Synthesis of (2*R*,4*S*,5*S*)-Epiallomuscarine, (2*S*,3*R*,5*S*)-Isoepiallomuscarine, and (2*S*,3*S*,4*S*,5*S*)-3-Hydroxyepiallomuscarine from α-D-Glucose[1]

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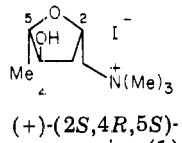
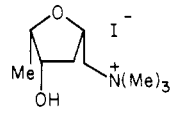
Received May 22, 1980

(2*R*,4*S*,5*S*)-Epiallomuscarine iodide (**4**) and two new muscarine analogues (**5** and **6**) have been synthesized from α-D-glucose. Furanose **10**, obtained in 64% overall yield from α-D-glucose, was reduced by lithium aluminum hydride to afford a 3:2 mixture of alcohols (**11a** and **11b**). Acetylation of **11a** gave acetate **13**. Hydrolysis of **13** was followed by oxidation to carboxylic acid **14**, which upon treatment with oxalyl chloride and subsequent treatment with dimethylamine afforded dimethylamide **15**. Reduction of **15** with lithium aluminum hydride and quaternization of the product amine with methyl iodide afforded **4**. The same methodology was employed to synthesize (2*S*,3*R*,5*S*)-isoepiallomuscarine (**5**) and (2*S*,3*S*,4*S*,5*S*)-3-hydroxyepiallomuscarine (**6**).

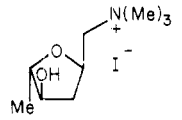
Muscarine (**1**), an alkaloid isolated from fly agaric [*Amanita muscaria* (L. ex Fr.) Quél], is a cornerstone of modern pharmacology, being one of the first substances known to reproduce responses induced by stimulation of the parasympathetic nervous system.[3] The rather simple structure of muscarine has defied elucidation for many years. The three asymmetric centers in **1** give rise to four racemates and are assigned according to the convention of Hardegger, Eugster, and Kogl.[4] In epimuscarine (**2**) and allomuscarine (**3**), the hydroxyl group and basic chain are on the same side of the annular plane, whereas in **1** and epiallomuscarine (**4**) they are on opposite sides. Epimuscarine (**2**), allomuscarine (**3**), and epiallomuscarine (**4**) differ from **1** by an inversion of the hydroxyl group at C-4 in **2**, by an inversion of the basic side chain at C-2 in **3**, and by an inversion of both these groups in **4**.



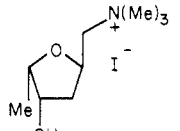
(+)-(2*S*,4*R*,5*S*)-muscarine (**1**)



(−)-(2*S*,4*S*,5*S*)-epimuscarine (**2**)



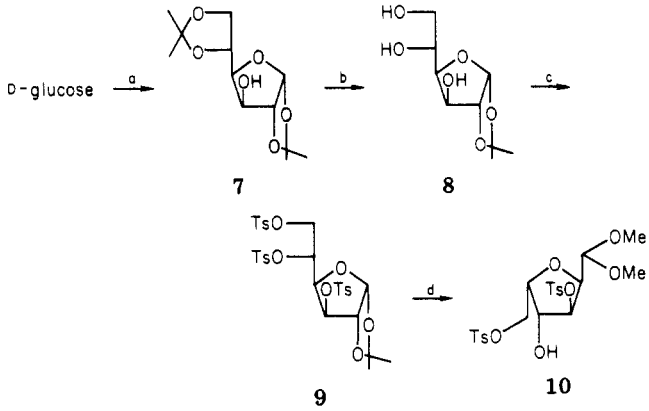
(−)-(2*R*,4*R*,5*S*)-allomuscarine (**3**)



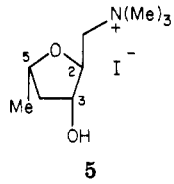
(+)-(2*R*,4*S*,5*S*)-epiallomuscarine (**4**)

These stereochemical possibilities posed problems of stereoselectivity in synthesis, as well as problems in the separation of stereoisomers and in configurational assignments. The chirality of all stereoisomeric muscarines have been reported by Eugster, one of the pioneers in muscarine chemistry.[5] The natural muscarines isolated so far are (+)-(2*S*,4*R*,5*S*)-muscarine, (−)-(2*R*,4*R*,5*S*)-allomuscarine, and (+)-(2*S*,4*S*,5*S*)-epimuscarine. It is of interest to the biogenesis of muscarines that identical chirality appears only at C-5.[5] The interest generated over the years by muscarines and their analogues is due to their marked physiological activity.[3-13] Although stereospecific synthesis of a number of muscarines including *dl*-muscarine,[7] *dl*-allomuscarine,[7] D(−)-allomuscarine,[8] and L(+)-muscarine[9,13] have been reported, simple stereospecific routes to **1** and its stereoisomers are still in demand. In connection with our studies on the synthesis of natural products by chirality transfer from carbohydrates, we have synthesized (2*R*,4*S*,5*S*)-epiallomuscarine (**4**) and two new muscarine analogues, (2*S*,3*R*,5*S*)-isoepiallomuscarine (**5**) and (2*S*,3*S*,4*S*,5*S*)-3-hydroxyepiallomuscarine (**6**) from α-D-glucose.

Scheme I[a]



[a] a, $ZnCl_2$, H_3PO_4, $(Me)_2CO$; b, H_3O^+; c, TsCl, C_5H_5N; d, MeOH (2% HCl).



