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A Divergent Synthesis of (+)-Muscarine and (+)-*epi*-Muscarine from D-Glucose

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Abstract—A novel stereospecific synthesis of (+)-muscarine and (+)-*epi*-muscarine has been achieved by utilizing D-glucose as a chiral precursor. The key steps of the synthesis involved stereospecific cyclization of 3,5-di-*O*-sulfonyl-D-glucofuranose derivatives into the corresponding 2,5-anhydrides, and stereospecific hydrogenation of 2,5-anhydro-L-*threo*-hex-2-enose ethylene acetal derivatives, thus providing an access to divergent intermediates for the preparation of both target molecules in a fully stereospecific manner.

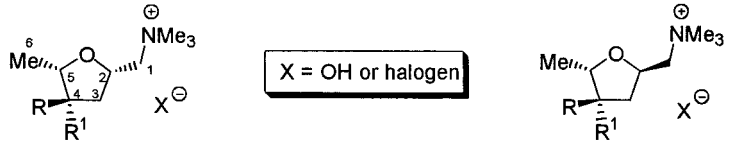
Introduction

(+)-Muscarine (**1**; Fig. 1) is a principal alkaloid of the poisonous mushroom *Amanita muscaria*, which shows a strong and specific cholinomimetic activity.[1] Consequently, its structure, chemistry and biological activity have been extensively studied.[2] There is a renewed interest in the muscarinic field due to the discovery of a relationship between cholinergic deficits and the pathology of Alzheimer's disease.[3] Hence, synthetic activity in this area has been considerable, and numerous syntheses of muscarine[4–9] and of many of its analogs[10,11] have been accomplished from different precursors. Major drawbacks of most of these approaches are either lack of selectivity or the usage of relatively expensive reagents and/or starting compounds. Apart from a recent synthesis of (−)-muscarine from *S*-malic acid,[9] none of the reported routes are suitable for the preparation of 5-substituted muscarine analogs.

In the course of our recent studies related to the preparation of enantiomerically pure muscarine stereoisomers by chirality transfer from D-glucose, the syntheses of (+)-*epiallo*-muscarine[12] (**4**) and (−)-*allo*-muscarine[13] (**3**) were already completed. Herein we report a divergent synthesis of (+)-muscarine (**1**) and (+)-*epi*-muscarine (**2**) based on D-glucose as a chiral precursor.[14]

Results and Discussion

The key steps in the synthesis of both targets **1** and **2** are: (*i*) the formation of the 2,5-anhydro-L-idose ethylene acetal derivatives **8** and **9** (Scheme 1) by an intramolecular S_N2 process which is expected to occur during an acid catalyzed alcoholysis of the protected furanoses[12,15] **6** and **7**; and (*ii*) a stereoselective catalytic reduction of the conformationally constrained dihydrofurans **12** and **15** which should be



1 R = OH; R^1 = H
(+)-Muscarine
2 R = H; R^1 = OH
(+)-*epi*-Muscarine

3 R = OH; R^1 = H
(−)-*allo*-Muscarine
4 R = H; R^1 = OH
(+)-*epiallo*-Muscarine

Figure 1. (+)-Muscarine and its biologically active stereoisomers.

Keywords: 2,5-anhydro sugars; D-glucose; (+)-muscarine; (+)-*epi*-muscarine; stereospecific synthesis.
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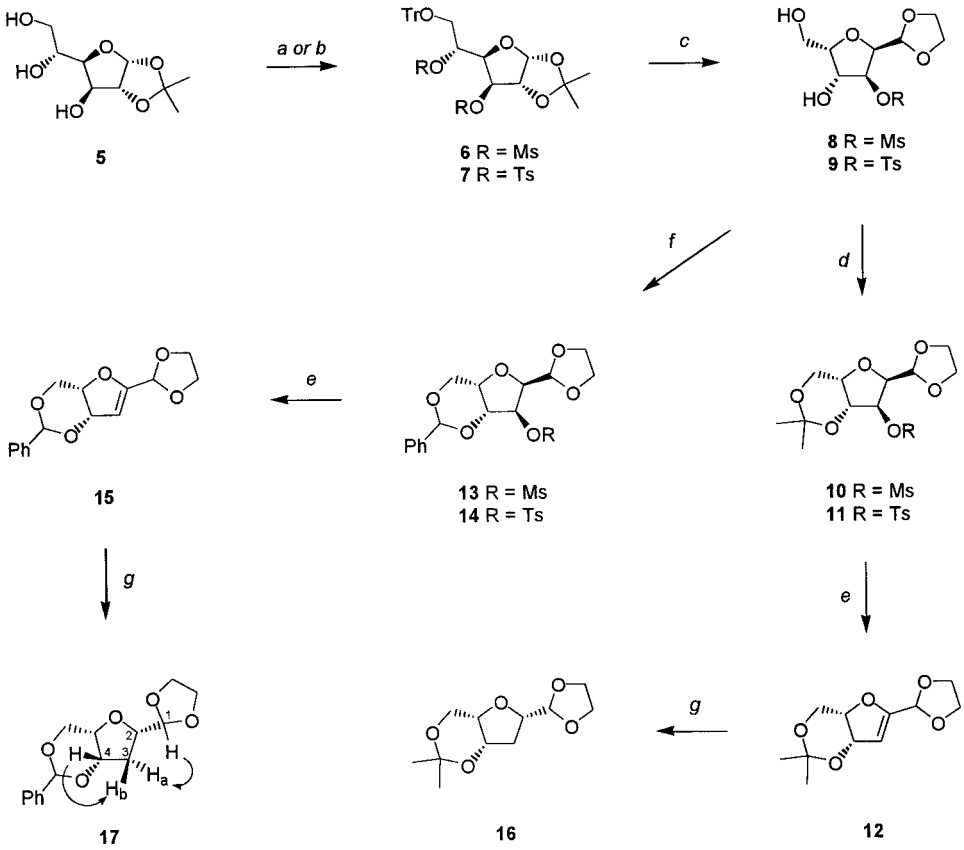
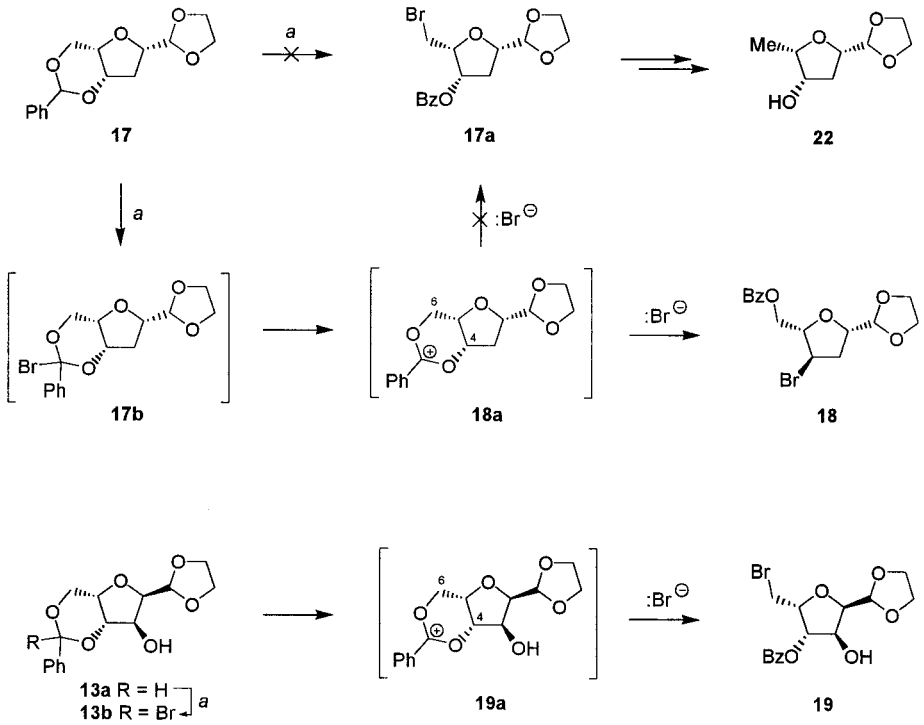


Scheme 1. (a) TrCl, Py, rt, 3 days, then MsCl, +4°C, 24 h, 100%; (b) TrCl, Py, rt, 3 days, then TsCl, rt 10 days, 100%; (c) ethylene glycol, TsOH, 80°C, 5 h, 53% of **8**; 54% of **9**; (d) $Me_2C(OMe)_2$, TsOH, rt, 24 h, 87% of **10**, 77% of **11**; (e) Bu_4NF, MeCN, N_2, reflux, 48 h, 76% of **12** from **10**, 82% of **12** from **11**, 67% of **15** from **13**, 86% of **15** from **14**; (f) $PhCH(OMe)_2$, TsOH, DMF, 70°C, 20 h, 60% of **13**, 86% of **14**; (g) H_2, PtO_2, EtOH, rt, 24 h, 94% of **16**, 91% of **17**.

available from the completely protected 2,5-anhydro-L-idose derivatives **10** and **11**, as well as from **13** and **14**.

For the cyclization studies both suitable protected 3,5-di-*O*-mesyl (**6**) and 3,5-di-*O*-tosyl (**7**) D-glucofuranose derivatives were first prepared. Monoacetone glucose (**5**),[16] was tritylated and subsequently mesylated in a one-pot procedure to afford the corresponding 3,5-di-*O*-mesyl-6-*O*-trityl derivative **6** in quantitative yield. Similarly, the 3,5-di-*O*-tosyl derivative **7** was prepared by successive treatment of **5** with trityl chloride and tosyl chloride. Both products **6** and **7** were isolated in pure form (TLC, ^1H and ^{13}C NMR) after the usual workup and used in the next step without further purification. Thus, treatment of crude **6** with ethylene glycol in the presence of toluene-4-sulfonic acid as a catalyst gave the 2,5-anhydro-L-idose derivative **8** (53% from **5**), while the 3,5-di-*O*-tosyl ester **7**, under the same reaction conditions, furnished the corresponding 3-*O*-tosyl derivative **9** in 54% overall yield.

