#-Butyrolactone Natural Products via Tributyltin-Hydride-Mediated Radical Cyclizations

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γ-BUTYROLACTONE NATURAL PRODUCTS VIA TRIBUTYLTIN-HYDRIDE-MEDIATED RADICAL CYCLIZATIONS

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ABSTRACT.—A new synthetic methodology using tributyltin hydride generates complex γ-butyrolactones via radical cyclization of α-bromo allylic esters with aryl or heteroaryl substituents at the distal position of the allylic double bond. Application of this chemistry has been made to two major families of natural products, the lignans (with racemic deoxypodorhizon as a target) and the Jaborandi alkaloids (with racemic pilocarpine/isopilocarpine as a target). For the lignan system, a highly convergent sequence provided for the efficient preparation of the cyclization precursor. The key cyclization gives a 46.4% yield of a 4:1 mixture of deoxypodorhizon and its cis epimer. Base isomerization of this mixture affords pure racemic deoxypodorhizon. For the alkaloid system, a slightly longer, but experimentally straightforward, route generates an imidazole derivative regiospecifically methylated on the α-nitrogen. From this allylic alcohol, the thermally unstable α-bromo allylic ester can easily be made. When this substrate is cyclized, a 4:1 mixture of isopilocarpine/pilocarpine results in 39.5% yield. This sequence provides an unusually direct route to pilocarpine via kinetic quench.

Butyrolactone-based natural products substituted at the C-3 and C-4 carbons are ubiquitous. Common examples include certain lignans (1), as exemplified by the antitumor agent deoxypodorhizon [**1**] (2), and certain imidazole alkaloids (3), as exemplified by the antiglaucoma prototype pilocarpine [**2**] (4).

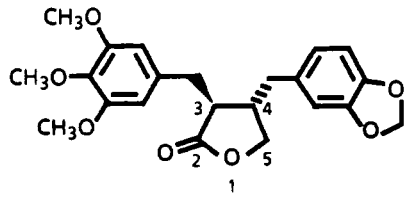
Although there are numerous published routes to substituted butyrolactones (5), such routes often suffer from a narrow range of applicability. Thus, a new synthetic approach of unusual flexibility is of obvious practical value.

RESULTS AND DISCUSSION

While exploring the coupling of dianion intermediates (6–11), we recognized that the combination of this transformation and several subsequent reactions to afford a butyrolactone was chemically equivalent to a direct one-step radical cyclization of an appropriately substituted allylic ester precursor. Therefore, we began a systematic examination of this latter class of reactions.

Both Stork *et al.* (12) and Ueno *et al.* (13) have employed open-chain α-bromoacetals as precursors for tetrahydrofuranyl ethers that, upon subsequent hydrolysis and oxidation, were then transformed into butyrolactones. The iodine atom transfer chemistry of Curran and Chang (14,15) followed by a dehalogenation step also produces butyrolactones in good yield. Although an earlier attempt at direct radical cyclization of a primary bromide allylic ester in the presence of azobisisobutyronitrile (AIBN) initiator/tributyltin hydride (TBTH) was equivocal (14), it was subsequently discovered (16) that minor adjustments in the reaction conditions along with the employment of secondary, rather than primary, bromide substrates provide moderate butyrolactone yields. This study demonstrated that α-bromo allylic esters **3** do indeed give the desired butyrolactones **6**, presumably via the intermediacy of radicals **4** and **5**. Cyclization of substrate esters that can afford a radical stabilized by an adjacent aromatic or heteroaromatic moiety should be especially facile. Slow addition (4–8 h) with a syringe pump of an AIBN/TBTH solution to a refluxing solution of the substrate affords optimal product formation. The major by-product is debrominated ester **7**.

Deoxypodorhizon [**1**], a typical unsymmetrically substituted lignan, exhibits moderate antitumor activity (2). Several successful total syntheses have been published



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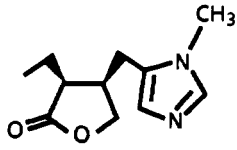

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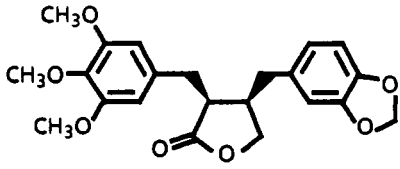

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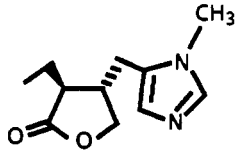

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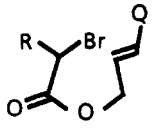

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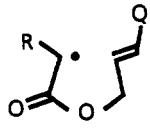

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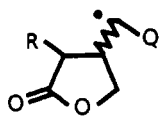

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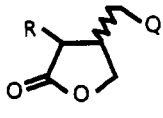

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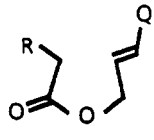


7

Q = aromatic or heteroaromatic

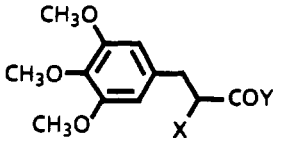
(11, 17–19). Recently, the conversion of deoxypodorhizon into steganacin, an even more potent antineoplastic prototype, was reported (20).

Although several classical synthetic routes to butyrolactone-containing lignans have been developed (21), free radical cyclizations have not heretofore played a major role. Yet, a simple radical cyclization strategy can involve, as its key step, just such a reaction performed on α-bromo allylic ester **8** by treatment with TBTH. Substrate **8**, in turn, is easily prepared by a convergent sequence employing commercially available carboxylic acids.

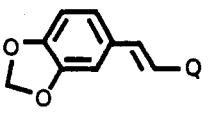
Conversion of hydrocinnamic acid [**9**] to its dianion followed by quenching with carbon tetrabromide (11) yields the α-bromo-acid **10**. The corresponding acid chloride **11** easily forms upon heating **10** with oxalyl chloride in C_6H_6. Fischer esterification of cinnamic acid [**12**] followed by careful reduction with diisobutyl-aluminum hydride gives the allylic alcohol **13**. Treatment of **11** with **13** in the presence of pyridine leads

to the desired substrate **8**, which is obtained as a pale yellow oil after a final chromatographic purification.

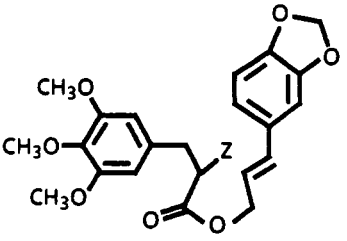
Addition of a C_6H_6 (or MeCN) solution of AIBN and TBTH to a refluxing C_6H_6 (or MeCN) solution of **8** was followed by further heating at reflux. MeCN consistently gave slightly improved yields of the cyclization products compared with the use of C_6H_6 as solvent. From the crude reaction mixture, careful cc affords both the debrominated allylic ester **14** (30.7% yield) as well as a lactonic fraction (46.4% yield) that consists of a 4:1 ratio (by ^{1}H-nmr integration) of the desired lignan product **1** and its stereoisomer **15**. This isomer ratio is very similar to that found by previous model studies (16) involving cyclizations of simpler substrates to 3,4-disubstituted butyrolactones.



9 X=H, Y=OH
10 X=Br, Y=OH
11 X=Br, Y=Cl



12 Q=COOH
13 Q=CH_2OH



8 Z=Br
14 Z=H

Although the above successful radical cyclization illustrates the efficacy of tributyltin hydride methodology as a general route to butyrolactones, an even more rigorous test of this strategy involves its application to the preparation of such alkaloidal butyrolactones as pilocarpine [**2**] and isopilocarpine [**16**].

Numerous imidazole-containing compounds occur as natural products. Besides the important amino acid histidine, by far the most common members of this group are the Jaborandi alkaloids that are found in South American plants of the family Rutaceae (3). Because of its utility as a major drug for the treatment of glaucoma (22), pilocarpine remains the best known Jaborandi alkaloid.