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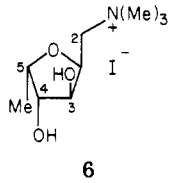

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The design of synthetic routes to **1** and its stereoisomers from carbohydrates must meet two requirements: (1) the

(1) (a) Presented in part at the 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979, CARB 45. (b) P. C. Wang, Z. Lysenko, and M. M. Joullié, *Tetrahedron Lett.*, 1657 (1978). (c) P. C. Wang, Z. Lysenko and M. M. Joullié, *Heterocycles*, **9**, 753 (1978).

(2) Taken in part from the Ph.D. thesis of Pen-Chung Wang, University of Pennsylvania, 1980.

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(6) P. Wasser, *Experientia*, **7**, 300 (1961).

(7) T. Matsumoto, A. Ichihara, and I. Ito, *Tetrahedron*, **25**, 5889 (1969).

(8) G. Fronza, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 3941 (1978).

(9) J. Whiting, Y.-K. Au-Yong, and B. Belleau, *Can. J. Chem.*, **50**, 3322 (1972).

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(13) A. M. Mubarak and D. M. Brown, *Tetrahedron Lett.*, 2453 (1980).

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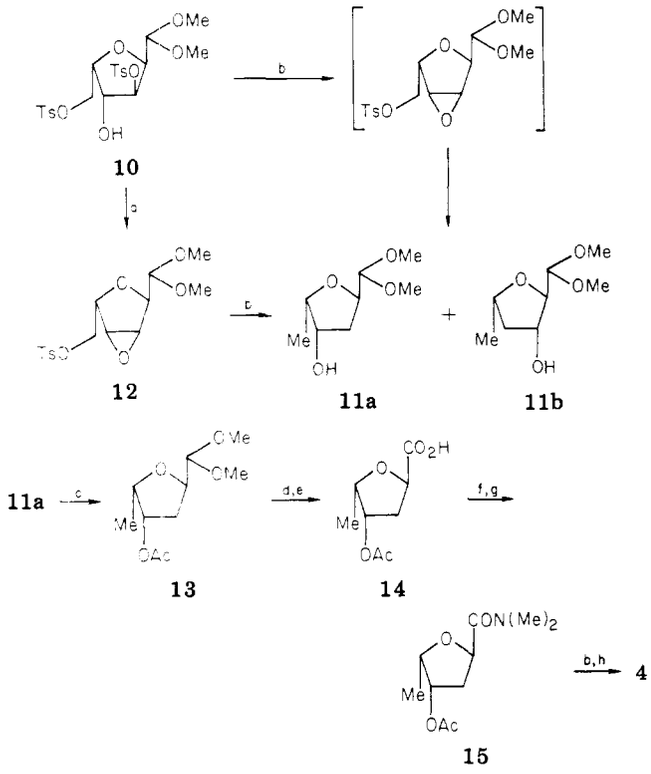
Scheme II[a]



[a] a, NaH, DMF; b, LAH, THF, c, Ac_2O, DMAP, C_5H_5N; d, H_3O^+; e, Jones reagent; f, $(ClCO)_2$, toluene; g, $(Me)_2NH$, toluene; h, MeI.

method selected for C–C bond formation at the anomeric center must be stereocontrolled; (2) C-2 must be appropriately substituted or amenable to substitution, so as to permit construction of the quaternary ammonium salt function. The solvolysis of sulfonic esters of sugars in acid media discovered by Defaye[14] provides an interesting route to 2,5-anhydro sugars. We felt that this methodology possessed great synthetic advantages: (1) a C–C linkage is introduced stereospecifically, thereby converting a sugar into a tetrahydrofuran, and (2) the resulting dimethyl acetal group at C-2 provides an excellent precursor for the construction of quaternary ammonium salts.

As shown in Scheme I, reaction of α-D-glucose with zinc chloride and 85% phosphoric acid in acetone gives 1,2,5,6-*O*-diisopropylideneglucofuranose (**7**).[15] Acid hydrolysis under mild conditions selectively removes the isopropylidene group at C-5 and C-6 to afford 1,2-*O*-isopropylideneglucofuranose (**8**).[15] Tosylation of **8** yields 1,2-*O*-isopropylidene-3,5,6-tri-*O*-tosyl-α-D-glucofuranose (**9**) which is then refluxed in methanol containing 2% concentrated hydrochloric acid to afford 2,5-anhydro-3,6-di-*O*-tosyl-L-idose dimethyl acetal (**10**) in 64% overall yield from α-D-glucose as a white crystalline solid.[16]

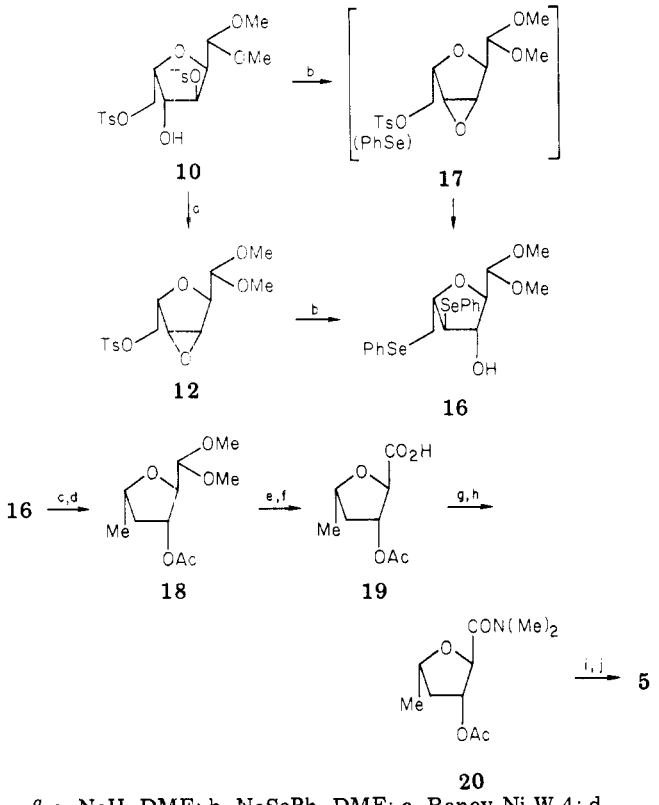
Our strategy for the synthesis of **4** required two transformations: construction of the tetrahydrofuran skeleton and introduction of the quaternary ammonium salt. We reasoned that if the two tosyl groups of **10** were reduced, the desired skeleton could be formed immediately with subsequent functionalization at C-1 providing the final target. The synthesis of **4** is shown in Scheme II.