In the next steps studies were performed with both isopropylidene and benzylidene protection. Thus the reaction of **8** with 2,2′-dimethoxypropane under the toluene-4-sulfonic acid catalysis afforded the expected 4,6-*O*-isopropylidene derivative **10** in 87% yield. The 3-*O*-tosyl ester **9** under the same reaction conditions gave 77% yield of **11**. Both 3-sulfonates **10** and **11** readily reacted with tetrabutylammonium fluoride, in boiling acetonitrile, to afford the corresponding 2,3-unsaturated derivative **12** in 76 and 82% yield, respectively. Condensation of **8** with α,α′-dimethoxytoluene in DMF, in the presence of catalytic amounts of toluene-4-sulfonic acid, gave the corresponding 4,6-*O*-benzylidene derivative **13** (60%), which was subsequently treated with tetrabutylammonium fluoride to yield the olefin **15** (40% from **8**). However, successive treatment of **9** with α,α′-dimethoxytoluene and tetrabutylammonium fluoride led to the formation of **15** with considerably better overall yield (74% from **9**). Catalytic hydrogenation of both **12** and **15** (PtO_2, EtOH) took place stereospecifically, from the less hindered β-face, allowing the isolation of the corresponding 3-deoxy derivatives **16** (94%) and **17** (91%) as the only stereoisomers. The stereochemistry of **17** was unambiguously confirmed by *NOE* differential ^1H NMR spectroscopy, and the characteristic *NOE* relations are shown in Scheme 1. Upon irradiation of the multiplet at 4.48 ppm (2H, H-4 and H-6b), a significantly stronger *NOE* was observed with H-3b (2.35 ppm) than with H-3a (2.27 ppm). This result is consistent with a *cis* arrangement of H-4 and H-3b as well as with a *trans* relationship of H-4 and H-3a. However, an irradiation of H-1 (5.12 ppm) gave a strong *NOE* with H-3a thus proving a spatial vicinity of these protons, and consequently an α-orientation of the dioxolane acetal ring. Finally, the large vicinal coupling between H-2 and H-3b ($J_{2,3b}$=9.2 Hz) that is compatible with *cis* relationship of these protons additionally confirmed the L-*xylo* configuration of the molecule **17**. Compared to the target **2**, both intermediates **16** and **17** have the correct stereochemistry at all chiral centers. For the sake of better



Scheme 2. (a) NBS, $BaCO_3$, CCl_4, N_2, reflux, 1.5 h, 63% of **18**, 66% of **19**.

functional resemblance to the target, they must be further subjected to a C-6 deoxygenation process. This would lead to the 6-deoxy derivative **22** (Scheme 2), a potential divergent intermediate for the synthesis of both targets **1** and **2**. At first it has been planned to deoxygenate the C-6 via the 6-bromodeoxy derivative **17a**. It was further assumed that the compound **17** could be converted to **17a** by using the well known Hanessian–Hullar reaction, which was successfully used for the conversion of numbered 4,6-*O*-benzylidene sugar acetals into the corresponding 4-*O*-benzoyl-6-bromo-6-deoxy derivatives.[17] However, when the recommended reaction conditions were applied to the 3-deoxy-L-*xylo*-hexose **17** (NBS, $BaCO_3$, CCl_4↑↓),[17] the 4-bromodeoxy derivative **18** was unexpectedly formed in 63% yield; no traces of the expected 6-bromodeoxy derivative **17a** was observed. Conversely, L-*ido* derivative **13a**,[18] under the same reaction conditions, gave the expected 6-bromodeoxy derivative **19** as the only reaction product in 66% yield. The same reaction course was observed upon treatment of 3-*O*-mesyl derivative **13** with NBS in boiling tetrachloromethane.[18]

The difference in product distribution between the L-*xylo* and L-*ido* series may be due to different steric and presumably electronic effects. According to a proposed mechanism[19] of the process, the initial attack of a free radical at the benzylic hydrogen atom in both molecules **17** and **13a** would occur first. The resulting bromoacetals (**17b** and **13b**) could further collapse to the cyclic benzoxonium ions (**18a** and **19a**) and bromide anion. The reaction would then assume ionic character and the more-susceptible carbon atom would be attacked preferentially by bromide ion to give the corresponding *O*-benzoylated bromohydrin. It seems that the preferential nucleophilic attack at C-4 in the intermediate **18a** (leading to the formation of **18**) is due to the overcrowding of the primary center by the *syn*-oriented dioxolane acetal function. On the contrary, the C-4 in **19a** is presumably more crowded by the β-oriented

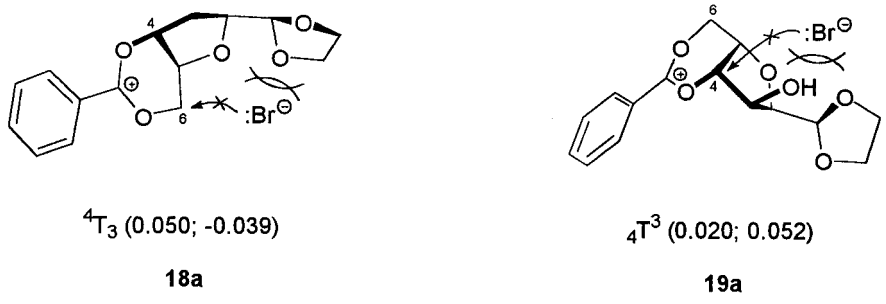
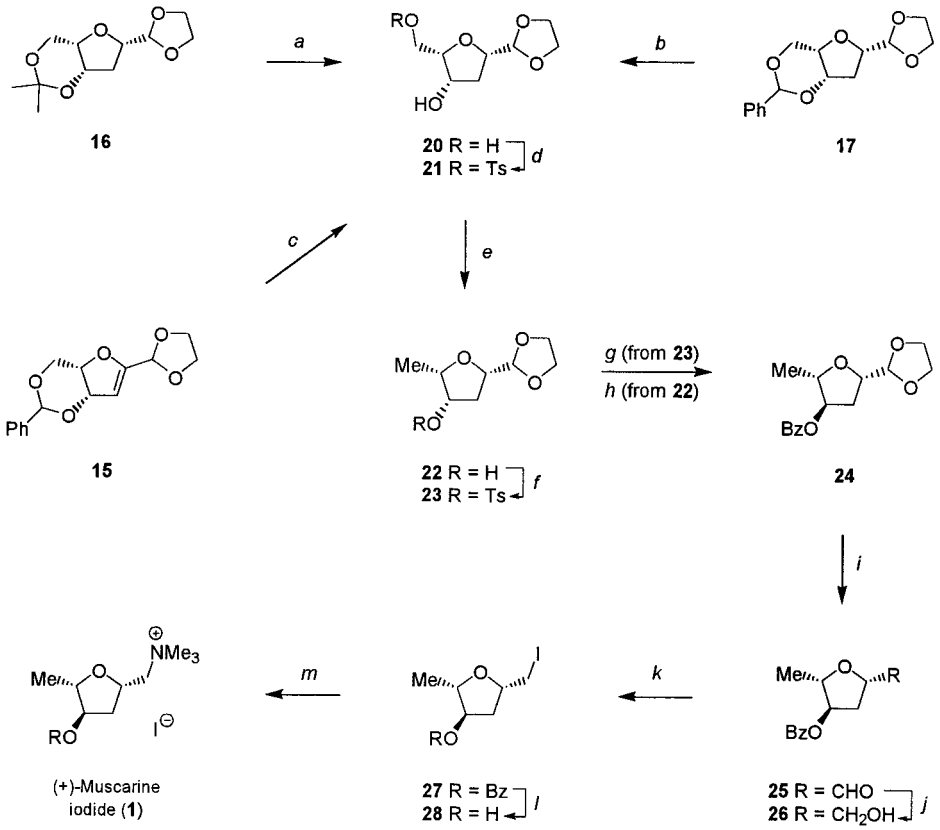


Figure 2. Stereochemical relationships in the optimized structures **18a** and **19a**. The numbers in parentheses denote values of formal charge at C-4 and C-6, respectively.



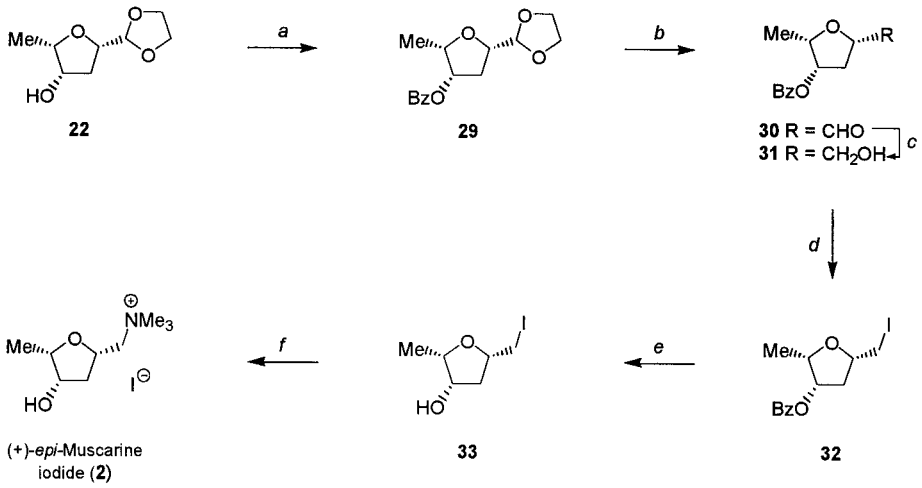
Scheme 3. (a) TFA, MeOH, rt, 0.5 h, 79%; (b) AcOH, H_2O, reflux, 7 h, 81%; (c) H_2, 10% Pd/C, EtOH, AcOH, rt, 16 h, 83%; (d) TsCl, Py, −28°C, 6 days, 80%; (e) $LiAlH_4$ THF, N_2, reflux, 4 h 90%; (f) TsCl, Py, rt, 48 h, 80%; (g) KOBz, DMF, 100°C, 24 h, 66%; (h) DEAD, $PhCO_2H$, Ph_3P, THF, 0°–rt, 20 h; (i) TFA, 6 M HCl, +4°C, 24 h; (j) $NaBH_4$, MeOH, rt, 2 h, 60% from **24**, 27% from **22**; (k) imidazole, Ph_3P, I_2, toluene, N_2, reflux, 3 h, 84%; (l) K_2CO_3, MeOH, THF, rt, 1.5 h, 83%; (m) Me_3N, EtOH, 80°C, 3 h, 93%.

dioxolane functionality, thus directing the nucleophilic attack towards the less-hindered C-6, whereupon the observed product **19** was formed. These assumptions were verified by molecular modeling studies.[20]

Preliminary molecular mechanics calculations (MM+) gave the low energy conformations of **18a** and **19a** with the tetrahydrofuran rings having the $^4T_3$ and the $_4T^3$ geometry, respectively (Fig. 2). These findings certainly do not exclude the existence of the other conformations, but apparently suggest that both intermediates **18a** and **19a** may occupy conformations suitable to explain the experimental results. Indeed, a careful examination of the optimized structure **18a** clearly indicated that the dioxolane acetal function does prevent approach of the nucleophile to C-6. On the contrary, the spatial arrangement of both C-2 and C-3 substituents in **19a** obviously causes serious overcrowding of the C-4. Moreover, semiempirical PM3 calculations performed on **18a** gave significantly different values for the formal charge at C-4 (0.050) and C-6 (−0.039), thus indicating a higher electrophilicity of C-4 in the intermediate **18a**. Conversely, concerning the calculated formal charges in **19a**, the C-6 (0.052) was shown to be somewhat more electrophilic than the C-4 (0.020). These findings appear to convincingly explain the experimental results.

