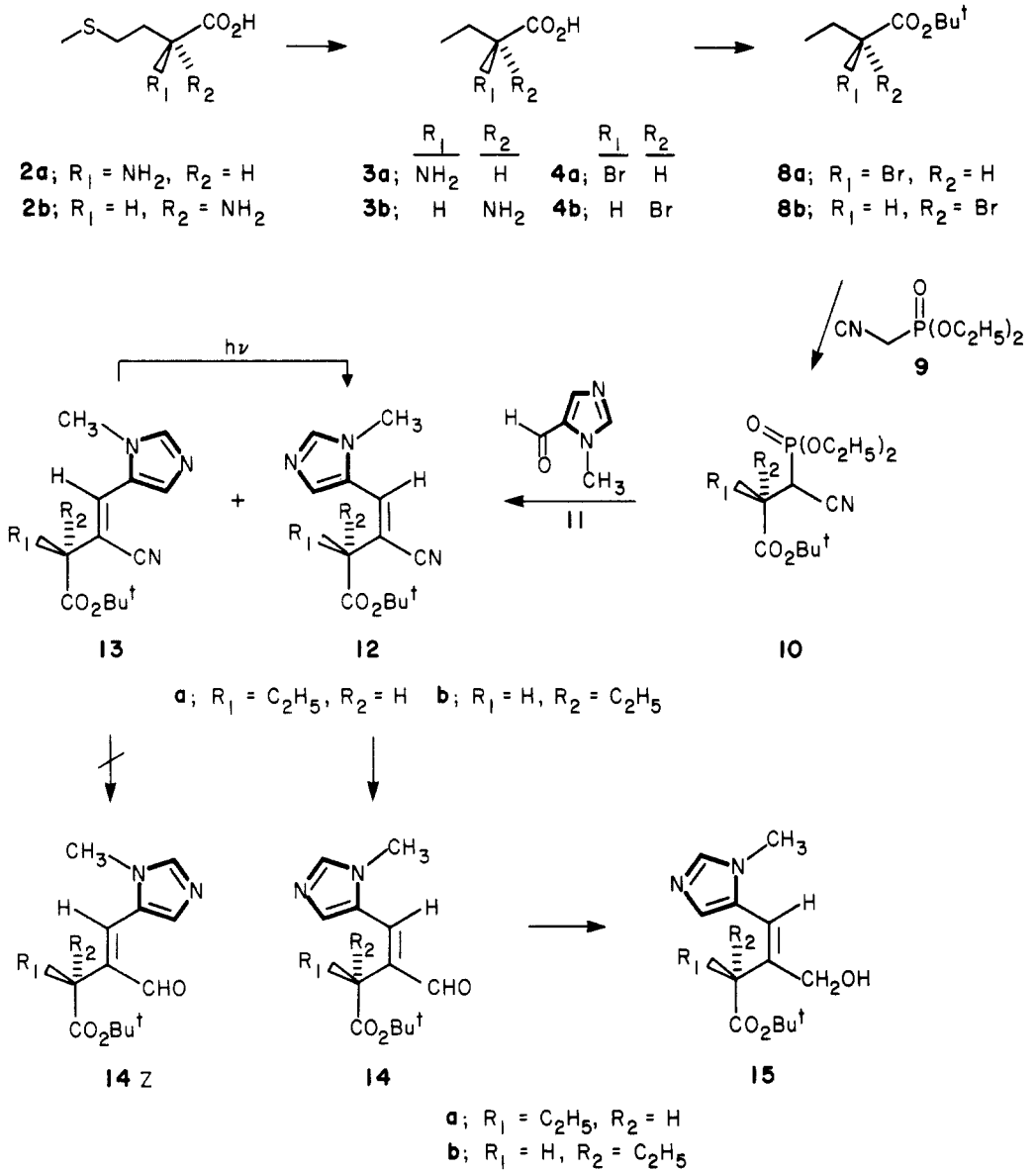
Alkylation of the anion of (cyanomethyl)phosphonate **9** (generated with potassium hydride in glyme) with (*R*)- and (*S*)-*tert*-butyl 2-bromobutyrate, **8b** and **8a**, respectively, gave the corresponding cyano phosphonates, **10b** and **10a**, in 89% yield (Scheme I). The most convenient protecting group for the carboxylate functionality proved to be the *tert*-butyl ester because of its stability in the subsequent transformations, and sodium hydride was inferior to potassium hydride for the alkylation.

(*R*)- and (*S*)-2-Bromobutyric acids, **4b** and **4a**, were made from the corresponding (*R*)- and (*S*)-2-aminobutyric acids **3b** and **3a**. (*R*)- and (*S*)-2-aminobutyric acids were conveniently and chirospecifically synthesized from D- and L-methionine, respectively, in 95% yield. Although the

(1) Recipient of a scholarship from the Consejo de Desarrollo Cientifico y Humanistico, Universidad Central de Venezuela, 1981–1985.
(2) Systemic name: (3*S*)-*cis*-3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl]-2(3*H*)furanone.
(3) (a) Goodman, L. S.; Gilman A. "The Pharmacological Basis of Therapeutics", 6th ed.; MacMillan: New York, 1980; p 97. (b) Manske, R. H. F.; Homes, H. L. "The Alkaloids"; Academic Press: New York, 1953; Vol. III, p 291.
(4) (a) Dreisbach, R. H. *J. Pharmacol. Exp. Ther.* **1961**, *131*, 257. (b) Dreisbach, R. H. *Am. J. Physiol.* **1963**, *204*, 497.
(5) Levy, B.; Ahliquist, R. P. *J. Pharmacol. Exp. Ther.* **1962**, *137*, 219.
(6) (a) Watson, P. G. *Br. J. Ophthalmol.* **1972**, *56*, 145. (b) Schwartz, B. *N. Engl. J. Med.* **1978**, *290*, 182.
(7) (a) Leopold, I. H.; Keates, E. *Clin. Pharm. Ther.* **1968**, *6* 262. (b) Worthen, D. M.; Zimmerman, T. J.; Wind, C. A. *Invest. Ophthalmol.* **1974**, *13*, 296. (c) Sanders, H. J. *Chem. Eng. News* **1985**, *63*(13), 30.
(8) (a) Gerrard, A. W. *Pharm. J.* **1975**, *5*, 86. (b) Hardy, E. *Bull. Soc. Chim. Fr.* **1875**, *24*, 497.
(9) Jowett, H. A. D. *J. Chem. Soc.* **1900**, *77*, 473; **1900**, *77*, 851; **1901**, *79*, 1331; **1901**, *79*, 580.
(10) Hill, R. K.; Barcza, S. *Tetrahedron* **1966**, *22*, 2889.
(11) Fregerslev, S.; Rasmussen, S. E. *Acta Chem. Scand.* **1968**, *22*, 2541.
(12) Jowett, H. A. D. *J. Chem. Soc., Abstr.* **1905**, *87*, 794.
(13) Preobrashenski, N. A.; Poljakowa, A. M.; Prebrashenski, W. A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1835.
(14) Dey, A. N. *J. Chem. Soc.* **1937**, 1057.
(15) DeGraw, J. I. *Tetrahedron* **1972**, *28*, 967.
(16) Link, H.; Bernauer, K. *Helv. Chim. Acta* **1972**, *55*, 1053.
(17) (a) Noordam, A.; Maat, L.; Beyerman, H. C. *Rec. J. R. Neth. Chem. Soc.* **1981**, *100*, 441. (b) Beyerman, H. C.; Matt, L.; Van Zon, A. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 246.