Compound **10** was treated with an excess of lithium aluminum hydride to afford a 3:2 mixture of alcohols **11a** and **11b** in quantitative yield. These alcohols had very similar infrared and ^1H NMR spectra which indicated that both desulfonylation and desulfonyloxylation had occurred. This reduction was believed to proceed through the intermediacy of epoxide **12**.[17] Support for this mechanism was provided by the reaction of **10** with sodium hydride in dimethylformamide which gave the presumed epoxide **12**. Reduction of **12** with an excess of lithium aluminum hydride afforded the same 3:2 mixture of alcohols previously obtained from **10**. The predominance of **11a** may be attributed to a preferred orientation of the coordinated reducing agent. After separation of the alcohols by column chromatography, **11a** was converted into the corresponding acetate (**13**) with acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Hydrolysis of **13** produced a sensitive aldehyde which was immediately oxidized with Jones reagent to the corresponding carboxylic acid (**14**). This acid was treated, in turn, with oxalyl chloride and dimethylamine to afford dimethylamide **15**. Reduction of **15** with lithium aluminum hydride followed by quaternization of the product amine with an excess of methyl iodide gave (2*R*,4*S*,5*S*)-epiallomuscarine iodide (**4**), $[\alpha]^{25}_D \geq 0°$, mp 194–195 °C, in 72% yield [lit.[5] $[\alpha]^{25}_D \geq 0°$ for the synthetic (2*R*,4*S*,5*S*)-epiallomuscarine iodide]. The (2*R*,4*S*,5*S*)-epiallomuscarine iodide prepared by us was found to be identical with the chiral sample prepared by Eugster.[18]

In view of the biological activity of the isomeric muscarines, we decided to synthesize structurally similar compounds. Previous changes incorporated in the muscarine structure have involved (1) variations in the quaternary ammonium group and methyl group at C-5 and (2) replacement of the tetrahydrofuran skeleton by a tetrahydrothiophene.[6] We chose to introduce variations at the C-3 and C-4 positions. (2*S*,3*R*,5*S*)-Isoepiallomuscarine (**5**), a compound which possesses the hydroxyl group at C-3 instead of C-4, could be prepared by modifying the route used to obtain **4**. Thus, dimethyl acetal **10** was treated with an excess of sodium phenyl selenide to afford diselenide **16**. Reductive removal of the phenylselenenyl group with W-4 Raney nickel[19] gave alcohol **11b**, identical with the minor component of the lithium aluminum hydride reduction of **10**. The formation of **15** was believed to proceed through the intermediacy of epoxide **17**, generated by rear-side attack of the hydroxyl group at C-4 and subsequent ring opening induced by nucleophilic attack of sodium phenyl selenide from the less sterically hindered side of C-4. The proposed path was supported by the observation that the reaction of **12** with an excess of sodium phenyl selenide also afforded **16**. The intermediacy of an epoxide under similar conditions was observed in the reaction of **10** with sodium acetate.[20] The direction of epoxide ring opening appears to be governed by a combination of steric and polar effects attributable to the groups adjacent to the epoxide ring. In the absence of polar effects, the direction of cleavage of the epoxide ring seemed to be dependent on the steric influence of the group adjacent to the epoxide ring.[21]

(14) J. Defaye and V. Ratovelomanana, *Carbohydr. Res.*, 17, 57 (1971).
(15) E. R. Blakeley, *Biochem. Prep.*, 7, 39 (1960).
(16) T. Ogawa, M. Matsui, H, Ohrui, H. Kuzuhara and S. Emoto, *Agric. Biol. Chem.*, 36, 1449 (1972).
(17) The intermediacy of an epoxide under similar condition was also observed in the lithium aluminum hydride reduction of methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside: E. Vis and P. Karrer, *Helv. Chim. Acta*, 37, 378 (1954).
(18) We are indebted to Dr. C. H. Eugster for making the comparison of our synthetic sample (**4**) with their synthetic (5*S*,4*S*,2*R*)-epiallomuscarine.
(19) Prepared according to L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, J. Wiley and Sons, Inc., New York, 1967, p 729.
(20) T. Ogawa, M. Matsui, H. Ohrui, H. Kuzuhara and S. Emoto, *Agric. Biol. Chem.*, 36, 1655 (1972).

Scheme III[a]



[a] a, NaH, DMF; b, NaSePh, DMF; c, Raney Ni W-4; d, Ac_2O, DMAP, C_5H_5N; e, H_3O^+; f, Jones reagent; g, $(ClCO)_2$, toluene; h, $(Me)_2NH$, toluene; i, LAH, THF; j, MeI.