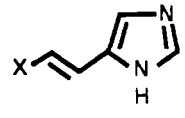
Several published discussions on structure-activity relationships in pilocarpine derivatives (3, 23–26) suggest that there are fairly restrictive structural requirements needed to evoke measurable biological responses. Thus, a simple alkyl chain at the C-3 position of the butyrolactone and some sort of aromatic or heteroaromatic group attached to a methylene moiety on C-4 appear minimally necessary for antiglaucoma activity (26).

The regiochemical and stereochemical features of pilocarpine complicate its efficient synthesis. Many previous approaches were tedious or involved very long sequences; nevertheless, even a non-exhaustive search of the literature reveals several different routes of varying success (27–32). Whereas earlier workers often concentrated on building up the imidazole system after first constructing the overall butyrolactone carbon skeleton, this generally resulted in low overall yields. Would a radical cyclization methodology similar to that pioneered with deoxypodorhizon provide sufficient synthetic flexibility to permit the preparation of pilocarpine and its analogues? The current ready access to the histidine degradation product urocanic acid [**17**] provides a convenient alternative sequence employing a preformed imidazole heterocycle. In conjunction with α-bromo butyryl bromide [**18**], these two commercially available starting materials provide all but one of the requisite carbon atoms of pilocarpine (although with rather scrambled functionality). We envisioned a strategy for the synthesis of pilocarpine that involves three key steps: efficient regiospecific preparation of allylic alcohol

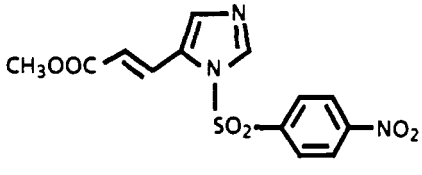
[19], generation of the crucial α-bromo allylic ester substrate [20], and reductive cyclization of **20** via TBTH/AIBN. Also of concern was performing an analysis of the relative stereochemistry of the C-3 and C-4 substituents in the resulting butyrolactone as well as considering ways to control the sequence's overall stereochemical outcome.

Any useful procedure for producing alcohol **19** must generate the α-*N*-Me imidazole uncontaminated by the γ-*N*-Me isomer [21]. Exploitation of a blocking group in a fashion similar to previous precedent (31) solved this potential complication. Urocanic acid [17] is converted to the highly crystalline methyl ester hydrochloride **22** by reaction with methanolic HCl. Selective acylation of the imidazole at the less hindered α-nitrogen is accomplished by reaction with *p*-nitrobenzenesulfonyl chloride in pyridine. Recrystallization of the crude product from nitroethane removes trace amounts of the unwanted α-sufonylation by-product **23** and leads to excellent recovery of the desired **24**. Reaction of **24** with trimethyloxonium tetrafluoroborate produces the intermediate α-*N*-Me, γ-*N*-sulfonylated salt **25** that, during a subsequent treatment with aqueous bicarbonate solution, undergoes hydrolysis to the α-*N*-Me ester **26**. Careful DIBAH reduction of the ester then gives the desired allylic alcohol **19** from which is prepared an analytically pure sample by cc. The remarkable crystallinity of intermediates **22** and **24** as well as the efficient purification of crude **19** via flash filtration are greatly beneficial to the overall efficiency of this route.

Esterification of **19** with commercially available α-bromo butyryl bromide [18] can be done at low temperature in THF or a halogenated solvent. The imidazole ring serves as a proton scavenger for the liberated HBr. For small scale work, it is particularly convenient to run the esterification in $CDCl_3$ in order to facilitate nmr monitor-



17 X=COOH
22 X=COOMe·HCl



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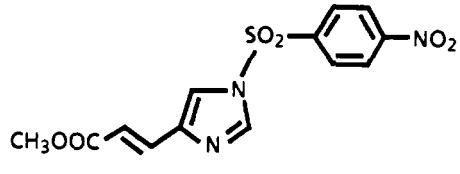

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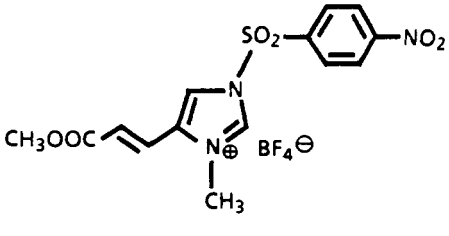

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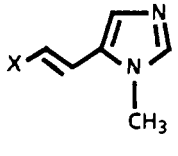
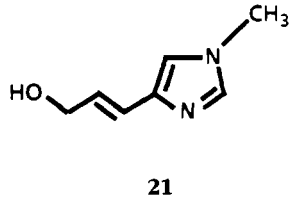


26 X=COOMe
19 X=CH_2OH



21

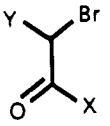
ing. Upon completion, the reaction mixture is extracted with dilute carbonate solution. Drying, filtration, and concentration of the ester are done as rapidly as possible without allowing the solution to rise above room temperature. Presumably as a result of intermolecular displacement of the α-bromide by the nucleophilic imidazole ring, ester **20** is quite labile. Thus, upon standing overnight at room temperature, a concentrated solution of ester **20** affords polar oligomeric decomposition products. Nevertheless, direct esterification in a halogenated solvent with attention to reaction time, concentration, and temperature reproducibly leads to the desired product **20** in reasonable yields and in a purity greater than 95% by nmr spectroscopy. Both Florisil and Si gel chromatography of the crude α-bromo allylic ester led to decomposition.

Given the thermal instability of **20**, radical cyclization with tributyltin hydride necessitated a modified protocol. This consists of syringe-pump addition over 5 to 8 h of a solution of ester **20**, TBTH, and AIBN to refluxing solvent followed by further heating at reflux for 8–10 h. As was the case for deoxypodorhizon, it was found that better yields and less polymer in the reaction mixture result from the use of MeCN in place of C_6H_6 as solvent. The resulting oily residue can be purified by cc. The extremely polar imidazole ring presented a significant challenge in the development of an effective chromatographic procedure, especially in regard to balancing the amount of adsorbent needed and the volume and polarity of the eluting solvent. In those esterification runs that involved the presence of **19** in slight excess, it was found that cyclization of the resulting bromo ester substrate gave a lactonic fraction contaminated with an inseparable amount of **19**. Thus, it is always better to have **19** serve as the limiting reagent during the esterification. With Florisil, column bleeding and limited resolution of components made this adsorbent less attractive. For routine use [affording only moderate recovery (39.5%) but extremely high product purity], 200 mesh Si gel and a polar solvent combination appear most useful. Approximately 20% of the corresponding debrominated allylic ester **27** was also isolated. While it is probable that more efficient cc of the crude radical cyclization mixture might be accomplished by preparative reversed-phase cc, the expense of this technique for applications involving multimillimole scale of substrate and reagents precluded its adoption.

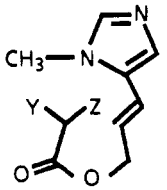
Examination of the stereochemistry of the product mixture after the tributyltin hydride cyclization was unambiguous because of ready access to authentic samples of both pilocarpine and isopilocarpine. Isomerization of commercial pilocarpine with an excess of refluxing alcoholic base followed by quenching with dilute acid leads to a virtually homogeneous sample of the thermodynamically more stable isopilocarpine stereoisomer. Both ^1H and ^{13}C nmr of the purified lactonic fractions from the radical cyclizations are consistent with the presence of an approximately 4:1 isopilocarpine-pilocarpine isomer mixture. These mixtures, when subjected to an alkoxide isomerization, are converted into spectroscopically homogeneous samples of isopilocarpine. For those experiments in which the esterification to form **20** had proceeded in a nearly optimal fashion, chromatography of the crude tributyltin hydride reaction mixture revealed that the lactonic fractions consist simply of the two butyrolactone diastereoisomers with no additional discernible impurities present.