0022-3263/86/1951-1713$01.50/0

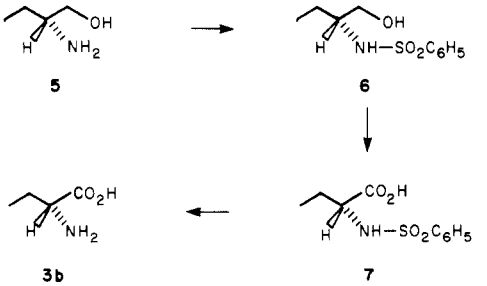
Scheme I. Synthesis of Precursor Allylic Alcohol 15 from 2-Bromobutyric Acid (4), (Cyanomethyl)phosphonate 9, and Imidazolealdehyde 11



synthesis of **3** by desulfurization of methionine has been reported,[18] no convincing data on the optical purity of the product have been presented. We found that using T-1 Raney nickel[19] in water at 75 °C for 5 h gave the highest yield without racemization. Other forms of RaNi (e.g., W-2) required longer reaction times and produced partially racemized product.

An alternate and more economical route to (*R*)-2-aminobutyric acid also was developed (Scheme II). D-2-Aminobutanol[20] (**5**) was protected as its (phenylsulfonyl)amide (**6**) and subjected to oxidation with oxygen in the presence of Pt[21] to afford the corresponding (*R*)-2-phenylsulfonamidobutyric acid (**7**). Subsequent cleavage of the (phenylsulfonyl) group resulted in the desired (*R*)-amino acid **3b** in 74% overall yield. The optical purity of the amino acids made by any of the previous routes was found to be >99% (the limits of detection) by diastereomer formation of the methyl esters with *N*-(phenylsulfonyl)-L-prolyl chloride and HPLC analysis.

Scheme II. Synthesis of (*R*)-2-Aminobutyric Acid (3b) from (*R*)-2-Aminobutanol (5)



Enantiomerically pure (*R*)- and (*S*)-2-bromobutyric acids, **4b** and **4a**, were prepared in 80% yield by deaminobromination of the corresponding D- or L-amino acids by using sodium nitrite and an excess of potassium bromide in acidic solution. To avoid racemization caused by the excess of bromide ions in solution, the reaction temperature was kept between −5 and 0 °C for 3 h. The optical purity of **4b** and **4a** that resulted was >99% (the limits

(18) (a) Fonken, G. S.; Mozingo, R. *J. Am. Chem. Soc.* **1947**, *69*, 1212. (b) Ohmori, S.; Takahashi, K.; Ikeda, M. *Z. Naturforsch, B: Anorg. Chem., Org. Chem.* **1981**, *36b*, 370.

(19) (a) Dominguez, X. A.; Cavazos-Opez, I.; Franco, R. *J. Am. Chem. Soc.* **1961**, *83*, 1625.

(20) (a) Pitre, D.; Grabitz, E. B. *Chimia* **1969**, *23*, 399. (b) Radke, F. H.; Fearing, R. B.; Fox, S. W. *J. Am. Chem. Soc.* **1954**, *76*, 2801.

(21) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

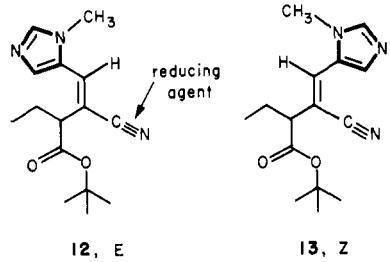
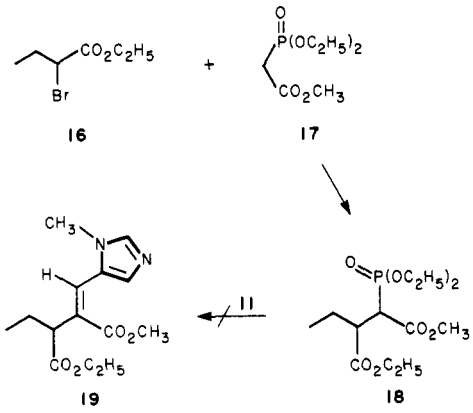


Figure 1. Approach of reducing agent to the unhindered side of nitrile in *E* isomer **12**. In the *Z* isomer **13**, approach from either direction is hindered.

Scheme III. Attempted Substitution of Phosphonoacetate 17 for Cyano Phosphonate 9



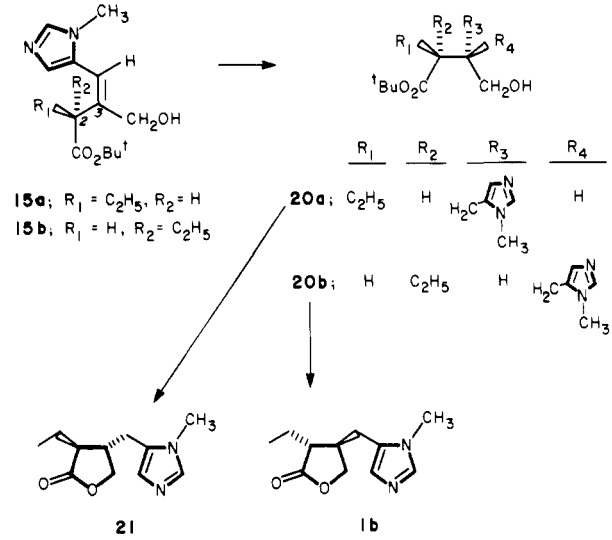
of detection) by HPLC analysis of the diastereomeric α-methylbenzylamide derivatives. Conversion of **4b** and **4a** to the *tert*-butyl esters **8b** and **8a** was achieved by treatment with isobutylene in dichloromethane and a catalytic amount of acid.

In analogy with the alkylation of cyano phosphonate **9** with α-bromo *tert*-butyl ester **8** we attempted to alkylate methyl (diethylphosphinyl)acetate (**17**) with α-bromoethyl ester **16** as shown in Scheme III. This approach was abandoned when we obtained a yield of only 60%, and the subsequent Wittig reaction with imidazolealdehyde **11** did not give any appreciable amount of olefin **19**.