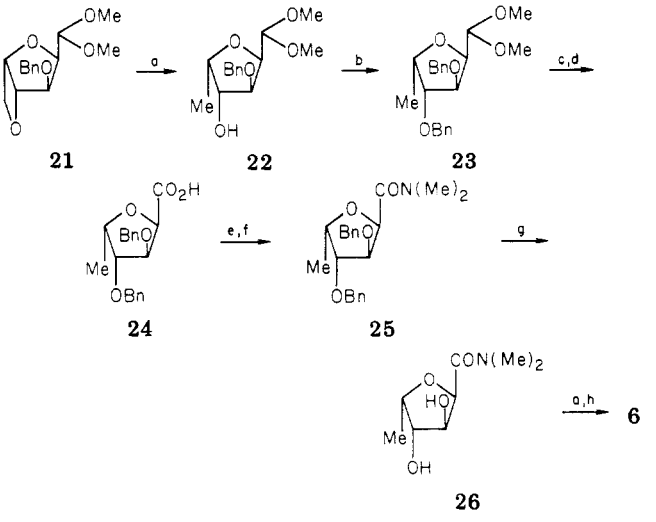
Conversion of **10** to isoepiallomuscarine is shown in Scheme III. Acetylation of **11b** with acetic anhydride and a catalytic amount of DMAP gave acetate **18**. Acid hydrolysis of **18** afforded the corresponding aldehyde which was immediately oxidized in situ with Jones reagent to give carboxylic acid **19**. Compound **19**, in turn, was treated with oxalyl chloride and dimethylamine to give dimethylamide **20**. The final transformation to **5** was accomplished by reduction of **20** with lithium aluminum hydride, followed by quaternization of the product amine with excess methyl iodide. Isoepiallomuscarine iodide (**5**) was obtained in 73% yield: mp 182 °C; $[\alpha]^{25}_D$ −26.5°.

The synthesis of 3-hydroxyepiallomuscarine (**6**) is shown in Scheme IV. The key intermediate (**21**) in the synthesis of **6** can be prepared from α-D-glucose in 36% overall yield.[14] Lithium aluminum hydride reduction of **21** opened the oxetane ring at C-6 to afford alcohol **22**. Benzylation of **22** with sodium hydride and benzyl chloride gave dibenzyl ether **23**. The sensitive aldehyde obtained on acid hydrolysis was oxidized to the corresponding acid (**24**). The overall yield for this one-pot hydrolysis and oxidation was 49%. The acid (**24**) was then treated with oxalyl chloride and dimethylamine to afford dimethylamide **25** in 75% yield. Catalytic hydrogenation of **25** gave diol **26**. Reduction of **26** with lithium aluminum hydride followed by quaternization of the product amine with excess methyl iodide afforded (2*S*,3*S*,4*S*,5*S*)-3-hydroxyepiallomuscarine iodide (**6**): mp 158–160 °C; $[\alpha]^{25}_D$ 0°.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. All reported values are uncorrected. Microanalyses were carried out at Galbraith Laboratory, Knoxville, TN, and Robertson Laboratory, Florham Park, NJ. Infrared spectra were obtained on a Perkin-Elmer 137 spectrometer with sodium chloride optics. Nuclear magnetic resonance spectra were obtained on either a Varian A-60A (60 MHz), Varian EM-360A (60 MHz), Varian HR-220 (220 MHz), or Bruker WH-360 (360 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane used as the internal standard. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Specific rotations are reported as $[\alpha]_D$ in units of degrees. Analytical thin-layer chromatography was performed on precoated silica gel plates (250 μm) with fluorescent indicator, supplied by E. Merck. Preparative thin-layer chromatography was performed on precoated silica gel plates (1000 μm) with fluorescent indicator, supplied by Analtech, Inc. Column chromatography utilized Merck silica gel 60 (70–230 mesh).

Scheme IV[a]



[a] a, LAH, THF; b, NaH, BnCl, DMF; c, H_3O^+; d, Jones reagent; e, $(ClCO)_2$, toluene; f, $(Me)_2NH$, toluene; g, H_2, Pd/C; h, MeI.

2,5-Anhydro-3,6-dideoxy-L-*lyxo*-hexose Dimethyl Acetal (11a) and 2,5-Anhydro-4,6-dideoxy-L-*lyxo*-hexose Dimethyl Acetal (11b). A two-necked, round-bottomed, 500-mL flask was fitted with a dropping funnel and a condenser protected with a drying tube. Lithium aluminum hydride, 2.0 g (0.05 mol), was placed in the flask with 200 mL of anhydrous tetrahydrofuran. After the mixture was stirred for 10 min, a solution of 10.3 g (0.02 mol) of ditosylate **10** in 50 mL of anhydrous tetrahydrofuran was added dropwise to the flask. Upon completion of the addition, the solution was refluxed for 6 h. The reaction was monitored by thin-layer chromatography (silica gel, ether). Excess hydride was decomposed by dropwise addition of moist ether (5–10% water) to the cooled mixture. Insoluble material was removed by filtration. The filtrate was washed with water and dried with magnesium sulfate. Removal of the solvents under reduced pressure gave a syrup consisting of alcohols **11a** and **11b**. The mixture was resolved by column chromatography (silica gel; ether–petroleum ether, 2:1) to afford 1.82 g (51% yield) of **11a** (silica gel, ether, R_f 0.43) and 1.25 g (35% yield) of **11b** (silica gel, ether, R_f 0.54).