Because Compagnone and Rapoport (32) have converted mixtures of pilocarpine and isopilocarpine into enolate **28**, performed a kinetic quench affording an excess of pilocarpine, and then used preparative hplc to separate out the pilocarpine, any synthetic sequence that gives a mixture of the two diastereoisomers (such as ours) also serves as a relay synthesis of pilocarpine.

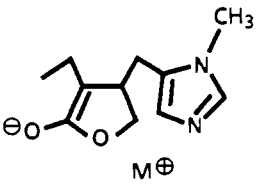
In an experiment demonstrating the feasibility of our methodology for the generation of analogues to pilocarpine and isopilocarpine, a sample of **19** was reacted with α-bromo acid bromide [**29**] in $CDCl_3$. After workup, the resulting crude ester **30** was



18 Y=CH_2Me, X=Br
29 Y=$(CH_2)_3Me$, X=Cl



20 Y=CH_2Me, Z=Br
27 Y=CH_2Me, Z=H
30 Y=$(CH_2)_3Me$, Z=Br
31 Y=$(CH_2)_3Me$, Z=H



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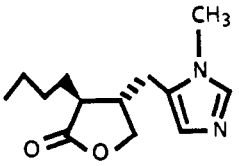

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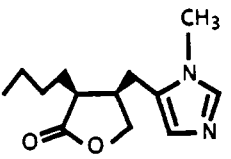

33

subjected to TBTH/AIBN treatment followed by cc from which debrominated ester **31** (22.8%) and a diastereoisomeric mixture of butyrolactones **32** and **33** (39.8%) were obtained. By nmr analysis, and in analogy to the pilocarpine/isopilocarpine system, tentative assignment of the two diastereoisomers (once again, in ca. 4:1 ratio) was made.

In conclusion, the above successful syntheses of both lignan and alkaloidal butyrolactones and their analogues demonstrate that radical-mediated cyclization with TBTH/AIBN provides a highly efficient route to such natural product classes.

EXPERIMENTAL

MATERIALS AND GENERAL PROCEDURES.—Melting points were determined with a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker spectrometer, generally with TMS as internal standard. Ir spectra were recorded with a Perkin-Elmer Model 1600 FT spectrophotometer. Ms was determined with a Kratos MS-801 DS55 spectrometer. All reactions were run under dry N_2 unless otherwise specified. Glassware for the tributyltin hydride and dianion reactions was assembled hot from a 115° oven, purged with N_2, and then flame-dried under vacuum. THF was distilled from sodium benzophenone ketyl immediately before use. Diisopropylamine was distilled from barium oxide immediately prior to use. Ligroine, $CHCl_3$, and EtOAc used in purifications were distilled before use. All reagents and starting materials were commercially available.

METHYL 3,4-(METHYLENEDIOXY)CINNAMATE.—A mixture of 250 ml MeOH, 10.0 g (52.0 mmol) of 3,4-(methylenedioxy)cinnamic acid (99% pure, predominately trans), and 30 drops of concentrated H_2SO_4 was heated to reflux. The slowly yellowing reaction mixture was refluxed overnight and allowed to cool to room temperature, whereupon several grams of solid $NaHCO_3$ was added. Solvent was removed and the oily residue was dissolved in 150 ml $CHCl_3$. The organic layer was washed with 2 × 50 ml distilled H_2O followed by 2 × 25 ml saturated brine. The $CHCl_3$ layer was dried over $MgSO_4$ and filtered, and the solvent was removed, giving an off-white solid (9.82 g) that was recrystallized from MeOH (9.25 g, 86.3%): mp 130–131°; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.58 (d, J = 15.8 Hz, 1H), 7.00 (s, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 6.24 (d, J = 15.8 Hz, 1H), 5.99 (s, 2H), 3.78 (s, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 167.5, 149.5, 148.3, 144.5, 128.7, 124.3, 115.6, 108.4, 106.4, 101.5, 51.5; eims *m/z* 206 (100%), 175, 145, 117, 95, 89; hreims *m/z* $[M]^+$ 206.0581 (calcd for $C_{11}H_{10}O_4$, 206.0579); ir ν max ($CDCl_3$) cm^{-1} 1704 (s), 1634 (m). Found C 63.89, H 4.89; calcd for $C_{11}H_{10}O_4$, C 64.06, H 4.89%.

3,4-(METHYLENEDIOXY)CINNAMYL ALCOHOL [**13**].—To a 150 ml three-neck round-bottom flask and under N_2 was added 2.06 g (10 mmol) of methyl 3,4-(methylenedioxy) cinnamate and 75 ml of anhydrous, redistilled CH_2Cl_2. After stirring for a few min, a homogeneous solution resulted whereupon 23 ml (2.3 equiv., 23 mmol) of DIBALH was added over 1 min. The reduction mixture was allowed to stir for 90 min. The reaction mixture was cooled to 0°, 10 ml of concentrated $KHSO_4$ was added, and the resulting solution was allowed to stir for 30 min. The solution was then extracted with 2 × 10 ml 0.5 N cold HCl and 3 × 10 ml saturated brine. The organic layer was dried over $MgSO_4$. Solvent was then removed to leave a white residue (1.292 g, 72.6%) that was recrystallized from CCl_4 to give 1.015 g (58%) of analytically pure **13**: mp 73–74°; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.93 (s, 1H), 6.83–6.73 (m, 2H), 6.55–6.49 (d, J = 15.9 Hz, 1H), 6.30–6.14 (dt, J = 15.8, 5.7 Hz, 1H), 5.95 (s, 2H), 4.30–4.28 (d, J = 5.2 Hz, 2H), 1.55 (s, 1H, OH); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 147.9, 147.2, 131.0, 130.8, 126.6, 121.0, 108.2, 105.6, 101.0 63.5; eims *m/z* 178 (100%), 135, 160, 150, 122, 103, 91; hreims *m/z* $[M]^+$ 178.0582 (calcd for $C_{10}H_{10}O_3$, 178.0630); ir ν max ($CDCl_3$) cm^{-1} 3611 (m), 3014 (w), 1608 (m). Found C 67.51, H 5.69; calcd for $C_{10}H_{10}O_3$, C 67.39, H 5.62%.

2-BROMO-3-(3,4,5-TRIMETHOXYPHENYL)PROPIONIC ACID [**10**].—To a flame-dried 250 ml Schlenk tube was added 80 ml THF under N_2. The solvent was cooled to 0°, and 2.24 ml (16 mmol) diisopropylamine and 10.66 ml (1.5 M, 16 mmol) *n*-BuLi were added, followed by stirring at 0° for 70 min. To the recooled (−78°) LDA solution there was added dropwise 1.92 g (8 mmol) of 3-(3,4,5-trimethoxyphenyl)-propionic acid in 10 ml THF over 10 min. The resulting dianion solution was stirred at −78° for 45 min, for 3 h at 0°, and for 2 h at room temperature. The reaction mixture was again cooled to −78°, and 10.616 g (4 equiv, 32 mmol) of CBr_4 in 6 ml THF was added as rapidly as possible. After 10 min, 6 ml concentrated NH_4Cl was added and the mixture was stirred overnight. The solvent was evaporated and the residue was partitioned between 60 ml H_2O, 60 ml concentrated Na_2CO_3, and 60 ml EtOAc. The aqueous layer was separated, cooled to 0°, and acidified with concentrated HCl to a pH of 2. After stirring at room temperature for 2 h, the acidified aqueous solution was extracted with 4 × 50 ml EtOAc. The combined organic layers were dried, filtered, and evaporated to a residual yellow oil (2.73 g) that was purified on 10 g of Si gel ($CHCl_3$). The chromatographed product was recrystallized from CCl_4 to give 2.131 g of pure white **10** (83.9%): mp 84–85°; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 8.55 (br s, 1H), 6.43 (s, 2H), 4.42 (distorted t, J = ca. 8 Hz, 1H), 3.83 (s, 9H), 3.42 (dd, J = ca. 14, 8 Hz, 1H), 3.18 (dd, J = ca. 14, 8 Hz, 1H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 174.5, 153.4, 137.1, 132.0, 106.1, 60.8, 56.0, 44.6, 41.0; ir ν max ($CDCl_3$) cm^{-1} 3494, 2942, 1704 (s), 1589, 1509; eims *m/z* 318, 238, 223, 195, 181 (100%), 148, 136, 119; hreims *m/z* $[M]^+$ 318.0093 (calcd for $C_{12}H_{15}BrO_5$, 318.0102).