Proceeding from alkylated (cyanomethyl)phosphonate **10**, the next step was Wittig coupling with 1-methyl-5-imidazolecarboxaldehyde (**11**).[22] Using potassium hydride as the base, a 6/4 mixture of *E*/*Z* olefins, **12**/**13**, was obtained in 95% yield. The two olefins showed a dramatic difference in chemical shift for the vinyl hydrogen (Δδ 0.7 ppm) and this was instrumental in assigning stereochemistry (see below). Selective reduction of the cyano group of **12** in the presence of the olefin and *tert*-butyl ester was accomplished by using W-2 Ra Ni and sodium hypophosphite in a mixture of pyridine, acetic acid, and water.[23] The aldehyde **14** was thus obtained in 64% yield along with 22% of recovered nitrile **12**. To avoid deactivation of the catalyst, the RaNi was added at 5 h-intervals over a period of 24 h at 50 °C with intense mixing. Different reaction times and/or temperatures resulted in overreduction of **1** and lower yields.

Reduction of the cyano group was possible only with the less hindered *E* isomers **12a** and **12b**; the *Z* isomers **13a** and **13b** remained unreactive under the same conditions. It is known[24] in simple models that reduction of nitriles

Scheme IV. Stereospecific Hydrogenation of Allylic Alcohols 15 and Lactonization to (+)- and (-)-Isopilocarpine



with Ra Ni is highly susceptible to steric hindrance. As is shown in Figure 1, in the *Z* olefin **13** the cyano group is shielded by the *tert*-butyl ester and the imidazole ring, thus approach by the reducing agent from either direction is severely restricted. The *Z* isomers **13a** and **13b** can be fully utilized, however, as they were converted to a 60/40 *E*/*Z* mixture by a simple photolytic isomerization in 10 min. Since the *E* and *Z* isomers **12** and **13** were readily separable, the overall yield of this step was not affected by the lack of reactivity of the *Z* isomer.

Conversion of the α,β-unsaturated aldehyde **14** to the allylic alcohol **15** was achieved cleanly in good yield by using 50 mol % of sodium borohydride and cerium chloride in methanol at 0 °C to prevent reduction of the double bond.[25] Larger amounts of sodium borohydride or longer reaction times resulted in reduction of the *tert*-butyl ester as well, and the use of DIBAL at −78 °C resulted in lower yields of **15**.

The relative stereochemistry of the olefins was determined by a NOESY ^{1}H NMR experiment on the allylic alcohol **15**. Observation of dipolar coupling between the vinyl hydrogen and the hydroxymethyl hydrogens and dipolar coupling between the allylic methine hydrogen and the C4 imidazole hydrogen confirmed that **15** was indeed the *E* isomer. The optical purity of **15** was established as better than 98% (the limits of detection) by diastereomer formation with α-methoxy-α-(trifluoromethyl)phenacetyl chloride and analysis by HPLC.

(+)- and (-)-Isopilocarpine (1b and 21). Hydrogenation of the allylic alcohols **15b** and **15a** (Scheme IV) resulted in quantitative yields of the respective saturated compounds **20b** and **20a**, diastereomerically and optically pure. Lactonization of **20a** and **20b** then proceeded in a mixture of TFA–water at room temperature in 97% yield. The stereochemical course of this hydrogenation was determined by ^{1}H NMR analysis and HPLC coelution experiments with (+)-pilocarpine and (+)-isopilocarpine as standards. We found that the reduction of **15b** and **15a** and lactonization led exclusively to the trans lactones **1b** and **21**, respectively. In order to determine whether a possible hydrogen-bonding effect between the primary alcohol and ester was responsible for this stereospecific reduction, we blocked the hydroxy group in **15** as its

(22) Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, *33*, 3758.
(23) Backeberg, O. G.; Staskun, B. *J. Chem. Soc.* **1962**, 3961.
(24) (a) Staskun, B.; Backeberg, O. G. *J. Chem. Soc.* **1964**, 5880. (b) Vaues, T.; Staskun, B. *J. Chem. Soc.* **1965**, 5775.
(25) Luche, J.-L.; Rodriquez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

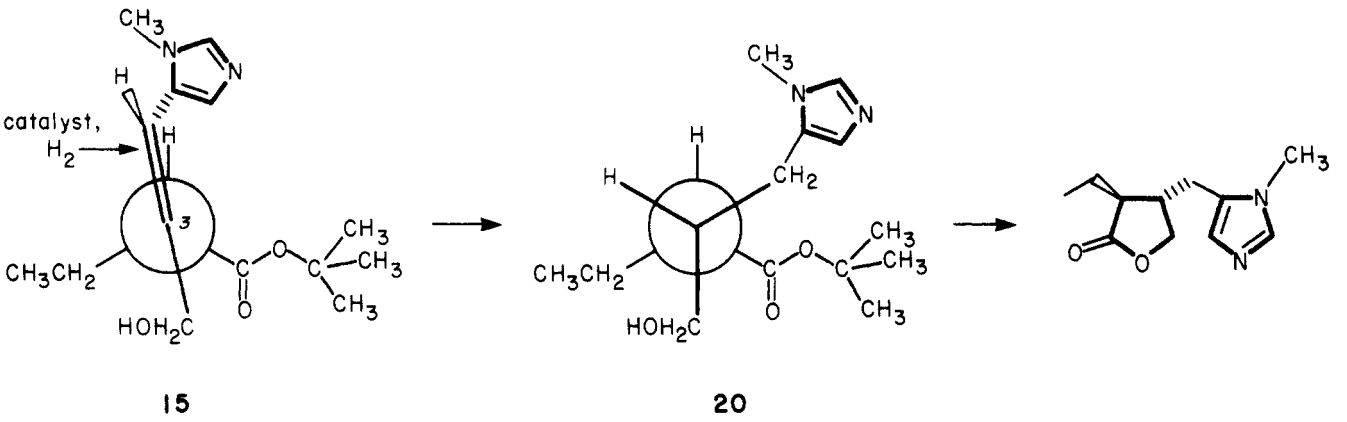


Figure 2. Stereospecific hydrogenation of allylic alcohols **15** via approach from the less hindered side of the olefin in the most stable C2–C3 conformation. Example shown is **15a** → **20a** → **21**. In the same way, **15b** → **20b** → **1b**.

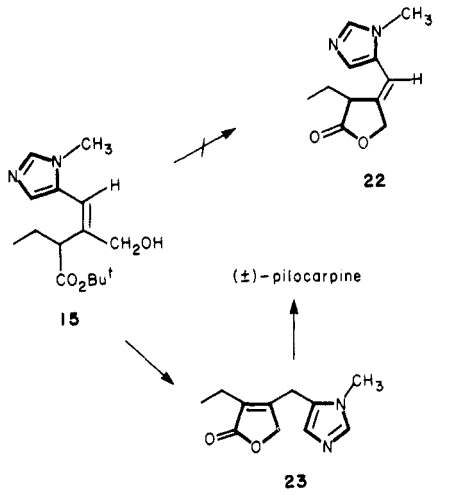
TBDMS ether. When this ether was subjected to hydrogenation, the trans lactone was again obtained exclusively, eliminating any hydrogen bonding influence on the stereochemistry of the hydrogenation.

To explain this specific asymmetric reduction, we assume that the reducing agent approaches the double bond from the less hindered side of the most stable conformation around the C2–C3 bond of **15** as is shown in Figure 2. According to this model, the catalyst/hydrogen complex reduces the double bond from the side opposite to the *tert*-butyl ester group on C2. Therefore, the configuration at C2 induces the stereochemistry at C3 and, hence, results in the trans lactone.