11a: IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, 3 H), 1.25–1.30 (m, 1 H), 2.00–2.10 (m, 1 H), 2.15 (br s, 1 H), 3.40 (s, 6 H), 3.90–4.00 (m, 1 H), 4.07–4.34 (m, 3 H). Anal. Calcd for $C_8H_{16}O_4$: C, 54.52; H, 9.15. Found: C, 54.63; H, 9.02.

11b: IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 3 H), 1.51–1.70 (m, 1 H), 2.25–2.40 (m, 1 H), 2.65–2.86 (br s, 1 H), 3.43 (s, 3 H), 3.45 (s, 3 H), 3.84 (t, 1 H), 4.13–4.23 (m, 1 H), 4.30 (d, 1 H), 4.30–4.40 (m, 1 H). Anal. Calcd for $C_8H_{16}O_4$: C, 54.52; H, 9.15. Found: C, 54.88; H, 8.83.

2,5:3,4-Dianhydro-L-talose Dimethyl Acetal *p*-Toluenesulfonate (12). 2,5-Anhydro-3,6-di-*O*-tosyl-L-idose dimethyl acetal (1.55 g, 3 mmol) in 20 mL of anhydrous *N*,*N*-dimethylformamide was treated with 160 mg of sodium hydride (3.3 mmol) as a 50% dispersion in mineral oil. After 2 h at room temperature, the stirred mixture was diluted with 150 mL of ether and then

(21) N. R. Williams, *Adv. Carbohydr. Chem.*, **25**, 155 (1970).

with a small amount of water (about 5 mL). The organic phase was separated, washed with water, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to afford the crude epoxide as a syrup which was then purified by column chromatography (silica gel; ether–petroleum ether, 1:1) to give 930 mg (93% yield) of epoxide **12**: IR (neat) 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.46 (s, 3 H), 3.44 (s, 3 H), 3.47 (s, 3 H), 3.80 (q, 2 H), 4.05–4.11 (m, 3 H), 4.20–4.30, (m, 2 H), 7.35 (d, 2 H), 7.80 (d, 2 H). Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.86. Found: C, 52.06; H, 5.89.

Lithium Aluminum Hydride Reduction of 12. The procedure described for the transformation of **10** to **11a** and **11b** was used herein. 2,5:3,4-Dianhydro-L-talose dimethyl acetal *p*-toluenesulfonate, 664 mg (2 mmol), was reduced with 200 mg (5 mmol) of lithium aluminum hydride in refluxing anhydrous tetrahydrofuran to afford, after workup, the same mixture of alcohols, **11a** and **11b**, obtained from **10**.

Acetylation of 2,5-Anhydro-3,6-dideoxy-L-*lyxo*-hexose Dimethyl Acetal 11a. Alcohol **11a**, 528 mg (3 mmol), was dissolved in 10 mL of anhydrous pyridine and treated with 420 μL of acetic anhydride in the presence of a catalytic amount of DMAP. After 2 h at room temperature, the stirred reaction mixture was poured into 200 mL of ether. The ether solution was washed first with a saturated aqueous copper sulfate solution to remove pyridine and then with a saturated sodium chloride solution. The organic extract was dried over magnesium sulfate and the solvent evaporated to dryness under reduced pressure to afford 595 mg (91% yield) of acetate **13**. The oily product could be used directly in the next step without further purification. An analytical sample was obtained by column chromatography (silica gel; ether–petroleum ether, 1:1). **13**: IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (d, 3 H), 1.20–1.30 (m, 1 H), 2.20–2.25 (m, 1 H), 2.18 (s, 3 H), 3.40 (s, 6 H), 4.06–4.25 (m, 2 H), 4.24–4.25 (m, 1 H), 4.22–4.30 (m, 1 H).

2,5-Anhydro-3,6-dideoxy-L-*lyxo*-hexonic Acid 4-Acetate (14). A solution of 440 mg (2 mmol) of acetate **13** in 80% acetic acid (10 mL) and 2 N hydrochloric acid (0.1 mL) was heated at 65 °C for about 2 h. On cooling, the mixture was poured into ice–water (20 mL), neutralized with sodium bicarbonate, and then extracted with dichloromethane (3 × 50 mL). The dichloromethane solution was dried with magnesium sulfate and evaporated under reduced pressure to give the crude aldehyde intermediate. The aldehyde was dissolved in 30 mL of acetone and treated with Jones reagent (prepared from 66.7 g of chromium trioxide, 53.3 mL of concentrated sulfuric acid, and 180 mL of water) added dropwise at 0 °C. The reaction proceeded rapidly with the formation of a green precipitate. Additional reagent must be used if the orange color of the reaction mixture disappears. After 2 h at 0 °C the excess reagent is destroyed by adding small amounts of acidified sodium sulfite solution until the orange color of the medium is dissipated and only a green sludge remains. Ether (30 mL) may be added to hasten the separation of the precipitate. After removal of the supernatant liquid, the residue was triturated with solvent. The combined extracts were evaporated under reduced pressure and the residue was then purified by column chromatography (silica gel, ether) to give 200 mg of carboxylic acid **14**, isolated in 53% overall yield from acetate **13**. **14**: IR (neat) 3400, 3100, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H), 2.10 (d, 3 H), 2.20–2.92 (m, 2 H), 4.00–4.50 (m, 1 H), 4.72 (t, 1 H), 5.12–5.60 (m, 1 H), 10.32 (br s, 1 H). Anal. Calcd for $C_8H_{12}O_5$: C, 51.05; H, 6.43. Found: C, 50.87; H, 6.32.