Due to the undesirable outcome of the last reaction, an alternative procedure for introduction of 6-deoxy functions into the molecules **16** and **17** has been developed. Selective removal of the 4,6-*O*-isopropylidene protective group in **16**, achieved with 10% trifluoroacetic acid in methanol, gave the corresponding diol **20** in 79% yield, while the action of diluted acetic acid onto **17** afforded 81% yield of **20** (Scheme 3). Finally, the intermediate **20** was more conveniently prepared directly from **15** in 83% yield, by a one-pot procedure which included a catalytic hydrogenation of the double bond, and a hydrogenolytic removal of the benzylidene protection over 10% Pd/C. Monotosylation of the diol **20** at −28°C produced 6-*O*-tosyl derivative **21** (80%) which was subsequently treated with lithium aluminum hydride in boiling tetrahydrofuran, to give the key chiral intermediate **22** in 90% yield.

The seven-step synthetic sequence, which uses the tosyloxy leaving group as well as the benzylidene protection, obviously represents the most convenient route towards the divergent intermediate **22**, since it provided the highest overall yield of the desired product (24% from **5**). Reaction of **22** with tosyl chloride in pyridine gave the corresponding 4-*O*-tosyl derivative **23** in 80% yield. Compound **23** readily reacted with potassium benzoate, to give the chiral synthon **24** (66%) with an absolute configuration of all stereocenters corresponding to (+)-muscarine (**1**). Compound **24** was alternatively prepared directly from **22** by using the standard Mitsunobu conditions.[21] However, thus obtained sample **24** was slightly contaminated with unidentified aromatic impurities that remained in the sample even after repeated



Scheme 4. (a) BzCl, Py, rt, 24 h, 86%; (b) TFA, 6 M HCl, +4°C, 24 h; (c) $NaBH_4$, MeOH, rt, 2 h, 59% from **29**; (d) imidazole, Ph_3P, I_2, toluene, N_2, reflux, 3 h, 90%; (e) K_2CO_3, MeOH, THF, rt, 1.5 h, 65%; (f) Me_3N, EtOH, 80°C, 3 h, 95%.

chromatographic purification. Fortunately, these impurities did not affect the course of the following reaction directed to the hydrolytic removal of the dioxolane protective group. Thus, treatment of **24** with a 4:1 mixture of trifluoroacetic and 6 M hydrochloric acid gave the unstable aldehyde **25**, which was immediately reduced with sodium borohydride to afford the primary alcohol **26**. It appeared that the four-step sequence realized via the 4-*O*-tosyl derivative **23** represents a slightly more convenient procedure for the preparation of **26**, since it provided a somewhat higher overall yield (32% from **22**) compared to the three-step sequence based on Mitsunobu reaction (27% from **22**). Reaction of **26** with iodine, imidazole and triphenylphosphine, according to the methodology developed by Garegg and Samuelsson,[22] gave the known[7] iodo derivative **27** in 84% yield. *O*-Debenzoylation of **27** with potassium carbonate in methanol afforded 83% yield of the corresponding iodo alcohol **28**. Finally, compound **28** was converted to (+)-muscarine iodide (**1**) by treatment with trimethylamine in ethanol. Conversion of the intermediate **22** into the (+)-*epi*-muscarine iodide (**2**) is outlined in Scheme 4.

The sequence started with *O*-benzoylation of **22** whereupon the corresponding 4-*O*-benzoyl derivative **29** was obtained in 86% yield. Hydrolytic removal of the dioxolane protective group in **29**, followed by subsequent sodium borohydride reduction of the unstable aldehyde **30** gave the corresponding primary alcohol **31** in 59% yield (51% from **22**). Alternatively, when the last three-step process was carried out without chromatographic purification of the 4-*O*-benzoyl derivative **29**, the desired product **31** was obtained in an overall yield of 53% with respect to compound **22**. The intermediate **31** was finally converted to the (+)-*epi*-muscarine iodide (**2**) by using the same three-step sequence which was already applied for the conversion of **26** into the (+)-muscarine iodide (**1**; Scheme 3). The ^1H and ^{13}C NMR spectral data (Table 1) as well as physical constants of both **1** and **2** thus obtained were in reasonable agreement with those already reported.[7,8]

In conclusion, this paper describes a divergent 11-step synthesis of (+)-muscarine (**1**) and (+)-*epi*-muscarine (**2**) from commercially available monoacetone glucose (**5**) in 5

Table 1. ^1H and ^{13}C NMR spectral data for **1** and **2** (in D_2O)

Comp.	Chemical shift (δ) and J (Hz)									Reference
	H-1a	H-1b	H-2	H-3a	H-3b	H-4	H-5	H-6		
1	3.48	3.62	4.66	2.01	2.12	4.13	4.06	1.21		This work
	3.39	3.49	4.57	1.91	2.01	4.03	3.96	1.11		7
2	3.56	3.60	4.46	1.60	2.61	4.24	3.95	1.22		This work
	3.42	3.46	4.37	1.51	2.51	4.14	3.85	1.13		7
	$J_{1a,1b}$	$J_{1a,2}$	$J_{1b,2}$	$J_{2,3a}$	$J_{2,3b}$	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$	
1	14.0	9.1	1.8	9.5	6.4	13.7	5.9	2.4	2.5	This work
	14.0	9.2	1.8	9.6	6.3	13.7	5.7	2.3	2.5	7
2	13.9	3.1	9.7	5.9	8.7	14.3	1.9	6.0	3.5	This work
	13.9	3.3	8.2	5.7	8.7	14.3	1.9	6.0	3.5	7
	C-1	C-2	C-3	C-4	C-5	C-6	NMe_3			
1	73.21	74.66	40.23	77.87	86.77	21.89	56.70			This work
	73.51	74.85	40.53	78.13	86.91	22.11	57.09			7
2	72.96	73.99	41.97	74.16	83.45	16.18	56.84			This work
	73.00	73.95	41.96	74.16	83.43	16.15	56.82			7

and 7% overall yield, respectively. Although this new synthesis of **1** consists of more synthetic steps and has a lower overall yield than the earlier preparation from L-rhamnose (10% from seven steps),[5] it uses a less expensive and readily available starting material.[23] Compared with the previous carbohydrate based approaches[4] (each containing at least one non-specific synthetic step), the new synthesis of both targets **1** and **2** from D-glucose was realized in a fully regio- and stereospecific manner. Moreover, appropriate C-6 modifications of the 2,5-anhydro derivatives of type **20** or **21**, may provide access to potential divergent intermediates for the preparation of a variety of 5-substituted (+)-muscarine analogs.

Experimental

General methods

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on a Perkin–Elmer 141 MC polarimeter. IR spectra were recorded with a Specord 75IR spectrophotometer. NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from tetramethylsilane. Mass spectra were recorded on Finnigan-MAT 8230 and VG AutoSpec mass spectrometers. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Column chromatography was carried out using Kieselgel 60 (under 0.063 mm; E. Merck). Flash column chromatography was performed using ICN silica 32–63. All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under diminished pressure at a bath temperature below 35°C.