(+)-Pilocarpine (1a). The controlling chiral carbon for ultimate determination of the absolute stereochemistry is C4 (furanone numbering, 1) since the substituent groups are fixed and not epimerizable. On the other hand, the configuration at C3 can be readily epimerized to afford either diastereomer with the desired stereochemistry relative to C4. On the basis of this argument, it is obvious that D-2-aminobutyric acid (**3b**) was needed as educt for synthesis of the lactone with the stereochemistry at C4 corresponding to that of (+)-pilocarpine. Thus the synthetic sequence was carried out starting with **3b**, and optically pure (+)-isopilocarpine was obtained in 46% overall yield, allowing for recycles. Epimerization of (+)-isopilocarpine (**1b**) to (+)-pilocarpine (**1a**) then was accomplished under nonequilibrating conditions. Kinetic protonation,[26] in which the lactone enolate was generated and quenched at −78 °C, was the method of choice. Benzoic acid, aqueous sodium sulfate, and 2,4,6-tribromophenol gave cis/trans ratios of about 55/45. The best cis/trans ratio (75/25) was obtained with 2,6-di-*tert*-butyl-4-methylphenol. In addition to kinetic protonation, we also trapped the ester enolate of **1b** as its TBDMS ether. Hydrogenation of the double bond of this ketene acetal was not stereoselective and gave many products.

Of the numerous methods reported[27] for separation of (+)-pilocarpine (**1a**) and (+)-isopilocarpine (**1b**), HPLC is by far the most convenient. With this technique, we were able to separate **1a** and **1b** on a practical scale using a preparative normal-phase column with a mixture of isopropyl alcohol–hexane–ammonium hydroxide.[27b]

Scheme V. Synthesis of (±)-Pilocarpine



(±)-Pilocarpine. An alternative synthetic route was explored in which the hydrogenation–lactonization sequence (**15** → **20** → **1**/**21**) of Scheme IV was to be reversed. The strategy here was to lactonize first, forming β-exo-unsaturated lactone **22** as shown in Scheme V. Hydrogenation now from the less hindered face should lead to cis lactone, the chiro-inducer in this case being the enantiomeric α-carbon. This approach failed, however, when all methods for lactonization (acid, neutral, basic, and thermal) were accompanied by double-bond migration and led exclusively to the conjugated α,β-unsaturated lactone **23**. Hydrogenation of this unsaturated lactone **23** gave (±)-pilocarpine quantitatively. The entire sequence of seven steps from (±)-α-bromobutyric acid (**4**) to (±)-pilocarpine is extremely efficient and is completed in 57% overall yield, allowing for recycles. Since practical scale resolution of this racemic alkaloid using tartaric acid has been reported,[12] this sequence offers an alternative route to (+)-pilocarpine worthy of consideration. A few attempts were made to effect asymmetric hydrogenation of **23**, but these all failed.

Conclusion

In summary, we have developed a practical and versatile synthesis of (+)-pilocarpine (**1a**) from the educt (*R*)-α-aminobutyric acid (**3b**). The sequence initially gives (+)-isopilocarpine (**1b**) which is epimerized to **1a**. By using (*S*)-α-aminobutyric acid as educt, the enantiomers can be prepared, thus making all four stereoisomers available. A

(26) (a) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, 421. (b) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.

(27) (a) Dunn, D. L.; Thompson, R. E. *J. Chromatgr.* **1983**, *264*, 264. (b) Dunn, D. L.; Scott, B. S.; Dorsey, E. D. *J. Pharm. Sci.* **1981**, *70*, 446. (c) Noordam, A.; Waliszewski, K.; Olieman, C.; Maat, L.; Beyerman, H. C. *J. Chromatgr.* **1978**, *153*, 271. (d) Urbanyi, T.; Piedmont, A.; Willis, E.; Manning, G. *J. Pharm. Sci.* **1976**, *65*, 257. (e) Nunes, M. A.; Brochmann-Hanssen, E. *J. Pharm. Sci.* **1974**, *63*, 716. (f) Massa, V.; Gal. F.; Susplugas, P.; Maestre, G. *Trav. Soc. Pharm. Montepellier* **1970**, *30*, 267.

related sequence, starting with (±)-α-bromobutyric acid, results in a highly efficient synthesis of (±)-pilocarpine. In all cases, the key and versatile intermediate is (cyanomethyl)phosphonate **10**.

Experimental Section

General Methods. Unless otherwise specified, all reactions were carried out in oven-dried flasks at room temperature under an argon or nitrogen atmosphere with magnetic stirring. After extraction, organic solvents were dried over $MgSO_4$, filtered, and evaporated under reduced pressure on a rotary evaporator. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (glyme) were distilled from sodium/benzophenone. Diisopropylamine, triethylamine, and *N*-methylmorpholine were distilled from CaH_2. Methanol was distilled from magnesium methoxide; dimethylformamide (DMF) was decanted from molecular sieves, 4 Å. Dichloromethane and chloroform were distilled from P_2O_5. Other solvents (Mallinckrodt) were used without further purification. Melting points are uncorrected and were measured with a Buchi (capillary) apparatus. Unless otherwise specified, ^1H NMR spectra were obtained at 250 MHz as $CDCl_3$ solution by using Me_4Si as internal standard. Column chromatography was performed with 63–200-μm silica gel 60 (EM Reagents). TLC was done with aluminum-backed silica gel plates (E. Merck). Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

D- or L-2-Aminobutyric Acids (3b or 3a) from D- or L-Methionine (2b or 2a). To L-methionine (25 g, 168 mmol), dissolved in 2 L of water, was added 250 g of T_1 Raney Nickel. The mixture was heated with vigorous stirring for 4 h at 75 °C. The catalyst was then removed by centrifugation, and the aqueous solution was extracted with a 1% solution of 8-hydroxyquinoline in $CHCl_3$ (2 × 500 mL) and then washed with $CHCl_3$ (3 × 600 mL). Evaporation of the aqueous phase gave 16.7 g, 96% yield, of L-2-aminobutyric acid (**3a**): mp 275 °C (lit.[18a] mp 275 °C dec); ^1H NMR (D_2O) δ 1.05 (t, 3 H), 1.95 (m, 2 H), 3.80 (t, 1 H). Identical results were obtained from D-methionine (**2b**).

(*R*)-2-((Phenylsulfonyl)amino)butanol (6). D-2-Aminobutanol (**5**, 29 g, 325 mmol) and Na_2CO_3 (39 g, 370 mmol) in H_2O (250 mL) were vigorously stirred for 3 h with phenylsulfonyl chloride (65 g, 370 mmol), then acidified to pH 2 (concentrated HCl), and extracted with EtOAc (3 × 200 mL). The extracts were dried and evaporated to give 70 g, 94% yield, of sulfonamide **6**: mp 76–77 °C from benzene/isooctane; ^1H NMR δ 0.70 (t, 3 H, J = 7 Hz) 1.42 (m, 2 H, J = 7 Hz), 2.84 (br s, 1 H), 3.19 (br s, 1 H), 3.54 (m, 2 H), 5.52 (br s, 1 H), 7.47–7.93 (m, 5 H). Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.4; H, 6.5; N, 6.1. Found: C, 52.1; H, 6.3; N, 5.9.