2,5-Anhydro-3,6-dideoxy-*N,N*-dimethyl-L-*lyxo*-hexonamide 4-Acetate (15). Carboxylic acid **14**, 200 mg (1.06 mmol), was dissolved in 20 mL of dry toluene and cooled to 0 °C. Oxalyl chloride (105 μL, 1.2 mmol) was added and the reaction mixture was heated to 100 °C, with stirring, for 2 h. The solvent was evaporated under reduced pressure to afford the crude acid chloride which was used without further purification to prepare the corresponding amide. The acid chloride was dissolved in dry toluene (20 mL) and cooled to 0 °C. Dimethylamine was passed into the solution to saturation. After 1 h at 0 °C the flask was removed from the ice bath and the mixture stirred at room temperature for another 12 h. At this point, the reaction mixture was poured into 100 mL of ether and washed once with 5% hydrochloric acid solution and then with water (3 × 10 mL). The ether solution was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude amide. Purification by column chromatography (silica gel, ether) gave 160 mg of amide **15**, a 70% overall yield from **14**. **15**: IR (neat) 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, 3 H), 1.73–2.30 (m, 1 H), 2.35–3.0 (m, 1 H), 2.10 (s, 3 H), 2.97 (s, 3 H), 3.10 (s, 3 H), 3.97–4.42 (m, 1 H), 4.90 (t, 1 H), 5.38 (br s, 1 H). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 8.08; N, 6.50. Found: C, 55.65; H, 7.99; N, 6.47.

(2*R*,4*S*,5*S*)-Epiallomuscarine (4). A solution of amide **15**, 108 mg (0.5 mmol), in 10 mL of tetrahydrofuran was added dropwise to a suspension of 40 mg (1 mmol) of lithium aluminum hydride in 20 mL of tetrahydrofuran. The mixture was heated at reflux for 2 h. Excess hydride was then decomposed by dropwise addition of moist ether (5–10% water) to the cooled mixture. Insoluble material was removed by filtration. The filtrate was washed with ether and dried with magnesium sulfate. Removal of the solvent under reduced pressure gave the crude amine which was quaternized with excess methyl iodide (about 0.1 mL) in anhydrous ether to afford epiallomuscarine iodide as a white crystalline solid. Recrystallization of the crude product from toluene–acetone gave 108 mg of **4** (72% yield) as white needles: mp 194–195 °C; $[\alpha]^{25}_D \geq 0°$ (lit.[4,5] mp 159–160 °C for (±)-epiallomuscarine iodide; $[\alpha]^{25}_D \geq 0°$ for the synthetic (2*R*,4*S*,5*S*)-epiallomuscarine iodide); IR (KBr) 3300 cm^{-1}; NMR (Me_2SO-d_6) δ 1.11 (d, 3 H), 1.66–1.82 (m, 1 H), 1.95–2.11 (m, 1 H), 3.11 (s, 9 H), 3.41 (d, 2 H), 3.86–3.95 (m, 1 H), 3.98 (m, 1 H), 4.52 (br s, 1 H), 4.89 (d, 1 H).

2,5-Anhydro-4,6-di-*Se*-phenyl-4,6-diseleno-L-*mannose* Dimethyl Acetal (16). Diphenyl diselenide (3.2 g, 0.01 mmol) was dissolved in 50 mL of anhydrous *N,N*-dimethylformamide and to this solution was then added 1 g (0.026 mol) of sodium borohydride over a period of 20 min. After 2 h at room temperature (i.e., disappearance of the yellow color of the solution), the mixture was heated to 80 °C whereupon 4.0 g (0.0078 mol) of ditosylate **10** in 15 mL of *N,N*-dimethylformamide was added dropwise with stirring. The progress of this reaction was followed by thin-layer chromatography (silica gel; ether–petroleum ether, 1:1, R_f 0.37). On completion, the reaction mixture was poured into 200 mL of ether, and the ether layer was then washed with water and saturated aqueous sodium chloride. The organic fraction was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product. After column chromatography (silica gel; ether–petroleum ether, 1:2), 3.3 g (85% yield) of diselenide product (**16**) was isolated as a syrup: IR (neat) 3400, 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.73 (br s, 1 H), 3.02 (dd, 1 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.35–3.60 (m, 2 H), 3.88 (dd, 1 H), 4.09–4.20 (m, 2 H), 4.26 (d, 1 H), 7.10–7.25 (m, 6 H), 7.35–7.60 (m, 4 H); exact mass calcd for $C_{20}H_{24}O_4Se_2$ m/e 488.0005, found m/e 488.0005.

Reaction of 12 with Sodium Phenyl Selenide. Diphenyl diselenide (3.2 g, 0.01 mol) was dissolved in 50 mL of anhydrous *N,N*-dimethylformamide and then treated with 1 g (0.026 mol) of sodium borohydride, added in portions over a period of 20 min. After ~2 h at room temperature (i.e., disappearance of the yellow color of the solution), the mixture was heated to 80 °C and 2.6 g (0.0078 mol) of the epoxide **12** in 15 mL of *N,N*-dimethylformamide was added with stirring. The reaction was followed by thin-layer chromatography (silica gel; ether–petroleum ether, 1:1, R_f 0.37). On completion of the reaction, the mixture was poured into 200 mL of ether, and the ether layer was then washed with water and saturated aqueous sodium chloride. The organic extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product. Column chromatography (silica gel; ether–petroleum ether, 1:2) afforded 3.4 g (92%) of **16**.

