A Synthesis of Pilocarpine

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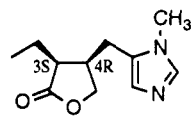
Pilocarpine (1) was synthesized in seven steps starting from 2-acetylbutyrolactone. Chirality was introduced by asymmetric reduction of enone **4** and transferred via a Claisen rearrangement. A mild procedure for the preparation of 1,5-disubstituted imidazoles in the last synthetic operation led to pilocarpine unaccompanied by isopilocarpine.

Pilocarpine (1), first isolated in 1875 from the leaves of *Pilocarpus jaborandi*,[1] is a leading therapeutic agent for the treatment of narrow and wide angle glaucoma.[2] The sole source for pilocarpine during the past century has been from the leaves of a tree (*P. microphyllus*) that grows only in the tropical rainforests of Brazil and Paraguay. Man's continued devastation of these forests will inevitably lead to its disappearance as well as the loss of many other medicinally important natural products. At a glance, pilocarpine is a deceptively simple looking molecule. The stereospecific construction of the imidazole moiety cis to the ethyl group on the butyrolactone ring represents a challenge that has attracted seven independent syntheses.[3] Three of these give optically active materials;[3a-c] none produce the alkaloid without its undesirable C_3 epimer, isopilocarpine. In this report, we describe a four-step synthesis of pilocarpine (1) from acetylbutenolide **4**.



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Chemical degradation of pilocarpine through its imidazole ring has produced several derivatives of homopilopic acid[4] which may hypothetically serve as precursors in the biogenetic pathway. When considering possible synthetic approaches to this alkaloid, we felt that homopilopic aldehyde **7** would be a suitable intermediate for the delayed preparation of the imidazole moiety. The first key intermediate of the synthesis, unsaturated acetylbutyrolactone **4**, has been described by Hoye[5] as unstable, a finding which is contrary to a report by Liotta.[6] Our efforts revealed that **4** was indeed unstable *under the conditions used for its generation.* Starting from commercial 2-acetylbutyrolactone, selenenylation proceeded in a straightforward manner affording seleno lactone **2** in 94% yield. Only the corresponding epoxide could be isolated from the selenoxide elimination under the oxidative conditions utilizing hydrogen peroxide.[7] When the oxidative elimination was carried out in the presence of excess cyclopentadiene, however, good yields of endo and exo bicyclo ketones **3n** and **3x** were obtained in a 2.3:1 ratio, respectively.[5] Flash vacuum thermolysis of ketones **3n** and **3x** worked beautifully to give prochiral enone **4** as a white solid in 95% yield. While the problem of establishing asymmetry at C_3 and C_4 has been partially overcome through modifications of optically active starting materials,[3a,b] our synthetic plan is based on a reagent-controlled approach where asymmetry would be introduced by an enantioselective reduction of ketone **4** and transferred via a Claisen rearrangement. Among the various asymmetric reducing agents which have been reported for chiral reductions,[8] we found (+)-β-chlorodiisopinocamphenylborane[9] [(+)-Ipc_2BCl] to be the reagent of choice. By necessity, reduction occurred under mild conditions with high regio- and enantiospecificity. The desired (*R*)-alcohol **5** was produced in 60% chemical yield[10]

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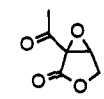
(5) Hoye, T. R.; Caruso, A. J.; Magee, A. S. *J. Org. Chem.* **1982**, *47*, 4152.

(6) Liotta, D.; Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* **1981**, *22*, 3043.

(7) The following epoxide was isolated as a colorless liquid from the reaction: ^1H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 4.36 (dd, J = 11.8, 1.5 Hz, 1 H), 4.45 (d, J = 1.5 Hz, 1 H), 4.48 (d, J = 11.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.8 (q), 58.8 (s), 62.2 (d), 67.1 (t), 167.4 (s), 197.0 (s); IR ($CHCl_3$) 3005, 1800, 1720, 1400, 1360, 1090, 1070 cm^{-1}; MS, *m/z* (rel intensity) 142 (M^+, 23.8), 43 (100).