2-BROMO-3-(3,4,5-TRIMETHOXYPHENYL)PROPIONYL CHLORIDE [**11**].—A solution of 0.645 g (2.02 mol) of 2-bromo-3-(3,4,5-trimethoxyphenyl)propionic acid, 50 ml C_6H_6, and 1.15 ml (6 equiv, 12.13 mmol) oxalyl chloride was refluxed under N_2 for 30 min followed by heating at 60° for 12 h. The solvent was evaporated to a yellow oil weighing 0.66 g (96.8%): ^{1}H nmr ($CDCl_3$ 250 MHz) δ 6.43 (s, 2H), 4.69 (distorted t, J = ca. 7 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.47 (dd, J = ca. 14, 7 Hz, 1H), 3.23 (dd, J = ca. 14, 7 Hz, 1H); ir ν max ($CDCl_3$) cm^{-1} 17.84 (s), 1591 (s).

3,4-(METHYLENEDIOXY)CINNAMYL 2-BROMO-3-(3,4,5-TRIMETHOXYPHENYL)PROPIONATE [**8**].—At 0° over 45 min a solution of 1.114 g (3.30 mmol) of 2-bromo-3-(3,4,5-trimethoxyphenyl)propionyl chloride in 10 ml of THF was added dropwise to a solution of 0.587 g (3.30 mmol) of 3,4-(methylenedioxy)cinnamyl alcohol, 1.6 ml (6 equiv; 12 mmol) of pyridine, and 10 ml of THF. The reaction mixture was stirred at 0° for 2 h and at room temperature for 20 h. After dilution with 20 ml of ice-cold H_2O, the solution was extracted with EtOAc (2 × 30 ml). The combined organic layers were extracted with 0.5 N HCl (2 × 10 ml), concentrated $NaHCO_3$ (2 × 10 ml), and saturated brine (10 ml). The organic layer was dried over $MgSO_4$ and filtered, and the volatiles were evaporated to leave a yellow oil (1.56 g). The crude sample was purified by chromatography on 20 g Si gel. The elution solvent was 4% $CHCl_3$/96% $(C_2H_5)_2O$. Eleven 10-ml fractions were collected. Combined fractions 3–9 weighed 0.976 g and were pure ester **8** (82.2%): ^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.91 (s, 1H), 6.82–6.74 (m, 2H), 6.57 (d, J = 16 Hz, 1H), 6.43 (s, 2H), 6.11–5.99 (m, 1H), 5.96 (s, 2H), 4.76 (d, J = 6.5 Hz, 2H), 4.42 (distorted t, J = ca. 8 Hz, 1H), 3.81 (s, 9H), 3.49–3.39 (m, 1H), 3.23–3.14 (m, 1H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 169.1, 153.2, 148.1, 147.8, 137.2, 134.8, 132.3, 130.3, 121.6, 120.1, 108.3, 106.2, 105.8, 101.2, 66.6, 60.8, 56.1, 45.1, 41.4; ir ν max ($CDCl_3$) cm^{-1} 1738 (s), 1652 (m); eims *m/z* 478, 221, 194, 161, 131, 103, 82; hreims *m/z* $[M]^+$ 478.0610 (calcd for $C_{22}H_{23}BrO_4$, 478.0627).

(±)-DEOXYPODORHIZON [**1**] AND ITS DIASTEREOISOMER **15**.—*Preparation of a 4:1 trans-cis mixture.*—A solution of 0.487 g (1.018 mmol) of α-bromoester **8** and 60 ml MeCN under N_2 was heated at reflux by an oil bath kept at 107°. Over a period of 3 h, a solution of 0.29 ml (1.05 equiv, 1.069 mmol) of TBTH and 18 mg (10 mol %) of AIBN in 20 ml MeCN was added, via a syringe-pump, to the refluxing α-

bromoester solution. The resulting mixture was refluxed for a further 10 h, cooled to room temperature, transferred into a separatory funnel, and washed with 4 × 10 ml ligroin. After removal of solvent, the residue had a weight of 0.555 g. The ir of the crude product shows a strong butyrolactone carbonyl stretch at 1771 cm^{-1}. Purification was done on a 20 g Si gel column. Elution solvents were: 600 ml of 10% EtOAc, 90% ligroin; 200 ml 15% of EtOAc, 85% ligroin; and 200 ml of 20% EtOAc, 80% ligroin. The first 15 fractions were 50 ml each, and the remaining fractions were 15 ml each. Fractions 9–35 corresponded to the reduced ester while fractions 50–60 were deoxypodorhizon (wt 0.189 g, 46.4% yield based on the α-bromoester starting material) isolated as a mixture of 4:1 trans (**1**)-cis (**15**) diastereoisomers. The weight of reduced ester **14** recovered was 0.125 g (30.7%). Overall recovery was 77.1%. Based upon isomerization experiments shown in following section, the two diastereoisomers can be assigned the following peaks as observed on the isomer mixture. (±)-Deoxypodorhizon [**1**] [=(±)-"*trans*-Deoxypodorhizon"]: ^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.75–6.65 (m, 1H), 6.55–6.45 (m, 2H), 6.36 (s, 2H), 5.94 (s, 2H), 4.21–4.14 (m, 1H), 3.86–3.84 (m, 1H), 3.83 (s, 9H), 2.92–2.85 (m, 2H), 2.67–2.40 (m, 4H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 178.3, 153.0, 147.7, 146.2, 136.6, 133.2, 131.4, 121.3, 108.6, 108.0, 106.0, 101.0, 71.0, 60.6, 55.9, 46.2, 40.8, 38.1, 35.0.

Extra peaks present in the 4:1 diastereoisomer mixture suggest the following tentative assignments for the other diastereoisomer. (±)-"*cis*-Deoxypodorhizon" [**15**]: ^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.75–6.67 (m, 1H), 6.56–6.45 (m, 2H), 6.36 (s, 2H), 5.93 (s, 2H), 4.04 (br s, 1H), 3.86–3.84 (m, 1H), 3.86 (s, 9H), 2.90 (m, 2H), 2.63–2.43 (m, 4H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 177.6, 153.2, 147.7, 146.2, 136.6, 134.2, 131.8, 121.7, 108.8, 108.2, 105.2, 101.0, 69.2, 60.6, 53.3, 45.1, 39.9, 32.6, 31.0.

For the lactone mixture: ir ν max ($CDCl_3$) cm^{-1} 1767 (s), 1590 (m); eims *m/z* of lactone mixture 400, 264, 181 (100%), 161, 135, 105, 77; hreims *m/z* $[M]^+$ 400.1518 (calcd for $C_{22}H_{24}O_7$, 400.1522).

RECOVERED DEHALOGENATED ESTER **14**.—^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.91 (s, 1H), 6.82–6.76 (m, 2H), 6.54 (d, J = 15.8 Hz, 1H), 6.43 (s, 2H), 6.15–6.01 (m, 1H), 5.93 (s, 2H), 4.70 (d, J = 6.5 Hz, 2H), 3.82 (s, 9H), 2.92 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 172.6, 153.2, 148.0, 147.6, 136.3, 136.2, 134.1, 130.5, 121.5, 121.1, 108.3, 105.7, 105.1, 101.1, 65.2, 60.8, 56.0, 36.0, 31.3; ir ν max (smear) cm^{-1} 1732 (s), 1589 (s).