Raney-Ni Reduction of 16. Sodium hydroxide (36 g) was dissolved in 150 mL of water in a 500-mL Erlenmeyer flask. The solution was heated to 50 °C on a water bath whereupon 30 g of Raney-Ni powder (Ni–Al, 50:50) was slowly added with stirring. The suspension was heated for another 50 min to complete the reaction. On cooling, the Raney Ni was triturated several times with water until the washings were neutral and then twice with anhydrous ethanol and tetrahydrofuran. To a suspension of the Raney Ni in tetrahydrofuran was added 1.5 g (3.1 mmol) of **16** in 10 mL of tetrahydrofuran. The mixture was stirred at room temperature for 2 h and then filtered with the aid of Celite. After the filtrate was dried with magnesium sulfate, the solvent was

evaporated to leave a syrup that was chromatographed on silica gel, using ether, to afford 0.533 g (96% yield) of alcohol **11b**. The product was found to be identical with the minor product obtained from the lithium aluminum hydride reduction of **10**.

Acetylation of 2,5-Anhydro-4,6-dideoxy-L-*lyxo*-hexose Dimethyl Acetal (11b). The procedure described for the transformation of **11a** to **13** was used herein. Alcohol **11b** (425 mg, 2.4 mmol) was treated with 420 μL of acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine to afford 504 mg (96% yield) of acetate **18**: IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, 3 H), 1.50–1.60 (m, 1 H), 2.38–2.55 (m, 1 H), 2.05 (s, 3 H), 3.40 (s, 6 H), 4.05 (dd, 1 H), 4.25 (d, 1 H), 4.25 (q, 1 H), 5.15–530 (m, 1 H).

2,5-Anhydro-4,6-dideoxy-L-*lyxo*-hexonic Acid 3-Acetate (19). The procedure described for the transformation of **13** to **14** was used herein. Acetate **18**, 440 mg (2 mmol), gave 188 mg (52% yield) of carboxylic acid **19**: IR (neat) 3500, 3100, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (d, 3 H), 1.45–1.90 (m, 1 H), 2.30–2.70 (m, 1 H), 2.10 (s, 3 H), 4.20–4.80 (m, 1 H), 4.65 (d, 1 H), 5.35–5.70 (m, 1 H), 7.50 (br s, 1 H). Anal. Calcd for $C_8H_{12}O_5$: C, 51.05; H, 6.43. Found: C, 50.79; H, 6.52.

2,5-Anhydro-4,6-dideoxy-*N,N*-dimethyl-L-*lyxo*-hexonamide 3-Acetate (20). The procedure described for the transformation of **14** to **15** was used herein. Carboxylic acid **19**, 200 mg (1.06 mmol), gave 160 mg (70% yield) of amide **20**: IR (neat) 1700, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 3 H), 1.59–1.70 (m, 1 H), 2.55–2.70 (m, 1 H), 2.10 (s, 3 H), 2.92 (s, 3 H), 3.15 (s, 3 H), 4.40 (q, 1 H), 4.80 (s, 1 H), 5.45–5.55 (m, 1 H); exact mass calcd for $C_{10}H_{17}NO_4$ *m/e* 215.1158, found *m/e* 215.1157.

(2*S*,3*R*,5*S*)-Isoepiallomuscarine (5). The procedure described for the transformation of **15** to **4** was used. Amide **20** (108 mg, 0.5 mmol) gave 110 mg (73% yield) of isoepiallomuscarine iodide as white needles: mp 182 °C; $[\alpha]^{25}_D$ −26.5°; IR (KBr) 3400 cm^{-1}; NMR (Me_2SO-d_6) δ 1.23 (d, 3 H), 1.35–1.55 (m, 1 H), 2.21–2.35 (m, 1 H), 3.15 (s, 9 H), 3.39 (s, 1 H), 3.45–3.55 (m, 1 H), 3.85–3.95 (m, 1 H), 4.05–4.25 (m, 2 H), 5.40 (d, 1 H). Anal. Calcd for $C_9H_{20}NO_2I$: C, 35.39; H, 6.69; N, 4.65. Found: C, 36.08; H, 6.78; N, 4.71.

Lithium Aluminum Hydride Reduction of 21. The procedure for the transformation of **10** to **11a** and **11b** was used herein. Compound **21** (1.2 g, 0.0043 mol) gave 1.1 g (90% yield) of 2,5-anhydro-3-benzyl-6-deoxy-L-idose dimethyl acetal (**22**): IR (neat) 3350, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (d, 3 H), 2.89 (br s, 1 H), 3.31 (s, 3 H), 3.39 (s, 3 H), 3.60 (d, 1 H), 3.80–4.10 (m, 2 H), 4.10–4.40 (m, 1 H), 4.54 (s, 2 H), 4.57 (d, 1 H), 7.25 (s, 5 H). Elemental analysis was carried out on the corresponding diol obtained from the debenzylation of **22**. Anal. Calcd for $C_8H_{16}O_5$: C, 49.98; H, 8.39. Found: C, 50.12, H, 8.21.

Benzylation of 22. 2,5-Anhydro-3-benzyl-6-deoxy-L-idose dimethyl acetal (**22**) (2.8 g, 0.01 mol) was dissolved in 50 mL of anhydrous *N,N*-dimethylformamide and treated with 530 mg of sodium hydride (0.011 mol as a 50% dispersion in mineral oil). The reaction mixture was stirred at room temperature for 2 h whereupon 1.26 mL (0.011 mol) of benzyl chloride was added. The mixture was then stirred at room temperature for 2 h. The resulting paste was diluted first with a small amount of water (about 10 mL) and then with 400 mL of ether. The organic layer was separated, washed with water, dried with magnesium sulfate, and concentrated to afford the crude product. After column chromatography (silica gel; ether–petroleum ether, 1:1) 2,5-anhydro-3,4-dibenzyl-6-deoxy-L-idose (**23**) was isolated as a syrup (3.2 g) in 86% yield: IR (neat) 1600, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3 H), 3.38 (s, 3 H), 3.40 (s, 3 H), 3.75 (d, 1 H), 4.08 (s, 1 H), 4.15–4.38 (m, 1 H), 4.48 (d, 1 H), 4.52 (s, 2 H), 4.60 (d, 1 H), 7.30 (s, 10 H).