(*R*)-2-((Phenylsulfonyl)amino)butyric Acid (7). To PtO_2 (1 g), reduced by shaking under H_2 (50 psi for 15 min in 150 mL of H_2O), was added ((phenylsulfonyl)amino)butanol **6** (1.60 g, 6.98 mmol), and oxygen was passed through the mixture at 55 °C for 48 h. The mixture was filtered. $NaHCO_3$ was added to the filtrate until it was faintly alkaline, and the aqueous solution was washed with EtOAc and then acidified (6 N, HCl) to pH 2. The acidic solution was extracted with EtOAc, and the extracts were dried and evaporated to give **7** (1.57 g, 92% yield): mp 131–132 °C from benzene/isooctane; ^1H NMR δ 0.90 (t, 3 H), 1.60–1.90 (m, 2 H), 3.92 (m, 1 H), 5.25 (d, 1 H), 7.45–7.90 (m, 5 H). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.4; H, 5.3; N, 5.7. Found: C, 49.4; H, 5.4; N, 5.7.

D-2-Aminobutyric Acid (3b). A mixture of **7** (1.50 g, 6.17 mmol), phenol (1.80 g, 19 mmol), and 48% HBr (24 mL) was refluxed for 30 min. After the mixture was cooled, it was washed with EtOAc and evaporated to a residue which was purified by ion exchange chromatography on Dowex Ag-1, X-8, 50–100 mesh, OH^-. After loading the column and washing it with H_2O, the amino acid was eluted with 1 N HOAc in 85% yield (540 mg): mp 279–281 °C dec (lit.[18a] mp 275 °C dec); identical with material obtained from D-methionine (**2b**).

L- or D-2-Bromobutyric Acid (4a or 4b). To 2 g (19.4 mmol) of 2-aminobutyric acid (**3**) and 8.2 g (69 mmol) of KBr dissolved in 46 mL of 2.5 N H_2SO_4 and cooled to −10 °C was added 2.06 g (30 mmol) of $NaNO_2$ over 1 h, keeping the temperature below −5 °C. After this mixture was stirred for 1.5 h at −5 °C, it was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried and evaporated, and the residue was distilled to give 2.52 g, 78% yield, of the bromo acid **4**: bp 95–98 °C/10 mm (lit.[28] bp 105–107 C/15 mm); ^1H NMR δ 1.05 (t, 3 H), 2.10 (m, 2 H), 4.10 (t, 1 H).

Optical Purity Determination of 2-Aminobutyric Acid and 2-Bromobutyric Acid. To determine the optical purity of the 2-aminobutyric acid (**3**), it was first converted to its methyl ester, and the ester was analyzed as its (phenylsulfonyl)proline amide. The 2-bromobutyric acid (**4**) was analyzed as its α-methylbenzylamide.

L- and D-Methyl 2-Aminobutyrate. A stream of dry hydrogen chloride was passed through a suspension of 206 mg (2 mmol) of 2-aminobutyric acid (**3**) in 15 mL of dry methanol. After all the amino acid was dissolved, the solution was cooled in an ice bath, and the introduction of gas continued until saturation. The reaction mixture was permitted to stand for 6 h at room temperature and then was concentrated to dryness in vacuo below 50 °C; 10 mL of methanol was added, and the concentration to dryness was repeated twice. The crystalline residue was recrystallized from methanol and ether to give 206 mg, 67% yield, of the methyl ester hydrochloride of 2-aminobutyric acid: mp 149 °C (lit.[29] mp 150 °C); ^1H NMR δ 1.15 (t, 3 H), 2.15 (m, 2 H), 3.80 (s, 3 H), 4.10 (m, 1 H).

L-(Phenylsulfonyl)proline Amides of L- and D,L-Methyl 2-Aminobutyrate. To 153 mg (1 mmol) of the methyl ester hydrochloride of 2-aminobutyric acid and 0.25 mL (2.3 mmol) of *N*-methylmorpholine, dissolved in 7 mL of THF was added 273 mg (1 mmol) of phenylsulfonylproline acid chloride,[21] and the solution was stirred at 0 °C for 6 h. Then 25 mL of 1/1 mixture of 10% H_3PO_4/ether was added and the organic layer was separated, washed with saturated sodium bicarbonate, dried, and evaporated to give 248 mg, 70% yield, of the desired amides: ^1H NMR δ 0.95 (t, 3 H), 1.60–1.95 (m, 6 H), 2.20 (m, 2 H), 3.12 (m, 1 H), 3.56 (m, 1 H), 3.80 (s, 3 H), 4.18 (m, 1 H), 4.55 (m, 1 H), 7.40–7.90 (m, 5 H). Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.2; H, 6.2; H, 6.2; N, 7.9. Found: C, 54.0; H, 6.3; N, 7.7.

HPLC of the L-L and L-D,L diastereoisomers was done by using an IBM normal-phase column, 60/40 hexane/EtOAc as eluting phase, monitoring at λ 260 nm, and a flow rate of 1.0 mL/min. Base-line separation was achieved, and both L- and D-2-ammobutyric acids were shown to be >99% (limit of detection) enantiomerically pure.

(+)-α-Methylbenzyl Amide of L- and D,L-2-Bromobutyric Acid. A solution of 47 mg (0.28 mmol) of L- or D,L-2-bromobutyric acid (**4**) in 5 mL of dry THF was cooled to −15 °C under nitrogen, and this solution was treated sequentially with 33 μL (0.3 mmol) of *N*-methylmorpholine and 39 μL (0.3 mmol) of isobutyl chloroformate and stirred at −15 °C for 1 min. To this mixture was added 45 μL (0.35 mmol) of (+)-α-methylbenzylamine, and the solution was stirred at −15 °C for 30 min. A 5% solution of citric acid (20 mL) was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with 20 mL of saturated sodium bicarbonate, dried, and evaporated to give 67 mg (94%) of the desired amides: mp 77–78 °C; ^1H NMR δ 1.00 (t, 3 H), 2.00–2.20 (m, 2 H), 4.15 (m, 1 H), 5.50 (m, 1 H), 6.65 (br s, 1 H), 7.30 (m, 5 H). Anal. Calcd for $C_{12}H_{16}NOBr$: C, 53.3; H, 5.9; N, 5.2. Found: C, 53.5; H, 6.1; N, 5.2.

HPLC analysis using an IBM normal-phase column, 10% EtOAc/hexane for elution, monitoring at λ 260 nm, with a flow rate of 1 mL/min gave base-line separation. An optical purity of 99% (limit of detection) was demonstrated for both L- and D-2-bromobutyric acids.