(8) For reviews on asymmetric ketone reduction, see: (a) Morrison, J. D. *Asymmetric Synthesis*: Academic Press: New York, 1983; Vol. 2, Chapters 2-5. (b) Brown, H. C. *Modern Synthetic Methods IV*; New York: Springer-Verlag, 1986; p 307. For recent developments, see: (c) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollman, T.; Kennedy, R.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402. (d) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

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(10) In an alternative synthetic sequence for the preparation of (*R*)-alcohol **5**, asymmetric reduction of endo and exo ketones **3n** and **3x** with (+)-Ipc_2BCl gave a separable mixture of crystalline diastereomeric alcohols with the (*R*)-configuration. Although the percent diastereomeric excesses are somewhat lower for these alcohols (75-92% ee), they can, in principle,

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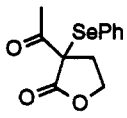
with an optical purity of greater than 92% as determined by 300-MHz ^1H NMR analysis of its Mosher ester.



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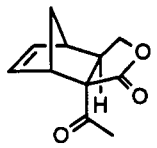

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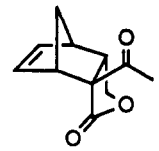

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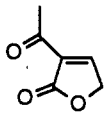

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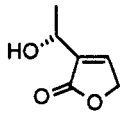

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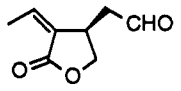

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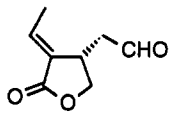
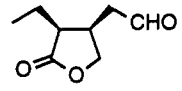


6a



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The Claisen rearrangement of (*R*)-allylic alcohol **5** as its vinyl ether appeared to be particularly suited for introducing the stereocenter at C_4.[11] The rearrangement would afford an exocyclic double bond and the (4*R*)-acetaldehyde side chain necessary for the formation of the imidazole ring. Using (*R*)-allylic alcohol **5**, rearrangement proceeded without loss of chirality and isolation of the vinyl ether intermediate to give a separable 2:1 mixture of the desired (4*R*)-*Z*-aldehyde **6** and its (4*S*)-*E*-diastereomer **6a** in 71% yield. While the functionally substituted C_4 substituent was readily available by this sequence, stereospecific hydrogenation of aldehyde **6** to give the cis diastereomer **7** was not as straightforward. The common hydrogenation solvents such as ethanol and ethyl acetate afforded the unexpected trans product as the major diastereomer under both 1 atm and 50 psi of hydrogen. Only when pyridine was used as a cosolvent with benzene did preferential hydrogenation occur from the least-hindered face. One plausible explanation for this enhanced cis specificity is formation of a pyridine–palladium complex which experiences a greater steric interaction from the (4*R*)-acetaldehyde side chain. This conclusion is not without precedence, as previously described by Sih.[12]

The completion of the synthesis of pilocarpine required elaboration of the aldehyde function to the requisite 1,5-disubstituted imidazole. Our primary concern was whether the imidazole ring could be prepared without epimerization at C_3. A method describing the preparation of 1,5-disubstituted imidazoles from imines by van Leusen et al.[13] was chosen because of the reportedly mild reaction conditions. Their procedure is based on the anionic [3 + 2] cycloaddition–elimination reaction of (*p*-tolylsulfonyl)-methyl isocyanide (TosMIC) with aldimines. The reaction is initiated by a mildly basic solution of potassium carbonate in methanol. We have found that under these conditions the formation of pilocarpine through the methyl imine of aldehyde **7** proceeded with only limited success (<15%). Similar low yields have also been reported for the synthesis of various 1,5-dialkylimidazoles[14] using the published procedure. On the basis of related transformations of tosyl oxazolines with various nucleophiles,[15] addition of methanol to the tosylimidazoline intermediate is believed to preclude the formation of the imidazole ring. It became clear that preparation of the 1,5-disubstituted imidazole moiety would require an absence of extraneous nucleophiles. Thus, when the reaction was performed under aprotic conditions and in the absence of excess methylamine, a 61% yield of pilocarpine (**1**) was obtained from aldehyde **7** without isolation of the aldimine intermediate. Moreover, the reaction proceeded without epimerization at C_3 and the present synthesis appears to be the first leading to pilocarpine unaccompanied by isopilocarpine.

Experimental Section

Melting points are uncorrected. Proton and carbon nuclear magnetic resonance spectra were measured at 300 and 75.4 MHz, respectively. Analytical thin-layer chromatography (TLC) was conducted on Merck precoated glass backed silica gel 60 F-254 plates, 0.25 mm layer thickness. Flash chromatography was performed using 230–400-mesh silica gel.