ISOMERIZATION OF **1/15** MIXTURE TO AFFORD PURE (±)-DEOXYPODORHIZON [**1**].—To a 25 ml round-bottom flask was added 80 mg (0.2 mmol) of the 4:1 trans/cis mixture of (±)-deoxypodorhizon prepared by the TBTH/AIBN reaction. To this was added a pre-mixed solution of NaOEt in EtOH [5 ml of EtOH and 25.3 mg (6 equiv, 1.1 mmol) Na]. The resulting mixture was refluxed 24 h, cooled to room temperature, dissolved in 20 ml CH_2Cl_2, and extracted with 2 × 10 ml of 0.5 N HCl. The aqueous layer was separated and further acidified with concentrated HCl to pH ca. 1 and then extracted with 2 × 15 ml CH_2Cl_2. The combined organic layers were washed with 10 ml of brine. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. After removal of the solvent, the residue had a weight of 25 mg. The aqueous layer was brought to pH ca. 8 and exhaustively extracted with CH_2Cl_2. After drying the new organic layers and removal of solvent, the resulting residue had a weight of 27 mg. The combined recovered lactonic product weighed 52 mg (65%). The nmr spectra of these two fractions were identical and were also identical to that of (±)-deoxypodorhizon which had been prepared both by our dianion coupling sequencing (11,33) and with material prepared by Tomioka *et al.* (18): ^{1}H nmr ($CDCl_3$, 250 MHz) δ 6.75–6.67 (m, 1H), 6.54–6.45 (m, 2H), 6.36 (s, 2H), 5.93 (s, 2H), 4.18 (dd, J = 7, 8 Hz, 1H), 3.86 (m, 1H), 3.83 (s, 9H), 2.91–2.89 (m, 2H), 2.63–2.43 (m, 4H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) 178.5, 153.2, 147.9, 146.4, 136.7, 133.3, 131.5, 121.5, 108.7, 108.3, 106.1, 101.1, 71.1, 60.8, 56.0, 46.4, 41.0, 38.3, 35.2; eims *m/z* 400, 264, 181, 161, 135, 105; hreims *m/z* $[M]^+$ 400.1556 (calcd for $C_{22}H_{24}O_7$, 400.1522).

UROCANIC ACID METHYL ESTER HYDROCHLORIDE [**22**].—To a precooled (0°) 250 ml round-bottom flask equipped with a reflux condenser, an N_2 bubbler, and an addition funnel was added 100 ml of MeOH followed by dropwise addition (from the funnel) of 2.0 ml (2.3 equiv) of acetyl chloride (exothermic!) over 30 min. After warming to room temperature over 30 min, 1.38 g (10 mmol) of urocanic acid was added and the resulting solution was stirred at room temperature for 30 min followed by heating at reflux for 16 h. After cooling to room temperature, the solvent was removed to afford a colorless white salt (1.80 g, 96%): mp 233–234°; ^{1}H nmr (D_2O, TSP, 250 MHz) δ 8.88 (s, 1H), 7.86 (s, 1H), 7.59 (d, J = 16 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 5.00 (s, 1H), 3.86 (s, 3H); ir ν max (KBr) cm^{-1} 1697 (s), 1585 (m). Found C 44.72, H 4.87; calcd for $C_7H_9ClN_2O_2$, C 44.57, H 4.82%.

UROCANIC ACID METHYL ESTER, FREE BASE.—To 1.80 g (9.65 mmol) of the ester hydrochloride in 35 ml H_2O was added an excess of $NaHCO_3$. The resulting solution was then extracted wtih 3 × 30 ml EtOAc. The EtOAc layers were combined, dried over $MgSO_4$, and filtered, and the volatiles were removed to afford a residual solid (1.40 g, 96.5%) that was recrystallized from CH_2Cl_2/C_6H_{12} (1.17 g, 84%): mp 100–101°; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 11.2 (br s, 1H), 7.95–7.7 (m, 2H), 7.55 (s, 1H), 6.55 (m, 1H), 3.9 (s, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 168.0, 137.1, 135.0, 122.5, 115.5, 51.6, 26.9; ir ν max

($CDCl_3$) cm^{-1} 1707; eims *m/z* 152 (100%), 121, 108, 93; hreims *m/z* $[M]^+$ 152.0562 (calcd for $C_7H_8N_2O_2$, 152.0586).

γ-*N*-(4-NITROBENZENESULFONYL) UROCANIC ACID METHYL ESTER [**24**].—To a 100 ml round-bottom flask under a stream of N_2 were added 3.263 g (17.3 mmol) of urocanic ester monohydrochloride and 60 ml pyridine. After gentle heating to dissolve the salt, the flask was cooled to 0° for 30 min. To the resulting solution was added 4.122 g (1.075 equiv, 18.6 mmol) of purified (via Soxhlet extraction using refluxing ligroin) 4-nitrobenzenesulfonyl chloride in portions over 5 min. The resulting solution was stirred at 0° for 8 h and then at room temperature for 48 h, whereupon the solution had changed to a milky, viscous syrup. The reaction mixture was poured into 250 ml of ice-cold H_2O. The desired product precipitated as a white mass, which, after 1 h, was filtered. The crude yellow crystals were recovered, air-dried overnight, and placed in an Abderhalden drying apparatus for 48 h. The crude product, 5.582 g (95.7%) after recrystallization from nitroethane, afforded pure **24** (5.263 g, 90.3%): mp 209–211°: ir ν max (KBr) cm^{-1} 3116, 3058, 3029, 2952, 1716 (s), 1647 (m), 1607, 1538, 1488, 1433, 1409, 1394, 1340, 1295, 1192, 1166, 1076; eims *m/z* 337, 306, 187, 151, 122 (100%), 92, 69; hreims *m/z* $[M]^+$ 337.0400 (calcd for $C_{13}H_{11}N_3O_6S$, 337.0450). Found C 46.31, H 3.30; calcd for $C_{13}H_{11}N_3O_6S$, C 46.29, H 3.29%.

α-*N*-METHYL-UROCANIC ACID METHYL ESTER [**26**].—Within an inflated N_2 glove bag, to a tared 75 ml weighing bottle was added 4.767 g (14.11 mmol) of γ-*N*-(4-nitrobenzenesulfonyl)urocanic acid methyl ester [**24**], 2.93 g (1.4 equiv, 19.08 mmol) of trimethyloxonium tetrafluoroborate, and 20 ml of nitromethane (Merck gold label). The container was capped, removed from the glove bag, and gently stirred at room temperature for 20 h. The container was then opened and the homogeneous yellow solution was transferred into a 50 ml flask. The container was washed with a small portion of nitromethane. The volatiles were removed on a rotary evaporator to yield a viscous yellow semi-solid. To this residue was added 35 ml of H_2O followed by 1 h of stirring. The solution was then gravity-filtered. The pH of the aqueous filtrate ws adjusted to 8–9 by carefully adding solid $NaHCO_3$ over 3–5 min. The resulting solution was stirred for 30 min. The pH of the solution was again checked to make certain the solution was still at pH 8–9. The solution was then transferred into a separatory funnel and washed with 3 × 20 ml Et_2O. The aqueous layer was next extracted with 3 × 40 ml of $CHCl_3$. The combined $CHCl_3$ layers were washed with 2 × 5 ml saturated brine and 2 × 5 ml H_2O, dried over $MgSO_4$, and filtered, and the solvent was evaporated to a yellow viscous oil that gradually solidified (2.30 g, 98.2%). The crude material was purified on a 25 g Si gel column. The solvent system used was MeOH-$CHCl_3$ (2.5:97.5) with 18-ml fractions taken. Fractions 4–11 were pure ester **26** (1.918 g, 82.0%): ^1H nmr ($CDCl_3$, 250 MHz) δ 7.53 (d, J = 16 Hz, 1H), 7.53 (br s, 1H), 7.46 (br s, 1H), 6.27 (d, J = 16 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 167.1, 140.8, 132.2, 129.6, 128.4, 115.5, 51.5, 32.1; eims *m/z* 166, 135 (100%), 108, 92, 80, 66, 53, 39; hreims *m/z* $[M]^+$ 166.0737 (calcd for $C_8H_{10}N_2O_3$, 166.0743); ir ν max ($CDCl_3$) cm^{-1} 2953, 2227, 1706, 1638, 1495, 1438, 1313, 1290, 1232, 1198, 1177, 1125. Found C 58.00, H 6.13; calcd for $C_8H_{10}N_2O_2$, C 57.81, H 6.01%.