2,5-Anhydro-3-*O*-methanesulfonyl-L-idose ethylene acetal (8). To a solution of **5** (5.0 g, 27.22 mmol) in dry pyridine (50 mL) was added trietyl chloride (10.12 g, 36.32 mmol) and the mixture was kept at room temperature for 3 days. After cooling to 0°C, mesyl chloride (4.5 mL, 57.75 mmol) was added dropwise to the stirred and cooled solution. The mixture was left at +4°C for 24 h, then poured onto ice (80 g) and acidified with 6 M HCl (120 mL). The separated precipitate was dissolved in CH_2Cl_2 (200 mL) and the solution was washed successively with cold 10% HCl (200 mL) and water (3×100 mL). Organic layer was dried and evaporated to give chromatographically homogenous **6** (14.04 g, ~100%) as a white amorphous powder: mp 170–171°C (decomp.); R_f 0.35 (CH_2Cl_2), R_f 0.46 (9;1 toluene–EtOAc); ^{1}H NMR ($CDCl_3$): δ 1.34 and 1.51 (2×s, 3H each, CMe_2), 2.90 and 3.19 (2×s, 3H each, 2×$MeSO_2$), 3.47 (dd, 1H, $J_{6a,6b}$=11.3 Hz, $J_{5,6a}$=4.7 Hz, H-6a), 3.65 (dd, 1H, $J_{5,6b}$=2.1 Hz, H-6b), 3.70 (dd, 1H, $J_{3,4}$=2.7 Hz, $J_{4,5}$=9.4 Hz, H-4), 5.02 (d, 1H, H-3), 5.97 (d, 1H, H-1), 7.21–7.51 (m, 15H, CPh_3). ^{13}C NMR ($CDCl_3$): δ 26.16 and 26.43 (C*Me*$_2$), 38.62 and 39.26 (2×$MeSO_2$), 62.36 (C-6), 75.82 (C-4), 76.35 (C-5), 80.26 (C-3), 82.80 (C-2), 87.66 (*C*Ph$_3$), 104.75 (C-1), 112.74 (*C*Me$_2$), 127.23, 127.90, 128.59 and 143.02 (C*Ph*$_3$). To a suspension of crude **6** (3.79 g, 6.12 mmol) in ethylene glycol (22 mL) was added toluene-4-sulfonic acid (0.379 g, 1.99 mmol) and the mixture was stirred at 80°C for 5 h. The reaction mixture was left at +4° overnight, then filtered through a Celite pad, and the precipitate washed with ethylene glycol. Combined filtrate and washings were poured into saturated NaCl solution (44 mL), neutralized with $NaHCO_3$, and extracted with EtOAc (6×20 mL). The extracts were combined, dried and evaporated to pale yellow oil. Flash column chromatography (EtOAc) of the residue afforded pure **8** (0.931 g, 53% from **5**) as a colorless syrup: $[\alpha]_D$=+29.6 (*c*, 0.19 in $CHCl_3$); R_f 0.24 (19:1 CH_2Cl_2–MeOH), R_f 0.27 (EtOAc); ν_{max} (film): 3430 (broad), 2940, 2880, 1370, 1200, 1100, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.72 (bs, 1H, exchangeable with D_2O, OH-6), 3.11 (s, 3H, $MeSO_2$), 3.84–4.15 (m, 6H, 2×H-6 and CH_2-dioxolane), 4.24 (dd, 1H, $J_{1,2}$=6.3 Hz, $J_{2,3}$=3.9 Hz, H-2), 4.28 (m, 1H, $J_{4,5}$=4.0 Hz, H-5), 4.38 (d, 1H, exchangeable with D_2O, $J_{4,OH}$=4.1 Hz, OH-4), 4.64 (m, 1H, $J_{3,4}$=2.0 Hz, H-4), 5.01 (dd, 1H, H-3), 5.11 (d, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 38.10 ($MeSO_2$), 61.53 (C-6), 65.24 and 65.46 (2×CH_2-dioxolane), 77.51 (C-4), 79.46 (C-2), 79.52 (C-5), 85.43 (C-3), 101.91 (C-1); CI-MS: *m*/*z* 569 ($2M^+$+1), 285 (M^++1). HR-MS: Calcd for $C_9H_{16}O_8S$: 284.0566. Found: *m*/*z* 284.0571.

2,5-Anhydro-3-*O*-*p*-toluenesulfonyl-L-idose ethylene acetal (9). Compound **5** (7.5 g, 34.06 mmol) was dissolved in anhydrous pyridine (75 mL), and trityl chloride (15.0 g, 53.8 mmol) was added. After 3 days at room temperature, to the solution was added tosyl chloride (20.25 g, 106.22 mmol) and the mixture was left at room temperature for 10 days. The mixture was poured into a stirred and cooled (0°C) solution of 6 M HCl (300 mL), whereupon a white precipitate was formed. The precipitate was collected by filtration, washed with cold water and dried at 35°C for 48 h. Chromatographically homogenous **7** (26.2 g, 100%) was thus obtained as a white amorphous solid: mp 128–129°C (decomp.); R_f 0.86 (2:1 EtOAc–light petroleum), R_f 0.65 (7:1 toluene–Me_2CO): ^{1}H NMR ($CDCl_3$): δ 1.27 and 1.42 (2×s, 3H, each, CMe_2), 2.43 and 2.48 (2×s, 3H, each 2×*Me*$C_6H_4SO_2$), 3.22 (dd, 1H, $J_{6a,6b}$=11.0 Hz, $J_{5,6a}$=2.8 Hz, H-6a), 3.33 (dd, 1H, $J_{5,6b}$=5.5 Hz, H-6b), 4.55 (dd, 1H, $J_{3,4}$=2.8 Hz, $J_{4,5}$=5.2 Hz, H-4), 4.75 (ddd, 1H, H-5), 4.79 (d, 1H, $J_{1,2}$=3.4 Hz, H-2), 4.93 (d, 1H, H-3), 5.71 (d, 1H, H-1), 7.41–7.86 (m, 23H, CPh_3 and 2×Me*C*$_6H_4SO_2$); ^{13}C NMR ($CDCl_3$): δ 21.75 and 21.82 (2×*Me*$C_6H_4SO_2$), 26.33 and 26.55 (C*Me*$_2$), 62.26 (C-6), 77.11 (C-5), 77.89 (C-4), 81.22 (C-3), 82.38 (C-2), 86.75 (*C*Ph$_3$), 104.39 (C-1), 112.7 (*C*Me$_2$), 127.06–145.5 (C*Ph*$_3$ and 2×Me*C*$_6H_4SO_2$). A mixture of crude **7** (26.0 g) and toluene-4-sulfonic acid (1.5 g, 7.89 mmol) in ethylene glycol (150 mL) was stirred at 80°C for 2 h. After the usual workup (see preparation of **8**), crude **9** remained as a crystalline solid. Recrystallization of the residue from toluene gave pure **9** (5.95 g) as white needles, mp 144–146°C. An additional amount of pure **9** (0.7 g) was obtained after purification of the mother liquor by flash column chromatography (2:1 EtOAc–light petroleum). Total yield of **9** was 6.65 g (54% from **5**). Recrystallization from toluene afforded an analytical sample **9**: mp 146°C; $[\alpha]_D$=+20.7 (*c*, 0.68 in $CHCl_3$); R_f 0.17 (2:1 EtOAc–light petroleum), R_f 0.13 (3:1 toluene–Me_2CO); ν_{max} (KBr): 3450–3260 (broad), 2970, 2920, 1610, 1360, 1190, 1100, 1060, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, *Me*$C_5H_4SO_2$), 2.73 (t, 1H, exchangeable with D_2O, $J_{6,OH}$=4.0 Hz, OH-6), 3.82–3.97 (m, 5H, 2×CH_2-dioxlane and H-6a), 4.03 (dd, 1H, $J_{6a,6b}$=12.7 Hz, $J_{5,6b}$=3.8 Hz,

H-6b), 4.14 (dd, 1H, $J_{1,2}$=6.1 Hz, $J_{2,3}$=4.2 Hz, H-2), 4.22 (m, 1H, $J_{4,5}$=4.2 Hz, $J_{5,6a}$=2.7 Hz, H-5), 4.30 (d, 1H, exchangeable with D_2O, $J_{4,OH}$=4.3 Hz, OH-4), 4.55 (dd, 1H, $J_{3,4}$=2.0 Hz, H-4), 4.91 (dd, 1H, H-3), 4.95 (d, 1H, H-1), 7.31–7.87 (m, 4H, $MeC_6H_4SO_2$). ^{13}C NMR ($CDCl_3$): δ 21.76 ($MeC_6H_4SO_2$), 61.66 (C-6), 65.21 and 65.35 (2×CH_2-dioxolane), 77.09 (C-4), 79.44 (C-2), 79.52 (C-5), 84.98 (C-3), 101.62 (C-1), 128.23, 129.81, 130.01 and 145.24 ($MeC_6H_4SO_2$); EI-MS: *m/z* 359 (M^+-1). Anal. Calcd for $C_{15}H_{20}O_8S$: C 49.99, H 5.59, S 8.90. Found: C 50.06, H 5.74, S 8.77.

2,5-Anhydro-4,6-*O*-isopropylindene-3-*O*-methanesulfonyl-L-idose ethylene acetal (10). A mixture of **8** (0.42 g, 1.51 mmol), toluene-4-sulfonic acid (0.0056 g, 0.03 mmol) and 2,2′-dimethoxypropane (7 mL) was stirred at room temperature for 24 h. The solution was poured into 10% NaCl solution (14 mL), neutralized with $NaHCO_3$ (0.01 g) and extracted with CH_2Cl_2 (3×10 mL). The extracts were combined, dried and evaporated. Flash chromatography (9:1 CH_2Cl_2–EtOAc) of the residue (0.52 g) yielded pure **10** (0.426 g, 87%) as a colorless syrup: $[\alpha]_D$=+72.4 (*c*, 0.64 in $CHCl_3$); R_f 0.28 (9:1 CH_2Cl_2–EtOAc), R_f 0.36 (1:1 EtOAc–light petroleum); ν_{max} (KBr): 3000, 2930, 1360, 1190, 1100, 930 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 and 1.41 (2×s, 3H each, CMe_2), 3.09 (s, 3H, $MeSO_2$), 3.80–4.11 (m, 6H, 2×CH_2-dioxolane and 2×H-6), 4.15 (m, 1H, $J_{5,6}$= 2.3 Hz, $J_{4,5}$=2.5 Hz, H-5), 4.28 (dd, 1H, $J_{2,3}$=3.6 Hz, $J_{1,2}$=7.2 Hz, H-2), 4.50 (dd, 1H, $J_{3,4}$=1.1 Hz, H-4), 4.88 (dd, 1H, H-3), 5.10 (d, 1H, H-1); ^{13}C NMR ($CDCl_3$) δ 19.20 and 28.42 (CMe_2), 37.94 ($MeSO_2$), 60.36 (C-6), 64.99 and 65.26 (2×CH_2-dioxolane), 72.66 (C-5), 74.08 (C-4), 80.19 (C-2), 84.55 (C-3), 97.53 (CMe_2), 101.85 (C-1). Attempted crystallization from MeOH gave small amount of the crystalline sample **10**, mp 112–114°C (decomp.), along with variety decomposition products that remained in the mother liquor. Due to instability of the product **10**, a correct microanalysis of HR-MS could not be obtained.