2-Acetyl-2-(phenylselenenyl)butyrolactone (2). A 1-L, three necked, round-bottom flask equipped with a 50-mL addition funnel and thermometer was charged with sodium hydride (5.15 g, 129 mmol, 60% oil dispersion washed 3× with dry pentane) and 300 mL of THF. To the stirred suspension was slowly added a solution of 2-acetylbutyrolactone (Aldrich, 15 g, 117 mmol) in 20 mL of THF while the reaction temperature was maintained at 0 °C. Following the addition (30 min), the resulting clear solution was allowed to stir an additional 30 min at 0 °C and was then rapidly treated with a solution of phenylselenenyl chloride (24.7 g, 129 mmol) in 50 mL of THF. After being stirred for 5 min at 0 °C, the reaction mixture was diluted with 300 mL of Et_2O, washed with 150 mL of saturated $NaHCO_3$, H_2O, and brine, and then dried ($MgSO_4$). Concentration and flash chromatography (15% EtOAc/hexane) afforded 31.1 g (94%) of seleno lactone **2**, mp 34–35 °C (Et_2O/hexane): ^1H NMR ($CDCl_3$) δ 2.10 (ddd, J = 13.0, 6.3, 2.7 Hz, 1 H), 2.65 (s, 3 H), 2.77 (m, 1 H), 4.24–4.38 (m, 2 H), 7.34–7.54 (m, 5 H); IR ($CHCl_3$) 3005, 1765, 1700 cm^{-1}; UV (EtOH) λ_{max} 203, 231, 270, 312 nm; MS, m/z (relative intensity) 284 (M^+ + 2, 6), 282 (M^+, 3), 43 (100). Anal. Calcd for $C_{12}H_{12}O_3Se$: C, 50.88; H, 4.27. Found: C, 50.95; H, 4.16.

Endo and Exo Ketones 3n and 3x. A 2-L, three-necked, round-bottom flask, equipped with a mechanical stirrer, a 100-mL addition funnel, and a thermometer, was charged with 700 mL of CH_2Cl_2, selenide **2** (49.0 g, 173 mmol), and cyclopentadiene (23.5 g, 346 mmol). The resulting solution was cooled to 0 °C (internal temperature) and vigorously stirred while 30% hydrogen peroxide (58.9 g, 519 mmol) was cautiously added dropwise. Following the addition of ca. 1 g of H_2O_2 and often with delay, a rapid temperature increase occurred, reaching a controlled maximum of 7 °C. Further treatment with H_2O_2 was stopped until the temperature descended between 0 and 4 °C, after which the entire addition was maintained in this range. Patience and care must be taken in order to avoid a potentially disasterous, rapid increase in reaction temperature resulting from an initial overaddition of H_2O_2. After being stirred for 1 h at 0 °C, the reaction mixture was stirred an additional 4 h at 25 °C and was then filtered. The solid was rinsed with 200 mL of CH_2Cl_2, and

be recrystallized to give enantiomerically pure compounds. Flash vacuum thermolysis of these alcohols gave the optically active (*R*)-allylic alcohol **5**. The Mosher esters of the thermolysis products confirmed the (*R*)-configuration and established their optical purity. The additional manipulation required of these diastereomers along with a generally lower optical purity demanded a search for an alternative approach.

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the filtrate washed with 300 mL of saturated $NaHCO_3$ (3×) and brine and dried ($MgSO_4$). Concentration and flash chromatography (40% Et_2O/hexane) afforded 17.96 g (54%) of endo ketone **3n** and 7.81 g (24%) of exo ketone **3x**. **3n**: mp 78–79 °C (Et_2O/hexane); R_f 0.42 (40% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.65 (d, J = 1.6 Hz, 2 H), 2.97 (br s, 1 H), 3.05 (dd, J = 9.7, 3.7 Hz, 1 H), 3.57 (br s, 1 H), 4.04 (dd, J = 9.7, 3.7 Hz, 1 H), 4.50 (dd, J = 9.7, 8.3 Hz, 1 H), 6.09 (dd, J = 5.6, 2.9 Hz, 1 H), 6.31 (dd, J = 5.6, 2.9 Hz, 1 H); IR ($CHCl_3$) 3000, 1755, 1710 cm^{-1}; UV (EtOH) λ_{max} 279 nm; MS, m/z (relative intensity) 192 (M^+, 1.3), 66 (100). **3x**: mp 64–65 °C (Et_2O/hexane); R_f 0.39 (40% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.53 (d, J = 8.0 Hz, 1 H), 1.63 (d, J = 8.0 Hz, 1 H), 2.48 (s, 3 H), 3.12 (br s, 1 H), 3.47 (br s, 1 H), 3.52 (m, 1 H), 3.82 (dd, J = 10.0, 3.3 Hz, 1 H), 4.31 (dd, J = 10.0, 10.0 Hz, 1 H), 6.38 (dd, J = 5.5, 3.0 Hz, 1 H), 6.40 (dd, J = 5.5, 3.0 Hz, 1 H); IR ($CHCl_3$) 3000, 1755, 1705 cm^{-1}; UV (EtOH) λ_{max} 279 nm; MS, m/z (relative intensity) 192 (M^+, 0.9), 66 (100).