α-*N*-METHYL-IMIDAZOLE ALLYLIC ALCOHOL [**19**].—To a 150 ml three-neck round-bottom flask under a stream of N_2 was added 1.60 g (9.64 mmol) of α-*N*-methylurocanic methyl ester and 60 ml of redistilled dry CH_2Cl_2. The resulting mixture was stirred at room temperature for several minutes to produce a homogeneous solution, whereupon 22.2 ml (22.2 mmol, 2.3 equiv) of DIBALH solution in C_6H_{12} was added over 1 min (modest bubbling). The mixture was stirred for 90 min at room temperature and cooled to 0°, and the reaction was quenched by adding 0.4 ml of 15% aqueous NaOH followed by 1.2 ml of H_2O. The white suspension was placed in the refrigerator overnight. After rewarming the reaction mixture to room temperature, the solvent was removed under vacuum. To the yellowish residue was added 60 ml of EtOH. The reaction mixture was refluxed for several minutes. The hot solution was then gravity-filtered and the volatiles removed under reduced pressure. The crude residue (1.436 g) was placed on a 25 g Si gel column. The solvent system used was MeOH-$CHCl_3$ (3:97). Twenty-four fractions, each of 18 ml, were collected. Fractions 10–18 had a combined weight of 0.899 g. Fractions 19–24 were also collected (0.085 g). The spectra of these two samples were identical and were consistent with the structure of desired product (74% yield of pure center-cut **19**). ^1H nmr ($CDCl_3$, 250 MHz) δ 7.33 (s, 1H), 7.05 (s, 1H), 6.43 (d, J = 16 Hz, 1H), 6.25–6.15 (m, 1H), 5.99 (br s, 1H), 4.29–4.27 (d, J = 5 Hz, 2H), 3.55 (s, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.8, 131.2, 130.9, 125.9, 114.9, 62.0, 31.8; ir ν max ($CDCl_3$) cm^{-1} 3600–3200, 2954, 1793, 1637, 1544, 1498, 1470, 1381, 1248, 1228, 1117, 1093; eims *m/z* 138 (100%), 121, 109, 95, 82, 68; hreims *m/z* $[M]^+$ 138.0784 (calcd for $C_7H_{10}N_2O$, 138.0793). Found C 60.47, H 7.38; calcd for $C_7H_{10}N_2O$, C 60.83, H 7.30%.

α-BROMO-*N*-METHYLIMIDAZOLE ALLYLIC ESTER (PILOCARPINE/ISOPILOCARPINE PRECURSOR) [**20**].—*Hydrobromide salt.*—At 0° over a 30-min period a solution of 0.117 ml (1 mmol) of α-bromobutyryl bromide dissolved in 3 ml of $CDCl_3$ was added to a solution of 0.138 g (1 mmol) of the al-

lylic imidazole alcohol **19** in 7 ml $CDCl_3$. The flask was cooled in an ice-bath. The reaction mixture was stirred a further 60 min at 0° and then at room temperature for an additional 90 min. Spectral data for the α-bromo-*N*-methylimidazole ester hydrobromide: ^{1}H nmr ($CDCl_3$, 250 MHz) δ 13.6 (br s, 1H), 9.6 (s, 1H), 7.49 (s, 1H), 6.58–6.35 (m, 2H), 4.96–4.63 (m, 2H), 4.22 (t, J = 7 Hz, 1H), 4.02 (s, 3H), 2.25–1.93 (m, 2H), 1.15–0.96 (t, J = 7 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 171.1, 135.4, 131.8, 131.2, 116.1, 115.9, 64.4, 47.4, 34.5, 28.1, 11.8; ir ν max ($CDCl_3$) cm^{-1} 3155, 2978, 2880, 1743, 1598, 1552, 1463, 1384, 1263, 1203, 1152, 1101, 908.

Conversion to the free base **20**.—The organic layer was extracted with K_2CO_3 (5%, cold, 2 × 2 ml) followed by saturated brine (2 ml). The organic layer was separated and dried over $MgSO_4$ and filtered, and the solvent was evaporated to leave **20** as a yellow syrup (0.228 g, 79.4%): ^{1}H nmr ($CDCl_3$), 250 MHz) δ 7.34 (s, 1H), 7.14 (s, 1H), 6.51 (d, J = 16 Hz, 1H), 6.12–6.01 (m, 1H), 4.80 (d, J = 7 Hz, 2H), 4.20 (t, J = 7 Hz, 1H), 3.63 (s, 3H), 2.2–1.9 (m, 2H), 1.05 (t, J = 8 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 169.1, 138.6, 129.4, 127.7, 122.2, 120.2, 65.7, 47.3, 31.6, 28.0, 11.6. Based on ^{1}H and ^{13}C nmr, the ester is contaminated with ca. 5% starting materials. Ir ν max ($CDCl_3$) cm^{-1} 3155, 2956, 2902, 1816, 1793, 1737 (s), 1654, 1603, 1560, 1469, 1383, 1248, 1154, 1092. This ester is unstable when neat (half-life ca. 8 h at room temperature).

ISOPILOCARPINE [**16**] AND PILOCARPINE [**2**] AS A 4:1 MIXTURE OF DIASTEREOISOMERS.—*Freshly prepared α-bromoester*.—To a solution of 0.138 g (1 mmol) of α-*N*-methyl allylic alcohol [**19**] and 7 ml CH_2Cl_2 was added dropwise at 0° over 30 min a solution of 3 ml CH_2Cl_2 and 0.117 ml (1 mmol) of α-bromobutyryl bromide. The reaction mixture was kept at 0° for 2 h and then warmed to room temperature over 2 h. The reaction mixture was extracted with K_2CO_3 (2 × 2 ml) and brine (2 ml). The organic layer was dried over $MgSO_4$ and the solvent evaporated to leave **20** as a yellow syrup (0.201 g, 0.7 mol).

Cyclization.—To the crude ester syrup was added 10 mg (10 mol %) AIBN, 0.198 ml (1.05 equiv, 0.735 mmol) TBTH, and 30 ml of dry MeCN. In a fresh 100 ml three-neck round-bottom flask equipped with a reflux condenser under an argon atmosphere was added 30 ml of dry MeCH. Using a syringe-pump, the α-bromoester solution (ester + AIBN + tributyltin hydride + MeCN) was added to the refluxing MeCN solution over a period of 5.5 h. The reaction mixture was refluxed an additional 9 h. After cooling, the reaction was extracted with ligroin (4 × 10 ml). The MeCN layer was separated and the solvent evaporated to leave a yellow syrup (0.232 g). The crude reaction mixture was purified by flash cc (20 g Si gel) [ca. 300 ml, iPrOH-ligroin-EtOAc (18:10:72) fractions 1–7 (50 ml each); ca. 1200 ml, iPrOH-ligroin-EtOAc-NH_4OH (18:10:72:0.2) fractions 8–67 (20 ml each), ca. 200 ml, iPrOH-EtOAc-ligroin-NH_4OH (30:10:60:0.2) fractions 68–78 (20 ml each)]. Fractions 44–78 as collected weighed 115 mg (39.5%) and were a 4:1 diastereoisomeric mixture of isopilocarpine and pilocarpine. Fractions 6–8 as recovered were the reduced ester **27** (58 mg, 19.9%). The overall mass balance was 60%. Observed peaks for both diastereoisomers were confirmed by comparison with authentic optically active pure materials obtained as free bases from commercially available salts. Note that the mixture exhibits a slight variation in chemical shifts compared to the pure, authentic free bases.