***tert*-Butyl (*R*)- or (*S*)-2-Bromobutyrate (8b or 8a).** A mixture of 24.2 g (14.5 mmol) of 2-bromobutyric acid (**4a** or **4b**), 200 mL of isobutylene, and 1.5 mL of concentrated sulfuric acid was shaken at room temperature for 3 days. The cooled solution was poured into 250 mL of saturated sodium bicarbonate and stirred for 1 h, and then the alkaline solution was extracted with chloroform (3 × 50 mL), dried, and evaporated. The residue was distilled to give 29.1 g, 90% yield, of the *tert*-butyl ester **8**: bp 70–74 °C/10 mm (lit.[30] bp 76 °C/15 mm); ^1H NMR δ 1.00 (t, 3

(28) Bellucci, G., Marioni, F., Marsili, A. *Tetrahedron* **1969**, *25*, 4167.
(29) Smith, E. L.; Polglase, W. J. *J. Biol. Chem.* **1949**, *180*, 1209.
(30) Bunting, J. W.; Murphy, J. *Can. J. Chem.* **1974**, *52*, 2640.

H), 1.43 (s, 9 H), 2.00 (m, 2 H), 4.05 (t, 1 H).

Diethyl [Cyano(1-(*tert*-butoxycarbonyl)propyl)methyl]-phosphonate (10a or 10b). Potassium hydride (5.70 g, 35% oil suspension, 50 mmol) was washed with hexanes (2 × 10 mL) and suspended in 50 mL of glyme in which diethyl (cyanomethyl)-phsophonate (8.9 g, 50 mmol)[31] was added dropwise. The mixture was stirred at room temperature for 1 h giving a homogeneous solution, and this solution, cooled to 0 °C, was added dropwise by cannula to 11.15 g (50 mmol) of *tert*-butyl 2-bromobutyrate in 20 mL of glyme. After having been stirred for 5 h at room temperature, the mixture was filtered, the precipitate was washed with ether, and the combined washings and filtrate were evaporated. The residue was chromatographed on silica gel, eluting with ether/CH_2Cl_2, 1/4, to give 14 g, 88% yield, of cyano phosphonate **10a** or **10b**: ^{1}H NMR δ 1.00 (t, 3 H), 1.40 (t, 6 H), 1.50 (2 s, 9 H), 1.80–2.10 (m, 2 H), 2.80 (m, 1 H), 3.20–3.50 (2 d, 1 H), 4.15 (m, 4 H). Anal. Calcd for $C_{14}H_{26}O_5NP$: C, 52.7; H, 8.1; N, 4.4. Found: C, 52.3; H, 8.2; N, 4.3.

***tert*-Butyl 3-Cyano-2-ethyl-4-(1-methyl-5-imidazolyl)-3-butenoate (12a, 12b; 13a, 13b).** Potassium hydride (4.15 g, 36.4 mmol, 35% oil suspension) was washed with hexanes (2 × 15 mL) and suspended in 150 mL of dry glyme. To this solution at 0 °C was added dropwise 11.59 g (36.4 mmol) of cyano phosphonate **10b** or **10a** in 15 mL of glyme. After this, the solution was stirred for 1 h at room temperature, 4.00 g (36.4 mmol) of freshly sublimed 1-methyl-5-imidazolecarboxaldehyde (**11**)[22] in 20 mL of dry glyme was added dropwise, and stirring was continued for 12 h at room temperature. The reaction was quenched by addition of 150 mL of water, the mixture was extracted with ether (3 × 200 mL), and the ether extracts were washed with water, dried, and evaporated to give 9.5 g, 95% yield, of an *E*/*Z* mixture of the olefins **12** and **13**. Chromatography using MPLC with ether/dichloromethane/methanol, 49/49/2, separated the isomers, present in an *E*/*Z* ratio of 63/37, into pure **12** and **13**. ^{1}H NMR of **12a**, **12b**: δ 1.00 (t, 3 H), 1.50 (s, 9 H), 1.80–2.10 (2 m, 2 H), 3.45 (s, 1 H), 3.65 (s, 3 H), 7.05 (s, 1 H), 7.56 (s, 2 H), 7.60 (s, 1 H). ^{1}H NMR of **13a**, **13b**: δ 1.00 (t, 3 H)8, 1.5 (s, 9 H), 1.80–2.10 (2 m, 2 H)8 3.05 (t, 1 H), 3.65 (s, 1 H), 6.85 (s, 1 H), 7.65 (s, 1 H), 8.05 (s, 1 H). Anal. Calcd for **12** or **13** $C_{15}H_{21}N_3O_2$: C, 65.4; H, 7.6; N, 15.3. Found for 12: C, 65.7; H, 7.5; N, 15.2. Found for 13: C, 65.6; H, 7.6; N, 15.2.

Isomerization of 13 to 12. A solution of 30 mg (0.11 mmol) of (*Z*)-**13b** or **13a** dissolved in 25 mL of degassed methanol through which N_2 was bubbled, was irradiated for 10 min with a 450-W Hanovia lamp by using a Corex filter. The solvent was then evaporated, and the residue was shown to consist of **12**/**13** in a ratio of 60/40 by ^{1}H NMR and HPLC. Using longer irradiation time or I_2 as a sensitizer did not change the ratio of isomers.

***tert*-Butyl 2-Ethyl-3-formyl-4-(1-methyl-5-imidazolyl)-(*E*)-3-butenoate (14a or 14b).** To 750 mg (2.72 mmol) of cyano olefin **12a** or **12b**, dissolved in 22 mL of a mixture of pyridine/acetic acid/water, 2/1/1, was added 1.5 g of sodium hypophosphite followed by 300 mg of W-2 Ra Ni. The mixture was stirred vigorously at 50 °C in a Morton flask for 3 h, 300 mg of Ra Ni was added, and the mixture was stirred for 5 additional h followed by another addition of 300 mg of W2 Ra Ni. This procedure was repeated twice, then the mixture was filtered, and the catalyst was washed with 20 mL of a mixture of hot pyridine/acetic acid/water, 2/1/1, followed by 50 mL of hot water. The combined washings and filtrate were extracted with 100 mL of CH_2Cl_2, dried, and evaporated to a residue which was chromatographed by using a mixture of ether/dichloromethane, 1/1, to give 167 mg, 22% yield, of recovered **12** and 488 mg, 64% yield, of aldehyde **14**: ^{1}H NMR δ 0.90 (t, 3 H), 1.43 (s, 9 H), 1.70–2.20 (2 m, 2 H), 3.65 (t, 1 H), 3.77 (s, 3 H), 7.10 (s, 1 H), 7.55 (s, 1 H), 7.65 (s, 1 H), 9.52 (s, 1 H). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.7; H, 7.9; N, 10.1. Found: C, 64.7; H, 8.0; N, 10.1.