2,5-Anhydro-4,6-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-L-idose ethylene acetal (11). Diol **9** (1.0 g, 2.78 mmol), toluene-4-sulfonic acid (0.01 g, 0.05 mmol) and 2,2′-dimethoxypropane (10 mL) were stirred at room temperature for 24 h. The usual workup gave crude **11**, which was purified by flash chromatography (2:1 light petroleum–EtOAc), to give colorless needles of pure **11** (0.86 g, 77%). Recrystallization from MeOH yielded an analytical sample **11**: mp 142–144°C; $[\alpha]_D$=+79.1 (*c*, 0.23 in $CHCl_3$); R_f 0.68 (2:1 EtOAc–light petroleum); ν_{max} (KBr): 3080, 3020, 2980, 2920, 2900, 1600, 1390, 1200, 1100, 930 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 and 1.35 (2×s, 3H each, CMe_2), 2.42 (s, 3H, $MeC_6H_4SO_2$), 3.53–4.92 (m, 4H, CH_2-dioxolane), 3.96 (m, 2H, $J_{5,6a}$=2.8 Hz, $J_{5,6b}$= 2.1 Hz, 2×H-6), 4.06 (m, 1H, $J_{4,5}$=2.8 Hz, H-5), 4.10 (dd, 1H, $J_{2,3}$=3.7 Hz, $J_{1,2}$=7.0 Hz, H-2), 4.44 (m, 1H, $J_{3,4}$=1.1 Hz, $J_{2,4}$=1.8 Hz, H-4), 4.81–4.91 (m, 2H, H-1 and H-3), 7.31–7.75 (m, 1H, $MeC_6H_4SO_2$); ^{13}C NMR ($CDCl_3$): δ 19.45 and 28.42 (CMe_2), 21.71 ($MeC_6H_4SO_2$), 60.52 (C-6), 65.03 and 65.16 (2×CH_2-dioxolane), 72.88 (C-5), 73.67 (C-4), 80.52 (C-2), 84.05 (C-3), 97.68 (CMe_2), 101.51 (C-1), 128.34, 129.66, 132.90 and 145.18 ($MeC_6H_4SO_2$); EI-MS: *m/z* 385 (M^+-Me). Anal. Calcd for $C_{18}H_{24}O_8S$: C 53.99, H 6.04, S 8.01. Found: C 54.34, H 6.30, S 8.36.

2,5-Anhydro-3-deoxy-4,6-*O*-isopropylidene-L-*threo*-hex-2-enose (12). *(Procedure A)* To a solution of **10** (0.418 g, 1.29 mmol) in dry acetonitrile (5 mL) was added Bu_4NF (1.69 g, 6.45 mmol) and the mixture was refluxed in an atmosphere of N_2 for 48 h. The mixture was evaporated and the residue (1.626 g) purified by flash chromatography (19:1 toluene–Me_2CO), to afford pure **12** (0.224 g, 76%) as colorless syrup.

Procedure B: a mixture of **11** (0.82 g, 2.05 mmol), Bu_4NF (2.85 g, 10.9 mmol) in acetonitrile (15 mL) was refluxed in an atmosphere of N_2 for 48 h. The workup followed by chromatographic purification according to procedure A, gave pure **12** (0.358 g, 82%) as a colorless syrup: $[\alpha]_D$=+86.3 (*c*, 1.1 in $CHCl_3$); R_f 0.25 (19:1 toluene–Me_2CO), R_f 0.6 (2:1 toluene–Me_2CO); ν_{max} (film): 3100, 3010, 2950, 2900, 1690, 1380, 1210, 1120, 1040, 970 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 and 1.38 (2×s, 3H each, CMe_2), 3.87 (dd, 1H, $J_{6a,6b}$=11.9 Hz, $J_{5,6a}$=6.8 Hz, H-6a), 3.90–4.09 (m, 5H, 2×CH_2-dioxolane and H-6b), 4.50 (m, 1H, $J_{4,5}$=6.6 Hz, H-5), 4.94 (dd, 1H, $J_{3,4}$=2.8 Hz, H-4), 5.24 (d, 1H, H-3), 5.52 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 22.96 and 26.51 (CMe_2), 58.97 (C-6), 65.29 and 65.33 (2×CH_2-dioxolane), 72.66 (C-4), 78.81 (C-5), 97.56 (C-1), 98.85 (CMe_2), 99.47 (C-3), 160.87 (C-2). HR-MS: Calcd for $C_{11}H_{16}O_5$: 228.0998. Found: *m/z* 228.0992.

2,5-Anhydro-4,6-*O*-benzylidene-3-*O*-methanesulfonyl-L-idose (13). To a solution of **8** (0.55 g, 1.93 mmol) in dry DMF (5.5 mL) was added toluene-4-sulfonic acid (0.06 g, 0.32 mmol) and α,α′-dimethoxytoluene (1.2 mL, 7.99 mmol). The mixture was stirred at 70°C for 20 h, then neutralized with $NaHCO_3$ (0.2 g), evaporated and the residue was extracted with CH_2Cl_2 (2×10 mL). The extracts were combined, dried and evaporated to yellow oil (0.5 g). Flash column chromatography (1:1 EtOAc–light petroleum) gave pure **13** (0.43 g, 60%) as a colorless syrup: $[\alpha]_D$=+47.4 (*c*, 0.23 in $CHCl_3$); R_f 0.76 (EtOAc). ν_{max} (film): 3040, 3000, 2960, 2910, 1620, 1400, 1370, 1200, 1160, 1100, 1020, 980, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.13 (s, 3H, $MeSO_2$), 3.82–4.05 (m, 4H, 2×CH_2-dioxolane), 4.1 (dd, 1H, $J_{6a,6b}$=13.1 Hz, $J_{5,6a}$=1.8 Hz, H-6a), 4.24 (m, 1H, $J_{4,5}$=2.4 Hz, H-5), 4.38 (dd, 1H, $J_{1,2}$=7.1 Hz, $J_{2,3}$= 3.7 Hz, H-2), 4.50 (d, 1H, H-6b), 4.74 (dd, 1H, $J_{3,4}$= 1.0 Hz, H-4), 5.08 (d, 1H, H-3), 5.17 (d, 1H, H-1), 5.48 (s, 1H, PhC*H*), 7.31–7.52 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 37.98 ($MeSO_2$), 65.06 and 65.34 (2×CH_2-dioxolane), 67.29 (C-6), 73.15 (C-5), 79.26 (C-4), 80.79 (C-2), 83.72 (C-3), 99.05 (Ph*C*H), 101.88 (C-1), 126.11, 128.24, 129.2 and 137.24 (Ph). CI-MS: *m/z* 373 (M^++1). HR-MS: Calcd for $C_{11}H_{20}O_8S$: 372.0879. Found: *m/z* 372.0888.

2,5-Anhydro-4,6-*O*-benzylidene-3-*O*-*p*-toluenesulfonyl-L-idose ethylene acetal (14). A mixture of **9** (5.5 g, 15.26 mmol), α,α′-dimethoxytoluene (9.7 mL, 64.62 mmol) and toluene-4-sulfonic acid (0.15 g, 0.79 mmol) in dry DMF (40 mL) was stirred at 70°C for 24 h. After neutralization with $NaHCO_3$ (0.8 g) the solvent was evaporated and the remaining crude residue was extracted with CH_2Cl_2 (2×20 mL). The combined extracts were dried and

evaporated to pale yellow syrup. Direct crystallization from MeOH yielded pure **14** (5.4 g) as colorless needles, mp 139–140°C. Flash chromatography (49:1, toluene–Me_2CO) of the mother liquor afforded an additional amount of pure **14** (0.50 g). Total yield 5.9 g (86%). An analytical sample **14** was obtained by recrystallization from MeOH: mp 139–140°C; $[\alpha]_D$=+64.5 (*c*, 0.34 in $CHCl_3$); R_f 0.73 (2:1 EtOAc–light petroleum); R_f 0.50 (4:1 toluene–Me_2CO). ν_{max} (KBr): 3080, 3020, 2900, 1600, 1370, 1190, 1100, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, $MeC_6H_4SO_2$), 3.58–3.97 (m, 4H, 2×CH_2-dioxolane), 4.07 (dd, 1H, $J_{6a,6b}$=12.8 Hz, $J_{5,6a}$=1.8 Hz, H-6a), 4.20 (m, 1H, $J_{4,5}$=2.2 Hz, H-5), 4.27 (dd, 1H, $J_{1,2}$=7.3 Hz, $J_{2,3}$=3.4 Hz, H-2), 4.47 (d, 1H, H-6b), 4.74 (m, 1H, H-4), 4.95 (m, 2H, H-1 and H-3), 5.45 (s, 1H, PhC*H*), 7.3–7.8 (m, 9H, Ph and $MeC_6H_4SO_2$); ^{13}C NMR ($CDCl_3$): δ 21.75 ($MeC_6H_4SO_2$), 65.05 and 65.17 (2×CH_2-dioxolane), 67.45 (C-6), 73.18 (C-5), 78.98 (C-4), 81.10 (C-2), 83.17 (C-3), 99.23 (Ph*C*H), 101.52 (C-1), 126.25–145.97 (Ph and $MeC_6H_4SO_2$). EI-MS: *m/z* 447 (M^+-1); CI-MS: *m/z* 449 (M^++1). Anal. Calcd for $C_{22}H_{24}O_8S$: C 58.92, H 5.39, S 7.15. Found: C 59.13, H 5.17, S 7.36.

2,5-Anhydro-4,6-*O*-benzylidene-3-deoxy-L-*threo*-hex-2-enose ethylene acetal (15). *(Procedure A)* A mixture of **13** (0.104 g, 0.28 mmol) and Bu_4NF (0.235 g, 0.9 mmol) in dry MeCN (2 mL) was refluxed in an atmosphere of N_2 for 48 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water (3×10 mL). Organic solution was dried and evaporated to brown syrup (0.08 g). Chromatographic purification on a column of flash silica (7:3 light petroleum–Me_2CO) afforded pure **15** (0.052 g, 67%) as a white crystalline solid.