(±)-*Isopilocarpine*.—^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.47 (s, 1H), 6.82 (s, 1H), 4.44–4.38 (m, 1H), 3.95–3.87 (m, 1H), 3.59 (s, 3H), 2.89–2.56 (m, 3H), 2.36–2.26 (m, 1H), 1.83–1.69 (m, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 178.2, 138.0, 128.1, 126.6, 70.8, 46.1, 38.6, 31.2, 27.0, 22.0, 10.8.

(±)-*Pilocarpine*.—^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.47 (s, 1H), 6.82 (s, 1H), 4.24–4.08 (m, 2H), 3.58 (s, 3H), 2.94–2.33 (m, underneath peaks for other isomer 4H), 1.94–1.77 (m, 1H), 1.67–1.49 (m, 1H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 177.8, 138.0, 128.4, 126.6, 69.6, 44.5, 36.9, 31.2, 21.0, 18.0, 11.9. For the mixture of both isomers: ir ν max (smear) cm^{-1} 1776 (s), 1505 (m); eims *m/z* 208, 179, 165, 149, 137, 129, 119, 109, 95 (100%), 81, 70; hreims *m/z* [M]$^+$ 208.1189 (calcd for $C_{11}H_{16}N_2O_2$, 208.1212).

Recovered debrominated allylic ester **27**.—^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.42 (s, 1H), 7.18 (s, 1H), 6.46 (d, J = 16 Hz, 1H), 6.20–6.08 (m, 1H), 4.71 (d, J = 6.5 Hz, 2H), 3.65 (s, 3H), 2.34 (t, J = 7.3, 2H), 1.73–1.64 (m, 2H), 0.92 (t, J = 7.3, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 173.3, 138.7, 127.8, 123.7, 119.9, 64.6, 36.0, 31.9, 26.8, 18.3, 13.5; ir ν max ($CDCl_3$) cm^{-1} 3113, 2962, 2875, 1737, 1660, 1540, 1495, 1458, 1420, 1387, 1352, 1256, 1176, 1118, 962, 732; eims *m/z* 208, 175, 147, 138 (100%), 121, 109, 95, 80, 70, 51, 43; hreims *m/z* [M]$^+$ 208.1201 (calcd for $C_{11}H_{16}N_2O_2$, 208.1212).

BUTYL ANALOGUES **32** AND **33** OF ISOPILOCARPINE AND PILOCARPINE.—*Freshly prepared α-bromo ester*.—In a procedure analogous to that for **20**, 0.138 g (1 mmol) of allylic alcohol **19**, 11 ml of CH_2Cl_2, and 0.258 g (1 mmol) of (±)-bromohexanoyl bromide were reacted together to afford an oily residue **30** that weighed 0.206 g (0.65 mmol): ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.41 (s, 1H), 7.21 (s, 1H), 6.53 (d,

J = 15.9 Hz, 1H), 6.19–6.08 (m, 1H), 4.80 (d, J = 6 Hz, 2H), 4.25 (t, J = 7.3 Hz, 1H), 3.64 (s, 3H), 2.16–1.94 (m, 2H), 1.52–1.25 (m, 4H), 0.92 (t, J = 7 Hz, 3H).

Cyclization.—To the ester was added 0.013 g (0.12 mol %) AIBN, 0.184 ml (1.05 equiv) TBTH, and 25 ml dry MeCN. To a fresh 100 ml three-neck round-bottom flask under Ar and equipped with a reflux condenser was added 25 ml dry MeCN. The α-bromoester/TBTH/AIBN solution was added dropwise to the refluxing MeCN over 4 h and then refluxed a further 10 h. After cooling to room temperature, the reaction mixture was transferred into a separatory funnel and extracted with 4 × 10 ml ligroin. The MeCN layer was separated and the solvent removed to provide a viscous yellow syrup (0.266 g). The crude products from two experiments were combined (total wt 0.479 g) and purified on 15 g of Florisil. The column was eluted with 400 ml iPrOH-EtOAc-ligroin (25:15:60). Fractions of 20 ml were collected. After fractions 1–20 were collected, the solvent polarity was increased. Next, with 300 ml iPrOH-EtOAc-ligroin (30:20:50), fractions 21–36 were collected. Then, with 200 ml iPrOH-EtOAc-ligroin (40:25:35), fractions 37–46 were collected. Finally, with 200 ml iPrOH-EtOAc-ligroin (45:30:25) and 300 ml MeOH-TEA (80:20), fractions 37–56 were collected. Fractions 21–56 with a combined weight of 122 mg (39.8%) were the isopilocarpine and pilocarpine *n*-butyl analogues **32** and **33**. Fractions 4–17 as collected were the reduced ester **31** (70 mg, 22.8%).

Compounds **32** *and* **33**.—By analogy to the isopilocarpine/pilocarpine diastereoisomers, the following tentative assignments for **32** and **33** have been made. (±)-Trans diastereoisomer **32**: ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.45 (s, 1H), 6.79 (s, 1H), 4.41 (dd, J = 7, 9.6 Hz, 1H), 3.93 (dd, J = 6.4, 9 Hz, 1H), 3.59 (s, 3H), 2.88–2.28 (m, 4H), 1.7–1.54 (m, 2H), 1.42–1.30 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H). (±)-Cis diastereoisomer **33**: ^{1}H nmr ($CDCl_3$, 250 MHz) δ (the other peaks are either the same or located underneath the trans diastereoisomer): 3.58 (s, 3H), 4.25–4.05 (m, 2H). For the lactone 4:1 mixture of diastereoisomers: eims *m/z* 236, 207, 193, 180, 163, 147, 137, 123, 111, 96 (100%), 85; hreims *m/z* $[M]^+$ 236.1514 (calcd for $C_{13}H_{20}N_2O_2$, 236.1520); ir ν max ($CDCl_3$) cm^{-1} 2962, 2931, 2873, 2860, 1771, 1628, 1504, 1466, 1421, 1379, 1346, 1263, 1173, 1114, 1023. For the lactone 4:1 mixture, the ^{13}C nmr, as expected, shows a relatively complex pattern of doubling, especially in the upfield region.

The recovered reduced ester **31**.—^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.40 (s, 1H), 7.17 (s, 1H), 6.46 (d, J = 16 Hz, 1H), 6.20–6.06 (m, 1H), 4.71 (d, J = 6 Hz, 2H), 3.61 (s, 3H), 2.35 (t, J = 7.3 Hz, 2H), 1.71–1.58 (m, 2H), 1.42–1.20 (m, 4H), 0.91 (t, J = 7 Hz, 3H); eims *m/z* 236, 166, 138 (100%), 121, 109, 99, 94, 80, 71; hreims *m/z* $[M]^+$ 236.1522 (calcd for $C_{13}H_{20}N_2O_2$, 236.1520); ir ν max (smear) cm^{-1} 3113, 2955, 2929, 2870, 1734, 1661, 1499, 1464, 1421, 1377, 1232, 1169, 1114, 961, 660.

(+)-ISOPILOCARPINE [**16**].—To 0.30 g (1.22 mmol) of commercial (+)-pilocarpine hydrochloride was added a solution of NaOEt (6 mmol) in EtOH (8 ml). The resulting mixture was allowed to reflux overnight. After cooling to room temperature, the solvent was removed, and the residue was dissolved in 10 ml H_2O and extracted with 2 × 5 ml $CHCl_3$. The aqueous solution was acidified with concentrated HCl and extracted with 2 × 5 ml $CHCl_3$ for a second time. The aqueous acidic solution was basified to ca. pH 10 with NH_4OH. The liberated isopilocarpine was extracted with 3 × 15 ml $CHCl_3$. The isopilocarpine-containing $CHCl_3$ layers were combined and dried over $MgSO_4$. The solvent was removed to afford a viscous colorless residue (0.223 g, 87.4%): ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.41 (s, 1H), 6.78 (s, 1H), 4.39 (dd, J = ca. 7, 9 Hz, 1H), 3.91 (dd, J = ca. 7, 9 Hz, 1H), 3.59 (s, 3H), 2.88–2.59 (m, 3H), 2.31–2.25 (m, 1H), 1.75–1.69 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 178.0, 137.8, 127.9, 126.5, 70.6, 45.9, 38.5, 30.9, 26.7, 21.8, 10.6; eims *m/z* 208, 170, 109, 96, 95 (100%), 83, 68, 51; hreims *m/z* $[M]^+$ 208.1230 (calcd for $C_{11}H_{16}N_2O_2$, 208.1212); ir ν max (smear) cm^{-1} 2966, 2935, 1779, 1506, 1460, 1383, 1351, 1236, 1178, 1111, 1016, 930, 819, 665.