***tert*-Butyl 2-Ethyl-3-(hydroxymethyl)-4-(1-methyl-5-imidazolyl)-(*E*)-3-butenoate (15a or 15b).** To a solution of **14a** or **14b** (728 mg, 2.62 mmol) and 866 mg (2.62 mmol) of $CeCl_3 \cdot 4.7 H_2O$ in 30 mL of methanol at 0 °C was added 49.4 mg (1.3 mmol) of sodium borohydride in small portions. After 5 min of stirring at 0 °C, 120 mL of water was added, and the mixture was extracted with chloroform (3 × 60 mL). The combined organic phase was dried and evaporated to an oil which was chromatographed by using methanol/dichloromethane, 5/95, affording 718 mg, 97% yield, of allylic alcohol **15a** or **15b**: mp 112–113 °C; ^{1}H NMR δ 0.82 (t, 3 H, J = 7.3 Hz), 1.47 (s, 9 H), 1.63 (m, 1 H), 1.65 (m, 1 H) 3.57 (s, 3 H), 3.60 (t, 1 H, J = 2.0 Hz), 4.18 (d, 1 H, J = 4.0 Hz), 4.38 (d, 1 H, J = 4.0 Hz), 6.44 (s, 1 H), 7.22 (s, 1 H), 7.45 (s, 1 H). Anal. Calcd for $C_{15}H_{24}O_3N_2$: C, 64.3; H, 8.6; N, 10.0. Found: C, 64.3; H, 8.7; N, 10.1.

***tert*-Butyl 2-Ethyl-3-(hydroxymethyl)-4-(1-methyl-5-imidazolyl)butanoate (20a or 20b).** To allylic alcohol **15** (105 mg, 0.38 mmol), dissolved in 20 mL of degassed methanol, was added 70 mg of 10% Pd/C, and the mixture was shaken for 1 h at room temperature at 50 psi of hydrogen. The mixture was then filtered, and the solvent was evaporated to give 104 mg, 97% yield, of the saturated alcohol **20a** or **20b**: mp 107–108 °C; ^{1}H NMR δ 0.92 (t, 3 H, J = 7.1 Hz), 1.49 (s, 9 H), 1.60–1.90 (m, 2 H), 2.45 (m, 1 H), 2.73 (m, 2 H), 3.58 (s, 3 H), 3.52 (dd, 1 H, J = 2 Hz), 3.71 (dd, 1 H, J = 2 Hz), 6.82 (s, 1 H), 7.38 (s, 1 H). Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.8; H, 9.2; N, 9.9. Found: C, 63.5; H, 9.4; N, 9.8.

(+)- or (−)-Isopilocarpine (1b or 21). A solution of **20a** or **20b** (850 mg, 3 mmol) in 20 mL of TFA/H_2O, 1/1, was stirred for 3 h at room temperature and then evaporated to a residue which was dissolved in 50 mL of cold saturated sodium bicarbonate. This alkaline solution was extracted with chloroform (3 × 25 mL), and the combined organic layer was washed with brine, dried, and evaporated to give 605 mg, 97% yield, of the trans lactone **1b** or **21**: ^{1}H NMR δ 1.00 (t, 3 H, J = 7.5 Hz), 1.72 (m, 2 H, J = 5.9 Hz), 2.27 (q, 1 H, J = 7.1 hZ), 2.66 (m, 2 H), 2.81 (q, 1 H), 3.56 (s, 3 H), 3.89 (q, 1 H, J = 9.3 Hz), 4.39 (q, 1 H, J = 9.3 Hz), 6.78 (s, 1 H), 7.40 (s, 1 H). (+)-Isopilocarpine nitrate was prepared as described[10]: mp 156–158 °C (lit.[10] mp 156–157 °C); $[\alpha]^{22}_D$ +35° (c 1, H_2O) (lit[9] $[\alpha]^{22}_D$ +35.7° (c 6.6, H_2O)).

Ethyl 3-(Diethylphosphinyl)-2-ethyl-3-(methoxycarbonyl)propionate (18). To potassium hydride (3.42 g, 35% oil suspension, 30 mmol) washed with hexanes (2 × 10 mL) and suspended in 60 mL of dry glyme at 0 °C was added dropwise 6.3 g (30 mmol) of methyl (diethylphosphinyl)acetate in 15 mL of dry glyme, and the mixture was stirred at room temperature for 1 h. This solution was cooled to 0 °C, 5.85 g (30 mmol) of ethyl 2-bromobutyrate in 15 mL of glyme was added dropwise, and the mixture was stirred for 16 h at 50 °C. The resulting mixture was filtered, and the filtrate was evaporated to an oil which was chromatographed, eluting with ether/CH_2Cl_2, 1/4, and gave 6.3 g, 60% yield, of the phosphono diester **18**: ^{1}H NMR δ 0.90 (t, 3 H), 1.35 (2 t, 6 H), 1.40–1.45 (2 s, 9 H), 1.60–2.00 (2 m, 2 H) 2.80–3.15 (m, 1 H), 3.10–3.25 (4 s, 1 H), 3.70–3.75 (2 s, 3 H), 4.15 (m, 4 H). Anal. Calcd for $C_{13}H_{25}O_7P$: C, 48.1; H, 7.7. Found: C, 47.7; H, 7.9.

Optical Purity of Alcohols 15 and 20. A mixture of allylic alcohol **15** (17 mg, 60 μmol), (−)- or (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (15 mg, 60 μmol) and 4-(dimethylamino)pyridine (0.07 mL, 60 μmol) in 2 mL of CH_2Cl_2 was stirred at 0 °C for 30 min. The mixture was washed with saturated $NaHCO_3$ (2 × 5 mL), and the organic layer was dried and evaporated to give the ester as an oil (29 mg, 96% yield): ^{1}H NMR δ 0.75 (t, 3 H, J = 7.2 Hz), 1.85 (s, 9 H), 1.85–2.00 (m, 2 H), 3.35 (s, 3 H), 3.49 (s, 3 H), 5.00 (m, 2 H), 6.22 (s, 1 H), 7.22 (s, 1 H), 7.31–7.47 (m, 6 H).

HPLC analysis of the total crude mixture using 50% EtOAc/hexane, λ = 260 nm, f = 1.5 mL/min, 25 × 4.5 mm IBM column, normal phase, showed **15** to be >98% optically pure. In the same way, saturated alcohol **20** was also demonstrated to be >98% pure, the limits of detection for this analytical system.

Epimerization of (+)-Isopilocarpine (1b) to (+)-Pilocarpine (1a). To 0.21 mL (1.5 mmol) of diisopropyl amine in 5 mL of tetrahydrofuran at 0 °C was added 0.97 mL (1.5 mmol) of *n*-butyllithium; the solution was stirred for 15 min and then cooled to −78 °C, and 100 mg (0.48 mmol) of (+)-isopilocarpine (**1b**) dissolved in 1 mL of tetrahydrofuran was added dropwise. This solution was stirred for 10 h at −78 °C and then 1 g of 2,6-di-*tert*-butyl-4-methylphenol dissolved in 1 mL of tetrahydrofuran was added. The solution was allowed to warm to room temperature, and 15 mL of 0.5 N HCl was added. This aqueous solution was washed with chloroform (2 × 25 mL), then the pH

(31) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

was adjusted to 8 with sodium bicarbonate, and it was extracted with chloroform (3 × 25 mL). The combined organic phase was dried and evaporated to give 98 mg, 98% yield, of a mixture of epimers in a ratio of 75/25 of (+)-pilocarpine (**1a**)/(+)-isopilocarpine (**1b**).