3-Acetyl-2(5*H*)-furanone (4). A straight piece of vycor tubing (overall length = 53 cm, i.d. = 12 mm) possessing a 14/20 male ground glass joint at one end and a 14/20 female one at the other was attached to a 25-mL pear-shaped flasked containing endo and/or exo ketone **3** (1.0 g, 5.2 mmol). The female end of the tube was next fitted to a vacuum pump via a male connector. Vacuum was applied (p = 0.01 mm) and the vycor tube was placed in a Lindberg oven (Model 55035, oven length = 36 cm) in such a way that the pear-shaped flask was projecting out of one end of the oven exit and the vacuum end out of the other. The oven exits were next insulated with glass wool and the apparatus was tilted at an angle of 30° in such a way that the receiving end was lower than the entrance. Pyrolysis took place at 425 °C upon distillation of the ketone directly into the oven tube by means of a Büchi Kugelrohr distillation apparatus (T = 165 °C, p = 0.01 mm). The product, unsaturated acetylbutyrolactone **4** was collected as a white solid (632 mg, 95%) by cooling the vacuum end of the tube (dry ice–acetone): mp 47–49 °C dec; ^1H NMR ($CDCl_3$) δ 2.85 (s, 3 H), 4.95 (d, J = 2.3 Hz, 2 H), 8.26 (t, J = 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.8 (q), 69.6 (t), 132.3 (s), 158.4 (d), 169.7 (s), 191.9 (s); IR ($CHCl_3$) 3005, 1770, 1700, 1070 cm^{-1}; HRMS, m/z calcd for $C_6H_6O_3$ (M^+) 126.0317, found 126.0315.

(3*R*)-3-(1-Hydroxyethyl)-2(5*H*)-furanone (5). All manipulations of (+)-Ipc_2BCl were carried out in a glovebag under an atmosphere of argon. To a stirred suspension of (+)-β-chlorodiisopinocamphenylborane [(+)-Ipc_2BCl] (9.75 g, 30.4 mmol) in 100 mL of THF at −30 °C was added enone **4** (2.1 g, 15.2 mmol) under an argon blanket. After the solution was stirred for 3 days under argon at −30 °C, all of the ketone and most of the reducing agent had dissolved. After 5 days, the mixture was concentrated and the α-pinene formed during the reaction was removed under reduced pressure (0.01 mm, 8 h). The residue was then dissolved in 50 mL of Et_2O and stirred while diethanolamine (3.51 g, 33.4 mmol) was added. After 2 h the solid was filtered and washed with ether. Concentration of the filtrate and flash chromatography (20% EtOAc/CH_2Cl_2) of the residue afforded 1.16 g (60%) of alcohol **5** as a colorless oil, $[\alpha]^{23}_D$ = +34.6° (EtOH, c 0.011): bp 120 °C (p = 0.01 mm, bulb to bulb); R_f 0.28 (20% Et_2O/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 7.0 Hz, 3 H), 2.80 (d, 1 H, D_2O exchanged), 4.69 (m, 1 H), 4.84 (dd, J = 2.2, 2.2 Hz, 2 H), 7.33 (dd, J = 4.5, 2.2 Hz, 1 H); IR ($CHCl_3$) 3600, 3480, 3000, 1750, 1450, 1350, 1060, 840 cm^{-1}; MS, m/z (relative intensity) 127 (M^+, 0.4), 113 (97), 85 (100). Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.28; H, 6.29. The Mosher ester derivative of **5** (from (+)-MTPA-Cl) gave methylene signals at 4.77 and 4.83 ppm (300-MHz ^1H NMR spectrum) favoring a 92% ee for the downfield signal. (*R*)-MTPA ester: R_f 0.32 (50% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.56 (d, J = 7.0 Hz, 3 H), 3.54 (br s, 3 H), 4.83 (dd, J = 2.1, 2.1 Hz, 2 H), 5.90 (m, 1 H), 7.33 (dd, J = 3.7, 2.1 Hz, 1 H), 7.43 (m, 3 H), 7.53 (m, 2 H); IR ($CHCl_3$) 3000, 1760 cm^{-1}. (*S*)-MTPA ester: mp 74–75 °C; R_f 0.40 (50% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.61 (d, J = 7.0 Hz, 3 H), 3.57 (br s, 3 H), 4.77 (dd, J = 1.2, 1.2 Hz, 2 H), 5.92 (m, 1 H), 7.08 (dd, J = 3.6, 1.2 Hz, 1 H), 7.44 (m, 3 H), 7.54 (m, 2 H); IR ($CHCl_3$) 3000, 1760 cm^{-1}.