Procedure B: to a solution of 3-*O*-tosyl derivative **14** (1.67 g, 3.72 mmol) in dry acetonitrile (20 mL) was added Bu_4NF (4.0 g, 15.29 mmol) and the mixture was refluxed in an atmosphere of N_2 for 24 h. The solvent was evaporated off; the residue was purified by flash chromatography (49:1 toluene–Me_2CO) to yield pure **15** (0.888 g, 86%) as colorless needless. Recrystallization from MeOH gave an analytical sample **15**: mp 91°C; $[\alpha]_D$=+130.2 (*c*, 0.42 in $CHCl_3$); R_f 0.68 (2:1 toluene–Me_2CO). ν_{max} (KBr): 3080, 3010, 2920, 1670, 1600, 1470, 1400, 1330, 1250, 1210, 1130, 1040, 950 cm^{-1}; ^1H NMR ($CDCl_3$); δ 3.96–4.10 (m, 4H, 2×CH_2-dioxolane), 4.13 (m, 1H, $J_{4,5}$=4.6 Hz, $J_{5,6a}$=3.0 Hz, $J_{5,6b}$=1.0 Hz, H-5), 4.29 (dd, 1H, $J_{6a,6b}$=13.7 Hz, H-6a), 4.65 (d, 1H, H-6b), 4.94 (dd, 1H, $J_{3,4}$=2.9 Hz, H-4), 5.47 (m, 2H, H-1 and H-3), 5.61 (s, 1H, PhC*H*), 7.25–7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 65.12 and 65.23 (2×CH_2-dioxolane), 66.27 (C-6), 76.32 (C-4), 77.2 (C-5), 97.58 (Ph*C*H), 98.08 (C-3), 101.14 (C-1) 126.17, 128. 21, 128.9 and 137.94 (Ph), 162.08 (C-2). EI-MS: *m/z* 276 (M^+). Anal. Calcd for $C_{15}H_{16}O_5$: C 65.21, H 5.84; Found: C 65.40, H 5.92.

2,5-Anhydro-3-deoxy-4,6-*O*-isopropylidene-L-*xylo*-hexose ethylene acetal (16). A solution of **12** (0.87 g, 3.81 mmol) in EtOH (20 mL) was hydrogenated over PtO_2 (0.08 g, 0.35 mmol) for 24 h at room temperature. The mixture was filtered and the catalyst washed with EtOAc. The filtrate and washings were combined and evaporated to give crude **16** that was purified by flash column chromatography (9:1 toluene–Me_2CO). Pure **16** (0.827 g, 94%) was obtained as a colorless syrup: $[\alpha]_D$=+19.7 (*c*, 1.16 in $CHCl_3$); R_f 0.4 (2:1 toluene–Me_2CO). ν_{max} (film): 3000, 2970, 2920, 1390, 1290, 1120, 970 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 and 1.40 (2×s, 3H, each, CMe_2), 2.07 (dd, 1H, $J_{2,3a}$=3.6 Hz, $J_{3a,3b}$=14.3 Hz, H-3a), 2.28 (ddd, 1H, $J_{2,3b}$=9.2 Hz, $J_{3b,4}$=5.3 Hz, H-3b), 3.72 (m, 1H, $J_{5,6}$=3.0 Hz, $J_{4,5}$=2.8 Hz, H-5), 3.81–4.08 (m, 6H, 2×CH_2-dioxolane and 2×H-6), 4.35 (m, 1H, H-4), 5.03 (d, 1H, $J_{1,2}$=7.1 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 19.56 and 28.38 (CMe_2), 35.38 (C-3), 60.65 (C-6), 65.09 and 65.14 (2×CH_2-dioxolane), 70.01 (C-4), 75.22 (C-5), 79.16 (C-2), 97.61 (CMe_2), 104.86 (C-1). CI-MS: *m/z* 231 (M^++1). HR-MS: Calcd for $C_{11}H_{18}O_5$: 230.1154. Found: *m/z* 230.1161.

2,5-Anhydro-4,6-*O*-benzylidene-3-deoxy-L-*xylo*-hexose ethylene acetal (17). Compound **15** (1.3 g, 4.7 mmol) in EtOH (15 mL) was hydrogenated over PtO_2 (0.13 g, 0.57 mmol) for 24 h. After workup as described above (preparation of **16**), crude **17** was obtained which was purified on a column of silica gel (100 g, 5:1 toluene–Me_2CO). Pure **17** (1.19 g, 91%) was isolated in the form of a colorless syrup: $[\alpha]_D$=+14.2 (*c*, 1.42 in $CHCl_3$); R_f 0.55 (2:1 toluene–Me_2CO). ν_{max} (film): 3090, 3010, 2950, 2930, 2900, 1620, 1410, 1220, 1130, 1110, 1000, 960 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.27 (m, 1H, $J_{3a,3b}$=14.6 Hz, $J_{2,3a}$=3.7 Hz, H-3a), 2.35 (ddd, 1H, $J_{2,3b}$=9.2 Hz, $J_{3b,4}$=4.9 Hz, H-3b), 3.76 (m, 1H, $J_{5,6a}$=2.1 Hz, $J_{5a,6b}$=1.0 Hz, H-5), 3.82–4.08 (m, 5H, 2×CH_2-dioxolane, and H-2), 4.13 (dd, 1H, $J_{6a,6b}$=13.1 Hz, H-6a), 4.48 (m, 2H, H-4 and H-6b), 5.12 (d, 1H, $J_{1,2}$=7.0 Hz, H-1), 5.45 (PhC*H*), 7.25–7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.46 (C-3), 65.22 and 65.29 (2×CH_2-dioxolane), 67.17 (C-6), 75.36 (C-5), 76.44 (C-4), 79.57 (C-2), 99.81 (Ph*C*H), 104.97 (C-1), 126.34, 128.31, 129.01 and 138.24 (Ph). CI-MS: *m/z* 279 (M^++1). HR-MS: Calcd for $C_{15}H_{18}O_5$: 278.1154. Found: *m/z* 278.1149.

2,5-Anhydro-6-*O*-benzoyl-4-bromo-3,4-dideoxy-L-*ribo*-hexose ethylene acetal (18). A mixture of **17** (0.097 g, 0.35 mmol), NBS (0.073 g, 0.41 mmol) and $BaCO_3$ (0.073 g, 0.41 mmol) in dry CCl_4 (5 mL) was refluxed in an atmosphere of N_2 for 1.5 h. The solvents were evaporated and the residue purified by column chromatography (17 g; 5:1 light petroleum–EtOAc) to yield pure **18** (0.079 g, 63%) as a colorless syrup: $[\alpha]_D$=−26.8 (*c*, 0.7 in $CHCl_3$); R_f 0.79 (9:1 light petroleum–EtOAc). ν_{max} (film): 3080, 2960, 2900, 1725, 1600, 1460, 1275, 1100, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.36 (ddd, 1H, $J_{3a,3b=}$13.4 Hz, $J_{2,3a}$=7.4 Hz, $J_{3a,4}$=5.9 Hz, H-3a), 2.55 (ddd, 1H, $J_{3b,4}$=6.9 Hz, $J_{2,3b}$=6.7 Hz, H-3b), 3.28–4.04 (m, 4H, 2×CH_2-dioxolane), 4.28–4.55 (m, 5H, H-2, H-4, H-5 and 2×H-6), 4.93 (d, 1H, $J_{1,2}$=3.4 Hz, H-1), 7.39–8.10 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 37.16 (C-3), 45.09 (C-4), 63.94 (C-6), 65.42 and 65.51 (2×CH_2-dioxolane), 78.81 (C-2), 85.38 (C-5), 103.76 (C-5), 103.76 (C-1), 128.36, 129.73 and 133.13 (Ph), 166.2 (C=O). CI-MS: *m/z* 357 (M^++1). HR-MS: Calcd for $C_{15}H_{17}BrO_5$: 356.0259. Found: *m/z* 356.0266.

2,5-Anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-L-idose ethylene acetal (19). A mixture of **13a** (0.10 g, 0.34 mmol) and $BaCO_3$ (0.04 g, 0.2 mmol) in dry CCl_4 (5 mL) was treated with NBS (0.073 g, 0.41 mmol) as described above. After 0.5 h the mixture was evaporated and the residue purified by

flash chromatography (49:1 CH_2Cl_2–Me_2–CO) to give pure **19** (0.084 g, 66%) as a solid. Recrystallization from CH_2Cl_2–hexane gave an analytical sample **19**: mp 142–143°C; $[\alpha]_D$=+44.6 (*c*, 0.24 in $CHCl_3$); R_f 0.74 (1:1 cyclohexane–Me_2CO). ν_{max} (KBr): 3430 (broad), 2980, 2920, 1730, 1610, 1290, 1130, 1090, 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.48–3.63 (m, 2H, $J_{6a,6b}$=10.2 Hz, $J_{5.6a}$=8.5 Hz, $J_{5,6b}$=6.3 Hz, H-6a and H-6b), 3.85–4.11 (m, 4H, 2×CH_2-dioxolane), 4.18 (dd, 1H, $J_{1,2}$=5.2 Hz, $J_{2,3}$=3.8 Hz, H-2), 4.54 (dd, 1H, $J_{3,4}$=1.2 Hz, H-3), 4.78 (ddd, 1H, $J_{4,5}$=3.4 Hz, H-5), 5.23 (d, 1H, H-1), 5.54 (dd, 1H, H-4), 7.41–8.06 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 27.34 (C-6), 65.26 and 65.38 (2×CH_2-dioxolane), 75.54 (C-3), 78.51 (C-4), 79.87 (C-5), 81.57 (C-2), 102.4 (C-1), 128.56, 129.1, 129.64 and 133.59 (Ph), 165.25 (C=O). CI-MS: *m/z* 373 (M^++1). Anal. Calcd for $C_{16}H_{19}BrO_8$: C 48.28, H 4.59. Found: C 48.00, H 4.32.

2,5-Anhydro-3-deoxy-L-*xylo*-hexose ethylene acetal (20). *(Procedure A)* A solution of **16** (0.77 g, 3.95 mmol) and CF_3CO_2H (0.8 mL) in MeOH (7.2 mL) was stirred at room temperature for 0.5 h, and then evaporated by co-distillation with toluene. Flash chromatography (2:1 toluene–Me_2CO) of the residue gave pure **20** (0.505 g, 79%) as a colorless syrup.

Procedure B: a solution of 4,6-*O*-benzylidene derivative **17** (1.1 g, 3.95 mmol) in glacial acetic acid (6 mL) and water (1 mL) was stirred at reflux temperature for 7 h. The mixture was evaporated by co-distillation with toluene and the remaining crude **20** was purified by flash chromatography (EtOAc), to afford pure **20** (0.606 g, 81%) as a colorless syrup.