Separation of (+)-Pilocarpine (1a) and (+)-Isopilocarpine (1b). Separation of (+)-pilocarpine (**1a**) and (+)-isopilocarpine (**1b**) was carried out on a 50-mg scale by using a Whatman Partisil Magnum 9 preparative HPLC column, 10 × 50 cm; flow rate = 5.6 mL/min; λ = 215 nm; mobile phase; 0.6% NH_4OH, 30% isopropyl alcohol, 70% hexanes; volume of injections, 0.5 mL. The separated fractions were dried and evaporated resulting in diastereomerically pure materials with an efficiency of 98%.

3,4-Didehydropilocarpine (23). A solution of allylic alcohol **15** (330 mg, 1.2 mmol) in 4 mL of trifluoroacetic acid/water, 1/1, was stirred at room temperature for 2 h and then evaporated leaving a residue which was dissolved in 3 mL of saturated sodium bicarbonate and extracted with chloroform (3 × 3 mL). The combined organic phase was dried and evaporated to give 239 mg, 98% yield, of lactone **23**: ^{1}H NMR δ 1.12 (t, 3 H), 2.35 (q, 2 H), 3.55 (s, 3 H), 3.73 (s, 2 H), 4.55 (s, 2 H), 6.83 (s, 1 H), 7.45 (s, 1 H). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 63.8; H, 7.0; N, 13.5.

(±)-Pilocarpine. A mixture of unsaturated lactone **23** (205 mg, 1 mmol) and 150 mg of 10% Pd/C in 100 mL of methanol was shaken at 50 psi of hydrogen for 24 h. The mixture was filtered, the catalyst was washed with 20 mL of warm methanol, and the filtrate and washing were combined and evaporated to give 202 mg, 98% yield, of (±)-pilocarpine as a colorless oil: ^{1}H NMR δ 1.08 (t, 3 H), 1.53 (m, 1 H), 1.83 (m, 1 H), 2.18 (dd, 1 H), 2.60 (m, 2 H), 2.80 (m, 1 H), 3.55 (s, 3 H), 4.05 (dd, 1 H), 4.15 (dd, 1 H), 6.75 (s, 1 H), 7.40 (s, 1 H).

Acknowledgment. We are indebted to Mark Distefano for preparing some of the starting materials and to John O'Connell for obtaining the NOESY spectrum.

The Photolysis of Carbamoyl Azides in the Presence of Carbodiimides

Walter Lwowski,* Suji Kanemasa, Roy A. Murray, V. T. Ramakrishnan, T. K. Thiruvengadam, Kunihisa Yoshida, and A. Subbaraj

Department of Chemistry, New Mexico State University, Las Cruces, New Mexico 88003

Received September 23, 1985

The photolysis of some *N,N*-dialkylcarbamoyl azides in the presence of carbodiimides gives two types of products: cyclic ammonio amates **1** (from *N,N*-dialkylamino isocyanates, formed by a photo-Curtius rearrangement of the azides) and five-membered mesoinoic 5-(dialkylamino)-1,2,4-triazoles **7**, the structure of which was confirmed by independent synthesis. The formation of **7** constitutes a novel reaction path of carbamoyl azides.

Dialkylcarbamoyl azides undergo photo-Curtius rearrangement to give transient *N,N*-dialkylamino isocyanates, which can be isolated in a matrix[1] or react in various ways[2] such as by adding nucleophiles[3] or heterocumulenes such as isocyanates,[4-6] isothiocyanates,[6,7] carbodiimides,[5] or acetylenes.[8] In an earlier short communication[5] we mentioned the formation of two isomeric products from the photolysis of carbamoyl azides in the presence of carbodiimides. The major isomer was assigned the structure **1**, analogous to that of other amino isocyanate–heterocumulene adducts. We shall show here that this is correct. The minor isomer was earlier[5] assigned structure **2**, which is not correct. Proof for its having the structure **7** is given below.

Results and Discussion

Solutions of dialkylcarbamoyl azides in diethyl- or diisopropylcarbodiimide, with or without dichloromethane diluent, were photolyzed to give mixtures of two isomers. Their ratio was not very reproducible from run to run and appears not to depend much on concentration (over a range of 1.3 mol % in dichloromethane to pure carbodiimide), temperature, or wavelength (300 or 254 nm). By NMR, the ratio was found to be between 1.5 and 1.9. Isolation always involved losses of the minor isomer, giving apparent ratios of 2.8 to 3.3 of the pure isomers. Separation of the mixture requires great care, because mixtures and the pure minor isomers are very hygroscopic. The NMR spectra of both isomers show all four alkyl groups to be unchanged and still attached to nitrogen. The mass spectra indicate that both isomers are monomeric 1:1 adducts. The infrared spectra of **1** show high frequency bands in the carbonyl region, such as 1790 cm^{-1} for **1a** (R = Me, R′ = *i*-Pr), whose minor isomer has the highest C=X band at 1662 cm^{-1}. Dialkylamino isocyanate generated thermally in the presence of carbodiimides did not produce any minor isomers—these were formed exclusively by photolysis of systems containing both dialkylcarbamoyl azide and carbodiimide. The two isomers could not be interconverted by photolysis or any other means tried. Conclusive structure proof is given below for **1**—for which details have not yet been published—and for the lesser isomers (**7**).

The Structure of Isomers 1. Isomers **1** are five-membered cyclic ammonio amates, analogous to those already described,[4-8] with an imino group in position 5. Like the former, they revert to the starting materials upon heating and by photolysis. Isomer **1a** (R = Me, R′ = *i*-Pr) was completely destroyed in 2 min at 212 °C. Thermolysis and photolysis of **1a** in dilute solution gave the dimer of

(1) Lwowski, W.; deMauriac, R. A.; Thompson, M.; Wilde, R. E.; Chen, S.-Y. *J. Org. Chem.* **1975**, *40*, 2608.
(2) Bertho, A. *J. Prakt. Chem.* **1928**, *120*. Scott, F. L. *Chem. Ind. (London)* **1954**, 959. Kametani, T.; Shiho, M. *J. Heterocycl. Chem.* **1971**, *8* 545. Koga, N. Koga, G. Anselme, J.-P. *Tetrahedron* **1972**, *28*, 4515.
(3) Lwowski, W.; deMauriac, R.; Mattingly, T. W., Jr.; Scheiffele, E. *Tetrahedron Lett.* **1964**, 3285.
(4) Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1967**, *32*, 1279.
(5) Lwowski, W.; deMauriac, R. A.; Murray, R. A.; Luenow, L. *Tetrahedron Lett.* **1971**, 425.
(6) Lockley, W. J. S.; Ramakrishnan, V. T.; Lwowski, W. *Tetrahedron Lett.* **1974**, 2621.
(7) Ramakrishnan, V. T.; Lwowski, W. *Tetrahedron Lett.* **1974**, 3249.
(8) Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, 4263.

0022-3263/86/1951-1719$01.50/0