ISOPILOCARPINE/PILOCARPINE NITRATE PREPARED FROM 4:1 DIASTEREOISOMERS ISOLATED FROM COLUMN CHROMATOGRAPHY.—A portion (78 mg) of isopilocarpine/pilocarpine produced by the TBTH reductive cyclization was dissolved in 2 ml of MeOH. To this was added enough concentrated HNO_3 to make the solution slightly acidic (pH ca. 6). To the acidified solution Et_2O was added dropwise, the milky solution was allowed to stay at room temperature for 30 min, and the suspension was placed in a refrigerator for 30 min. The white granular crystals were filtered under suction. The crystals were washed with a small portion of pre-chilled MeOH and finally with an additional portion of Et_2O. The mp of the crystals (90.6 mg, 89.1%) was 133–134° [lit. (34) mp for pure (±) isopilocarpine nitrate 134–135°]. Peaks assigned for nitrate diastereoisomers were based on comparison with authentic nitrate salts. Even after fractional crystallization, by ^{1}H nmr, our nitrate salts made from the 4:1 material were still mixtures of diastereoisomers. (±)-trans Diastereoisomer: ^{1}H nmr ($CDCl_3$, DMSO, 250 MHz) δ 9.05 (s, 1H), 7.58 (s, 1H), 4.44–4.38 (m, 1H), 3.95–3.87 (m, 1H), 3.8 (s, 3H), 3.55 (br s, 1H), 3.04–2.41 (m, 4H), 1.66–1.58 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H). (±)-cis Diastereoisomer: ^{1}H nmr ($CDCl_3$, DMSO, 250 MHz) δ 9.05 (s, 1H), 7.57 (s, 1H), 4.28–4.22 (m, 1H), 4.0–3.9 (m, 1H), 3.8 (s, 3H), 3.55 (br s, 1H), 3.0–2.4 (m, 4H), 1.7–1.4 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H).

In the same fashion, authentic (+)-isopilocarpine [made from base isomerization of (+)-pilocarpine] was converted to the nitrate: mp 156–156.5° [lit. (35) 158–158.5°]; ^{1}H nmr ($CDCl_3$, DMSO, 250 MHz) δ 9.05 (s, 1H), 7.57 (s, 1H), 4.44–4.38 (m, 1H), 3.94–3.82 (m, 1H), 3.81 (s, 3H), 3.43 (br s, 1H), 3.02–2.30 (m, 4H), 1.67–1.59 (m, 2H), 0.94 (t, J = 7 Hz, 3H).

In the same fashion, authentic (+)-pilocarpine (made from commercial pilocarpine hydrochloride that had been converted to its free base) was converted to the corresponding nitrate: mp 174–176° from MeOH/Et_2O [lit. (36) mp 175.5–176.5°]; ^{1}H nmr ($CDCl_3$, DMSO, 250 MHz) δ 9.06 (s, 1H), 7.59 (s, 1H), 4.29–4.23 (m, 2H), 4.01–3.96 (m, 1H), 3.81 (s, 3H), 3.65–3.35 (br s, 1H), 3.05–2.50 (m, 3H), 1.77–1.63 (m, 1H), 1.62–1.44 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H).

ISOMERIZATION OF (±)-4:1 ISOPILOCARPINE/PILOCARPINE CYCLIZATION MIXTURE TO (±)-ISOPILOCARPINE.—To 0.050 g (0.2 mmol) of center-cut butyrolactone mixture isopilocarpine-pilocarpine (4:1) was added a solution of NaOEt (0.5 mmol) in EtOH (3.5 ml). The resulting mixture was allowed to reflux 6 h. After cooling to room temperature, the solvent was removed at reduced pressure. The residue was diluted with 6 ml of H_2O and washed with 2 × 5 ml of $CHCl_3$. The aqueous solution was acidified (to pH 1) with concentrated HCl and extracted again with 2 × 5 ml of $CHCl_3$. The aqueous solution was kept at room temperature while it was carefully brought to pH 9–10 by the dropwise addition of NH_4OH, whereupon the basified solution was then extracted with 3 × 10 ml of $CHCl_3$. The final $CHCl_3$ extracts were combined, dried, and filtered, and the solvent was removed to afford a residue (0.030 g) consisting of virtually pure (±)-isopilocarpine. This is best ascertained by monitoring the total integral for two characteristic multiplets for each isomer. Thus, the ratio of the combined integral for the peaks centered at δ = 4.4 and 3.9 (isopilocarpine) to the combined integral for the peaks centered at δ = 4.2 and 4.1 (pilocarpine) was 4.2 to 1 before isomerization. After isomerization, the ratio had increased to at least 25:1.

(+)-PILOCARPINE FREE BASE [2].—To 1.0 g (4.08 mmol) of commercial (+)-pilocarpine hydrochloride in 10 ml of distilled H_2O was added excess $NaHCO_3$ followed by extraction with 4 × 10 ml $CHCl_3$. The $CHCl_3$ layers were combined and washed with 5 ml of saturated brine. The $CHCl_3$ layer was dried over $MgSO_4$ and filtered, and the solvent was removed to give a colorless viscous liquid (0.921 g, 92.1%): ^{1}H nmr ($CDCl_3$, 250 MHz) δ 7.42 (s, 1H), 6.76 (s, 1H), 4.23–4.17 (m, 1H), 4.08–4.04 (m, 1H), 3.59 (s, 3H), 2.92–2.82 (m, 1H), 2.74–2.61 (m, 2H), 2.47–2.36 (m, 1H), 1.93–1.76 (m, 1H), 1.66–1.49 (m, 1H), 1.10 (t, J = 7.4 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 177.3, 137.4, 127.9, 126.0, 69.06, 43.8, 36.2, 30.5, 20.5, 17.4, 11.3; eims *m/z* 208, 121, 109, 95, (100%), 83, 68, 51; hreims *m/z* $[M]^+$ 208.1201 (calcd for $C_{11}H_{16}N_2O_2$, 208.1212); ir ν max ($CDCl_3$) cm^{-1} 3155, 2969, 2904, 1774, 1639, 1561, 1504, 1468, 1382, 1216, 1172, 1098, 1026.

(+)-PILOCARPINE HYDROCHLORIDE.—To an excess of methanolic HCl (ca. 1 ml) was added 250 mg (1 mmol) of the (+)-pilocarpine free base. To the resulting homogeneous solution was added Et_2O, until the solution changed to a white cloudy emulsion. The flask was stored at 0° for 30 min and then at room temperature for 30 min. The crystals were filtered and washed with cold MeOH (0.250 g, 87%): mp 205–206° [lit. (37) mp 204–205°]; ^{1}H nmr ($CDCl_3$, 250 MHz) δ 9.17 (s, 1H), 7.56 (s, 1H), 4.31–4.23 (m, 1H), 4.03–3.96 (m, 1H), 3.85 (s, 3H), 3.01–2.95 (m, 1H), 2.85–2.50 (m, 3H), 1.80–1.66 (m, 1H), 1.64–1.49 (m, 1H), 1.05 (t, J = 7.3 Hz, 3H). The HCl proton is too broad to observe.

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