(4*R*)-(*Z*)-Dehydrohomopilopic Aldehyde (6). A resealable pressure tube (Ace Glass) under argon was charged with 30 mL of freshly distilled and degassed ethyl vinyl ether, (*R*)-alcohol **5** (500 mg, 3.90 mmol), and recrystallized mercuric(II) acetate (1.23 mg, 1.0 equiv). The resulting solution was heated between 135 and 140 °C for 24 h. After cooling, concentration of the reaction mixture and flash chromatography (3% Et_2O/CH_2Cl_2) of the residue afforded 288 mg (48%) of **6** and 138 mg (23%) of the *E*-diastereomer **6a**. Continued elution using 20% Et_2O/CH_2Cl_2 afforded 58 mg (11%) of starting alcohol **5**. Aldehyde **6**: colorless oil, $[\alpha]^{23}_D$ +84.7° ($CHCl_3$, c 0.01); R_f 0.38 (50% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 2.20 (dd, J = 7.3, 1.9 Hz, 3 H), 2.73 (dd, J = 19.3, 8.8 Hz, 1 H), 2.89 (dd, J = 19.3, 5.7 Hz, 1 H), 3.50 (m, 1 H), 3.88 (dd, J = 9.2, 5.3 Hz, 1 H), 4.56 (dd, J = 9.2, 8.5 Hz, 1 H), 6.30 (dq, J = 7.3, 2.6 Hz, 1 H), 9.82 (t, J = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 33.9 (d), 48.2 (t), 70.3 (t), 127.5 (s), 139.4 (d), 169.5 (s), 199.4 (d); IR ($CHCl_3$) 3005, 1750, 1723, 1670 cm^{-1}; MS, m/z (relative intensity) 154 (M^+, 15), 126 (70), 111 (69), 67 (96), 41 (100); HRMS m/z calcd for $C_8H_{10}O_3$ (M^+) 154.0630, found 154.0630. (4*S*)-*E*-diastereomer **6a**: colorless oil, R_f 0.22 (50% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.90 (dd, J = 7.4, 1.7 Hz, 3 H), 2.77 (dd, J = 18.9, 8.8 Hz, 1 H), 2.86 (dd, J = 15.7, 4.5 Hz, 1 H), 3.55 (m, 1 H), 3.85 (dd, J = 9.2, 5.3 Hz, 1 H), 4.48 (dd, J = 9.2, 8.5 Hz, 1 H), 6.83 (dq, J = 7.3, 1.6 Hz, 1 H), 9.76 (t, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.0 (q), 30.9 (d), 47.2 (t), 70.9 (t), 129.2 (s), 136.9 (d), 170.3 (s), 199.4 (d); IR ($CHCl_3$) 3000, 1755, 1723, 1680 cm^{-1}; MS, m/z (relative intensity) 154 (M^+, 11), 126 (60), 111 (49), 67 (83), 41 (100); HRMS, m/z calcd for $C_8H_{10}O_3$ (M^+) 154.0630, found 154.0628.