Procedure C: a solution of **15** (0.8 g, 2.9 mmol) in EtOH (20 mL) was hydrogenated over 10% Pd/C (0.3 g) for 4 h at room temperature. To the reaction mixture was then added glacial acetic acid (4 mL) and hydrogenation was continued for an additional 12 h. The mixture was filtered, the catalyst washed with EtOAc, and the combined filtrate and washings were evaporated by co-distillation with toluene. Flash column chromatography (EtOAc) of the residue afforded pure **20** (0.445 g, 83%) as a colorless syrup: $[\alpha]_D$=+10.9 (*c*, 1.34 in $CHCl_3$); R_f 0.19 (EtOAc). ν_{max} (film): 3420 (broad), 2940, 2900, 1110–1050, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.94 (ddd, 1H, $J_{3a,3b}$=14.0 Hz, $J_{2,3a}$=3.7 Hz, $J_{3a,4}$=1.8 Hz, H-3a), 2.32 (ddd, 1H, $J_{2,3b}$=9.5 Hz, $J_{3b,4}$=5.5 Hz, H-3b), 2.85 (bs, 1H, exchangeable with D_2O, OH), 3.78–4.11 (m, 8H, 2×CH_2-dioxolane, H-4, H-5 and 2×H-6), 4.24 (m, 1H, H-2), 5.0 (d, 1H, $J_{1,2}$=2.1 Hz, H-1), 5.30 (bs, 1H, exchangeable with D_2O, OH); ^{13}C NMR ($CDCl_3$): δ 35.51 (C-3), 61.84 (C-6), 65.54 and 65.67 (2×CH_2-dioxolane), 71.98 (C-2), 77.6 (C-4), 83.29 (C-5), 103.84 (C-1). CI-MS: *m/z* 191 (M^++1). HR-MS: Calcd for $C_8H_{14}O_5$: 190.0841. Found: *m/z* 19.0838.

2,5-Anhydro-3-deoxy-6-*O*-*p*-toluenesulfonyl-L-*xylo*-hexose ethylene acetal (21). To a cooled (−28°C) solution of **20** (0.87 g, 4.57 mmol) in dry pyridine (8 mL) was added a cold (−28°C) solution of tosyl chloride (1.4 g, 7.34 mmol) in dry pyridine (8 mL). The reaction mixture was left at −28°C for 6 days, then poured into 6 M HCl (30 mL) and the resulting emulsion was extracted with dichloromethane (3×20 mL). The extracts were combined, washed with water, dried and evaporated to yellow oil. Flash column chromatography (9:1 toluene−Me_2CO) yielded pure **21** (1.26 g, 80%) as a colorless syrup: $[\alpha]_D$=+15.4 (*c*, 0.78 in $CHCl_3$); R_f 0.47 (EtOAc). ν_{max} (film): 3520–3400 (broad), 2930, 2900, 1600, 1360, 1200, 1120, 980 cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.93 (d, 1H, $J_{3a,3b}$=14.0 Hz, H-3a), 2.27 (ddd, 1H, $J_{2,3b}$=8.8 Hz, $J_{3b,4}$=5.0 Hz, H-3b), 2.44 (s, 3H, **Me**$C_6H_4SO_2$), 3.73 (d, 1H, exchangeable with D_2O, $J_{4,OH}$=10.7 Hz, OH), 3.83–4.07 (m, 5H, 2×CH_2-dioxolane, and H-5), 4.15 (m, 2H, $J_{6a,6b}$=9.2 Hz, H-4 and H-6a), 4.31 (m, 2H, H-2 and H-6b), 4.95 (s, 1H, H-1), 7.33–7.8 (m, 4H, Me$C_6H_4SO_2$); ^{13}C NMR ($CDCl_3$): δ 21.67 (*Me*$C_6H_4SO_2$), 34.75 (C-3), 65.58 and 65.66 (2×CH_2-dioxolane), 68.94 (C-6), 70.93 (C-4), 78.13 (C-2), 81.56 (C-5), 103.45 (C-1), 128.1, 129.82, 132.98 and 144.79 (Me$C_6H_4SO_2$). CI-MS: *m/z* 345 (M^++1). HR-MS: Calcd for $C_{15}H_{20}O_7S$: 344.0930. Found: *m/z* 344.0939.

2,5-Anhydro-3,6-dideoxy-L-*xylo*-hexose ethylene acetal (22). A mixture of **21** (1.26 g, 3.66 mmol) and $LiAlH_4$ (0.7 g, 18.44 mmol) in dry THF (20 mL) was refluxed in an atmosphere of N_2 for 4 h. Excess of the reagent was decomposed by addition of EtOAc (1 mL), the mixture was filtered and the precipitate washed with EtOAc. The combined filtrate and washings were evaporated and the remaining crude **22** purified by flash chromatography (5:1 toluene–Me_2CO). Pure **22** (0.575 g, 90%) was thus obtained as a colorless syrup: $[\alpha]_D$=+43.4 (*c*, 1.03 in $CHCl_3$); R_f 0.23 (5:1 toluene–Me_2CO). ν_{max} (film): 3460 (broad), 3000–2900, 1450, 1110, 1090, 980 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (d, 3H, $J_{5,6}$=6.4 Hz, 3×H-6), 1.90 (d, 1H, $J_{3a,3b}$=14.0 Hz, H-3a), 2.26 (ddd, 1H, $J_{2,3b}$=9.2 Hz, $J_{3b,4}$=5.2 Hz, H-3b), 3.43 (d, 1H, exchangeable with D_2O, $J_{4,OH}$=11.0 Hz, OH), 3.76–4.11 (m, 6H, 2×CH_2-dioxolane, H-4, and H-5), 4.19 (d, 1H, H-2), 4.95 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 14.09 (C-6), 35.41 (C-3), 65.58 and 65.68 (2×CH_2-dioxolane), 72.31 (C-4), 77.04 (C-2), 80.19 (C-5), 103.78 (C-1). CI-MS: *m/z* 175 (M^++1). HR-MS: Calcd for $C_8H_{14}O_4$: 174.0892. Found: *m/z* 174.0885.

2,5-Anhydro-3,6-dideoxy-4-*O*-*p*-toluenesulfonyl-L-*xylo*-hexose ethylene acetal (23). To a solution of **22** (0.77 g, 4.42 mmol) in dry pyridine (10 mL) was added TsCl (2.5 g, 13.11 mmol) and the mixture was kept at room temperature for 48 h. The reaction mixture was poured into 6 M HCl (30 mL) and extracted with CH_2Cl_2 (4×15 mL). The combined extracts were washed with water, dried and evaporated to pale yellow oil. Flash chromatography (99:1 CH_2Cl_2–Me_2CO) of the residue gave pure **23** (1.165 g, 80%) as a colorless syrup: $[\alpha]_D$=+16.8 (*c*, 1.04 in $CHCl_3$); R_f 0.72 (EtOAc), R_f 0.55 (1:1 toluene–EtOAc). ν_{max} (film): 3010–2910, 1610, 1370, 1200, 1120, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, $J_{5,6}$=6.3 Hz, 3×H-6), 2.1 (ddd, 1H, $J_{3a,3b}$=15.0 Hz, $J_{2,3a}$=5.8 Hz, $J_{3a,4}$=2.0 Hz, H-3a) 2.33 (ddd, 1H, $J_{2,3b}$=8.6 Hz, $J_{3b,4}$=6 Hz, H-3b), 2.45 (s, 3H, *Me*$C_6H_4SO_2$), 3.79 (m, 1H, $J_{1,2}$=6.2 Hz, H-2), 3.8–4.02 (m, 5H, 2×CH_2-dioxolane and H-5), 4.84 (d, 1H, H-1), 4.9 (m, 1H, $J_{4,5}$=3.7 Hz, H-4), 7.3–7.83 (m, 4H, Me$C_6H_4SO_2$); ^{13}C NMR ($CDCl_3$): δ 14.47 (C-6), 21.73 (*Me*$C_6H_4SO_2$), 34.92 (C-3), 65.36 (2×CH_2-dioxolane), 78.16 (C-2), 78.39 (C-5), 82.16 (C-4), 104.45 (C-1), 127.81, 129.93, 133.9 and 144.94 (Me$C_6H_4SO_2$).

CI-MS: *m/z* 329 ($M^+ +1$). HR-MS: Calcd for $C_{15}H_{20}O_6S$: 328.0981. Found: *m/z* 328.0995.

2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-L-*ribo*-hexose ethylene acetal (24). A mixture of **23** (1.15 g, 3.5 mmol) and KOBz (2.5 g, 15.65 mmol) in DMF (30 mL) was stirred at 100°C for 24 h. The solvent was removed by high vacuum distillation, the residue was treated with CH_2Cl_2 (2×20 mL), and the combined extracts were filtered and evaporated to yellow oil. Chromatographic purification on a column of flash silica (CH_2Cl_2) afforded pure **24** (0.64 g, 66%) as a colorless syrup: $[\alpha]_D$=+0.5 (*c*, 1.7 in $CHCl_3$); R_f 0.7 (19:1 CH_2Cl_2–Me_2CO), R_f 0.72 (1:1 toluene–EtOAc). ν_{max} (film): 3000, 2950, 2900, 1730, 1610, 1460, 1390, 1290, 1130, 950 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (d, 3H, $J_{5,6}$=6.6 Hz, 3×H-6), 2.15 (ddd, 1H, $J_{3a,3b}$=13.8 Hz, $J_{2,3a}$=6.3 Hz, $J_{3a,4}$=2.4 Hz, H-3a), 2.25 (ddd, 1H, $J_{3b,4}$=5.9 Hz, $J_{2,3b}$=9.4 Hz, H-3b), 3.82–4.07 (m, 4H, 2×CH_2-dioxolane), 4.14–4.29 (m, 2H, $J_{1,2}$=5.5 Hz, $J_{4,5}$=2.7 Hz, H-2 and H-5), 4.93 (d, 1H, H-1), 5.15 (m, 1H, H-4), 7.4–8.06 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 19.78 (C-6), 32.97 (C-3), 65.43 and 65.56 (2×CH_2-dioxolane), 79.07 (C-2), 79.88 (C-4), 81.01 (C-5), 104.73 (C-1), 128.45, 129.65, 129.97 and 133.22 (Ph), 166.14 (C=O). CI-MS: *m/z* 279 ($M^+ +1$). HR-MS: Calcd for $C_{15}H_{18}O_5$: 278.1154. Found: *m/z* 278.1149.