2,5-Anhydro-3,4-dibenzyl-6-deoxy-L-idonic Acid (24). A solution of **23**, 850 mg (2.3 mmol), in a mixture of acetone (10 mL), tetrahydrofuran (10 mL), and 6 N sulfuric acid (10 mL) was heated at reflux until all of the starting material had been consumed (~4 h). The reaction was cooled to 0 °C and diluted with 30 mL of acetone. Jones reagent (prepared as described for **14**) was then added dropwise at 0 °C. A rapid reaction occurred with the formation of a green precipitate. The reaction mixture was kept at 0 °C overnight, then diluted with 400 mL of ether, and washed with saturated sodium chloride solution. The ether layer was dried with magnesium sulfate and then evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, ether) afforded 383 mg of 2,5-anhydro-3,4-dibenzyl-6-deoxy-L-idonic acid in 49% overall yield from **23**. **24**: IR (neat) 3100, 2950, 1720, 1600, 1595 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 3 H), 3.70 (d, 1 H), 4.18–4.40 (m, 1 H), 4.40 (d, 2 H), 4.48 (s, 4 H), 4.75 (d, 1 H), 7.23 (s, 10 H), 9.75 (br s, 1 H); exact mass calcd for $C_{20}H_{22}O_5$ *m/e* 342.1467, found *m/e* 342.1467.

2,5-Anhydro-3,4-dibenzyl-6-deoxy-*N,N*-dimethyl-L-idonamide (25). The procedure described for the transformation of **14** to **15** was used herein. Carboxylic acid **24**, 342 mg (1.0 mmol), gave 285 mg (75% yield) of **25**: IR (neat) 1670, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3 H), 2.80 (br s, 6 H), 3.78 (d, 1 H), 4.10–4.40 (m, 1 H), 4.38 (d, 1 H), 4.48 (s, 4 H), 4.90 (d, 1 H), 7.18 (s, 5 H), 7.28 (s, 5 H).

2,5-Anhydro-6-deoxy-*N,N*-dimethyl-L-idonamide (26). A solution of 2,5-anhydro-3,4-dibenzyl-6-deoxy-*N,N*-dimethyl-L-idonamide (738 mg, 2 mmol) in 25 mL of ethanol was hydrogenated at 1 atm in a Parr apparatus in the presence of 500 mg of 10% palladium on carbon. The progress of the reaction was monitored by thin-layer chromatography (ether–petroleum ether, 2:1) and shown to be complete after 10 h. The reaction mixture was diluted with 100 mL of ethanol and filtered through Celite. The Celite was rinsed with 30 mL of ethanol. Evaporation of the ethanol under reduced pressure and recrystallization of the residue from ethyl acetate–petroleum ether gave 340 mg (90% yield) of **26** as white needles: mp 166.5–167.5 °C; IR (KBr) 3250, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 3 H), 2.17 (s, 2 H), 2.97 (s, 3 H), 3.16 (s, 3 H), 4.12 (br s, 1 H), 4.41 (br s, 1H), 4.52 (q, 1 H), 4.66 (d, 1 H). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.79; H, 7.81; N, 7.23.

(2*S*,3*S*,4*S*,5*S*)-3-Hydroxyepiallomuscarine (6). The procedure described for the transformation of **15** to **4** was used herein. Amide **26**, 95 mg (0.5 mmol), gave 116 mg (73% yield) of **6** as white needles: mp 159–160 °C; $[\alpha]^{25}_D$ 0°; IR (KBr) 3300 cm^{-1}; NMR (Me_2SO-d_6) δ 1.12 (d, 3 H), 3.11 (s, 9 H), 3.39–3.45 (m, 1 H), 3.51–3.55 (m, 1 H), 3.75 (br s, 1 H), 4.02 (br s, 1 H), 4.18–4.20 (m, 1 H), 4.39 (d, 1 H), 5.17 (d, 1 H), 5.48 (d, 1 H). Anal. Calcd for $C_9H_{20}NO_3I$: C, 34.06; H, 6.36; N, 4.41. Found: C, 33.81; H, 6.40; N, 4.23.

Acknowledgment. We are thankful for partial support of this work by grants from the Research Corporation, Dow Chemical, and a Biomedical Research Support Grant (RR-07083-14) awarded by the University of Pennsylvania.

Registry No. **4**, 5487-32-1; **5**, 67492-44-8; **6**, 75378-64-2; **10**, 39022-34-9; **11a**, 68136-79-8; **11b**, 68136-78-7; **12**, 67492-43-7; **13**, 68665-74-7; **14**, 75378-65-3; **15**, 68116-31-4; **16**, 67492-40-4; **18**, 67492-41-5; **19**, 75378-66-4; **20**, 67492-42-6; **21**, 32445-69-5; **22**, 75378-67-5; **23**, 75378-68-6; **24**, 75378-69-7; **25**, 75378-70-0; **26**, 75378-71-1; 2,5-anhydro-6-deoxy-L-idose dimethyl acetal, 75378-72-2; α-D-glucose, 36468-84-5.