(3*S*,*cis*)-Homopilopic Aldehyde (7). A mixture of *Z*-aldehyde **6** (174 mg, 1.11 mmol) and 10% Pd/C (30 mg) in 10 mL of a pyridine/benzene (1:1) solution at 25 °C was hydrogenated under 1 atm for 1 h. The reaction mixture was filtered over a pad of Celite and then rinsed with CH_2Cl_2. Concentration of the filtrate afforded 165 mg (98%) of **7** and its trans diastereomer, isohomopilopic aldehyde, as a 3:2 mixture. Flash chromatography of the mixture (45% EtOAc/hexane) afforded pure **7** as a colorless oil, R_f 0.33 (75% Et_2O/hexane): ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3 H), 1.42 (m, 1 H), 1.81 (m, 1 H), 2.53 (dd, J = 18.5, 9.6 Hz, 1 H), 2.57 (q, J = 9.6 Hz, 1 H), 2.67 (dd, J = 18.5, 4.9 Hz, 1 H), 3.10 (m, 1 H), 4.00 (dd, J = 9.2, 3.7 Hz, 1 H), 4.34 (ddd, J = 9.2, 5.9, 1.9 Hz, 1 H), 9.84 (s, 1 H); IR ($CHCl_3$) 3000, 1770, 1725, cm^{-1}; HRMS, m/z calcd for $C_8H_{12}O_3$ (M^+) 156.0717, found 156.0717. Isohomopilopic aldehyde: colorless oil, R_f 0.30 (75% Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3 H), 1.76 (m, 2 H), 2.21 (m, 1 H), 2.64 (dd, J = 18.0, 8.8 Hz, 1 H), 2.77 (m, 1 H), 2.90 (dd, J = 18.0, 3.9 Hz, 1 H), 3.81 (dd, J = 9.3, 7.9 Hz, 1 H), 4.58 (dd, J = 9.3, 7.2 Hz, 1 H), 9.80 (s, 1 H); IR ($CHCl_3$) 3000, 1770, 1725, cm^{-1}; HRMs, m/z calcd for $C_8H_{12}O_3$ (M^+) 156.0717, found 156.0716.

Pilocarpine (1). To a mixture of aldehyde **7** (62.5 mg, 0.40 mmol) and anhydrous potassium carbonate (166 mg, 2.0 mmol) in a 6-mL solution of dry benzene–dichloromethane (1:1) solution was added a 2.3 M solution of methylamine in benzene (208 μL, 0.48 mmol). After being stirred for 2 h at 25 °C, the reaction mixture was concentrated (in vacuo, 25 °C) to an approximate volume of 3 mL and additional dichloromethane (3 mL) was added. Reconcentration to 3 mL followed by readdition of CH_2Cl_2 (3 mL) was performed 3 times to remove excess methylamine. To the resulting mixture were added *p*-tosylmethyl isocyanide (TosMIC, 175 mg, 0.9 mmol, 1 equiv) and triethylamine (281 μL, 2.0 mmol). The reaction mixture was stirred for 7 days and was then filtered. Concentration and flash chromatography (5% MeOH/CH_2Cl_2) afforded 50 mg (61%) of pilocarpine (**1**): $[\alpha]^{23}_D$ + 91° (EtOH, C 0.01); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7.2 Hz), 1.58 (m, 1 H), 1.92 (m, 1 H), 2.42 (dd, 1 H, J = 15.7, 11.5 Hz), 2.68 (m, 2 H), 2.83 (m, 1 H), 3.57 (s, 1 H), 4.11 (dd, 1 H, J = 9.1, 2.5 Hz), 4.20 (ddd, 1 H, J = 9.1, 5.4, 1.8 Hz), 6.81 (br s, 1 H), 7.43 (br s, 1 H); IR ($CHCl_3$) 2995, 1770, 1500, 1180 cm^{-1}; UV (EtOH) λ_{max} 217 nm; MS, m/z (relative intensity) 208 (M^+, 8), 95 (100).

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Registry No. **1**, 92-13-7; (±)-**2**, 144128-24-5; (±)-**3n**, 144178-82-5; (±)-**3x**, 144238-61-9; **4**, 80436-91-5; **5**, 144128-25-6; **6**, 144128-26-7; **6a**, 144128-28-9; **7**, 144128-27-8; (±)-2-acetylbutyrolactone, 98634-97-0; cyclopentadiene, 542-92-7.