2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-L-*ribo*-hexitol (26). *(Procedure A)* A solution of **24** (0.64 g, 2.3 mmol) in a mixture of trifluoroacetic acid (7 mL) and 6 M HCl (1.75 mL) was kept at +4°C for 24 h. The reaction mixture was evaporated by co-distillation with toluene to unstable oil. Thus obtained crude **25** (0.7 g) was immediately dissolved in MeOH (15 mL) and reduced with $NaBH_4$ (0.2 g, 5.29 mmol) at room temperature for 2 h. The mixture was poured into saturated NaCl solution (15 mL) and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were dried and evaporated to give crude **26**. Flash chromatography (4:1 toluene–EtOAc) of the residue afforded pure **26** (0.328 g, 60%) as a colorless syrup.

Procedure B: to a stirred and ice-cooled solution of alcohol **22** (0.7 g, 4.02 mmol), benzoic acid (0.95 g, 7.79 mmol) and triphenylphosphine (3.0 g, 11.44 mmol) in dry THF (40 mL) was added dropwise a solution of diethyl azodicarboxylate (3.5 mL, 22.22 mmol) in dry THF (15 mL). The mixture was stirred at 0°C for 15 min and then at room temperature for 20 h. The mixture was poured into saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (4×50 mL). The extract was dried and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2), to give **24** (1.5 g) contaminated with a small amount of aromatic impurities. The impure sample **24** was dissolved in a mixture of trifluoroacetic acid (8 mL) and 6 M HCl (2 mL) and the solution was kept at +4°C for 24 h. After workup as described above (procedure A), the remaining crude aldehyde **25** was dissolved in MeOH (15 mL) and treated with $NaBH_4$ (0.25 g, 6.61 mmol) at room temperature for 2 h. After the workup according to procedure A, crude **26** was obtained and purified by column chromatography (50 g; 9:1 toluene–Me_2CO). Pure **26** (0.26 g, 27% from **22**) was obtained as a colorless syrup: $[\alpha]_D$=−7.8 (*c*, 1.09 in $CHCl_3$); R_f 0.27 (4:1 toluene–Me_2CO). ν_{max} (film): 3460 (broad), 2990, 2940, 2890, 1730, 1610, 1290, 1130 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (d, 3H, $J_{5,6}$=6.5 Hz, 3×H-6), 2.04 (ddd, 1H, $J_{3a,3b}$=13.7 Hz, $J_{2,3a}$=5.6 Hz, $J_{3a,4}$=1.9 Hz, H-3a), 2.24 (m, 2H, $J_{2,3b}$=10.2 Hz, $J_{3b,4}$=6.3 Hz, H-3b and OH), 3.59 (ddd, 1H, $J_{1a,1b}$=11.9 Hz, $J_{1a,2}$=4.6 Hz, H-1a), 3.87 (ddd, 1H, $J_{1b,2}$=2.9 Hz, H-1b), 4.22 (dq, 1H, $J_{4,5}$=2.6 Hz, H-5), 4.32 (m, 1H, H-2), 5.14 (dd, 1H, H-4), 7.4–8.08 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 19.80 (C-6), 33.04 (C-3), 63.80 (C-1), 79.06 (C-5), 80.36 (C-2), 80.64 (C-4), 128.37, 129.55, 129.87 and 133.16 (Ph), 166.11 (C=O). CI-MS: *m/z* 237 ($M^+ +1$). HR-MS: Calcd for $C_{13}H_{16}O_4$: 236.1049. Found: *m/z* 236.1041.

2,5-Anhydro-4-*O*-benzoyl-1-iodo-1,3,6-trideoxy-L-*ribo*-hexitol (27). To a solution of **26** (0.29 g, 1.23 mmol) in dry toluene (25 mL) were added successively imidazole (0.198 g, 2.24 mmol), Ph_3P (0.742 g, 2.83 mmol) and iodine (0.568 g, 2.24 mmol). The mixture was refluxed while stirring in an atmosphere of N_2 for 3 h, and then evaporated. Flash column chromatography (toluene) of the residue (1.8 g) yielded pure **27** (0.355 g, 84%) which was crystallized from hexane to give colorless needless: mp 68°C, $[\alpha]_D$=−7.6 (*c*, 0.37 in $CHCl_3$); lit.[7] mp 68°C, $[\alpha]_D$=−11.67 (*c*, 0.93 in $CHCl_3$); R_f 0.88 (4:1 toluene–Me_2CO). ^1H NMR ($CDCl_3$): δ 1.38 (d, 3H, $J_{5,6}$=6.5 Hz, 3×H-6), 2.06 (ddd, 1H, $J_{3a,3b}$=13.8 Hz, $J_{2,3a}$=9.8 Hz, $J_{3a,4}$=6.3 Hz, H-3a), 2.30 (ddd, 1H, $J_{2,3b}$=5.4 Hz, $J_{3b,4}$=1.7 Hz, H-3b), 3.3 (dd, 1H, $J_{1a,b}$=10.2 Hz, $J_{1a,2}$=6.2 Hz, H-1a), 3.37 (dd, 1H, $J_{1b,2}$=4.9 Hz, H-1b), 4.19 (m, 1H, H-2), 4.3 (dq, 1H, $J_{4,5}$=2.5 Hz, H-5), 5.16 (dt, 1H, H-4), 7.42–8.1 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 9.36 (C-1), 20.15 (C-6), 38.62 (C-3), 77.83 (C-2), 80.36 (C-4), 81.46 (C-5), 128.5, 129.68, 129.87 and 133.32 (Ph), 166.11 (C=O). CI-MS: *m/z* 347 ($M^+ +1$).

2,5-Anhydro-1-iodo-1,3,6-trideoxy-L-*ribo*-hexitol (28). To a solution of **27** (0.355 g, 1.02 mmol) in dry THF (5 mL) was added saturated methanolic K_2CO_3 solution (1 mL) and the suspension was stirred at room temperature for 1.5 h. The mixture was poured into saturated NaCl solution (15 mL), acidified with 6 M HCl, and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were washed with brine, dried and evaporated. Column chromatography (50 g; 9:1 toluene–Me_2CO) of the residue (0.31 g) gave pure **28** (0.205 g, 83%) as a colorless syrup: $[\alpha]_D$=−33.3 (*c*, 0.88 in $CHCl_3$); lit.[7] $[\alpha]_D$=−30.7 (*c*, 0.87 in $CHCl_3$); R_f 0.38 (4:1 toluene–Me_2CO). ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, $J_{5,6}$=6.4 Hz, 3×H-6), 1.87 (ddd, 1H, $J_{3a,3b}$=13.3 Hz, $J_{2,3a}$=8.7 Hz, $J_{3a,4}$=6.1 Hz, H-3a), 2.03 (ddd, 1H, $J_{2,3b}$=2.9 Hz, $J_{3b,4}$=6.2 Hz, H-3b), 3.04 (bs, 1H, exchangeable with D_2O, OH), 3.21 (dd, 1H, $J_{1a,1b}$=10.2 Hz, $J_{1a,2}$=6.1 Hz, H-1a), 3.28 (dd, 1H, $J_{1b,2}$=4.8 Hz, H-1b), 3.95 (dq, 1H, $J_{4,5}$=3.3 Hz, H-5), 4.02 (dt, 1H, H-4), 4.11 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$): δ 10.63 (C-1), 19.95 (C-6), 40.87 (C-3), 77.22 (C-2 and C-4), 83.31 (C-5). CI-MS: *m/z* 243 ($M^+ +1$).

(+)-Muscarine iodide (1). A sealed tube containing **28** (0.19 g, 0.78 mmol) and ethanolic 40% Me_3N (8 mL) was heated at 80°C for 3 h. The volatiles were evaporated and the syrupy residue partitioned between distilled water (4 mL) and EtOAc (3 mL). After removal of the aqueous

phase, the organic layer was washed with water (2 mL). The combined aqueous solutions were evaporated by co-distillation with toluene, to yield pure alkaloid **1** (0.22 g, 93%) as a pale yellow solid. (For ^{1}H and ^{13}C NMR spectral data see Table 1). Recrystallization from 2-propanol afforded needles: mp 147–149°C, $[\alpha]_D$=+7.6 (*c*, 0.4 in EtOH); lit.[7] mp 149°C, $[\alpha]_D$=+6.36 (*c*, 0.35 in EtOH).

2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-L-*xylo*-hexose ethylene acetal (29). To a solution of **22** (0.162 g, 0.93) in dry pyridine (4 mL) was added benzoyl chloride (0.5 mL, 4.3 mmol). The mixture was kept at room temperature for 24 h, then acidified with 6 M HCl (12 mL) and extracted with CH_2Cl_2 (4×8 mL). The extracts were combined, washed successively with water and saturated $NaHCO_3$ solution, dried, and concentrated to an oil. Column chromatography on silica gel (40 g; 7:1 toluene–Me_2CO) afforded pure **29** (0.222 g, 86%) as a colorless syrup: $[\alpha]_D$=−6.7 (*c*, 0.86 in $CHCl_3$); R_f 0.51 (4:1 toluene–Me_2CO). ν_{max} (film): 3000–2900, 1720, 1600, 1270, 1120, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 3H, $J_{5,6}$=6.4 Hz, 3×H-6), 2.14 (ddd, 1H, $J_{3a,3b}$=14.6 Hz, $J_{3a,4}$=1.8 Hz, $J_{2,3a}$=5.5 Hz, H-3a), 2.56 (ddd, 1H, $J_{2,3b}$=8.2 Hz, $J_{3b,4}$=6.4 Hz, H-3b), 3.84–4.06 (m, 5H, 2×CH_2-dioxolane and H-2), 4.12 (m, 1H, $J_{4,5}$ 3.7H-5), 4.98 (d, 1H, $J_{1,2}$=5.8 Hz, H-1), 5.48 (m, 1H, H-4), 7.4–8.14 (Ph); ^{13}C NMR ($CDCl_3$): δ 14.47 (C-6), 34.91 (C-3), 65.37 and 65.39 (2×CH_2-dioxolane), 75.54 (C-4), 78.60 (C-2), 78.59 (C-5), 104.95 (C-1), 128.48, 129.69, 130.07 and 133.18 (Ph), 166.0 (C=O). CI-MS: *m*/*z* 557 ($2M^+$+1), 279 (M^++1). HR-MS: Calcd for $C_{15}H_{18}O_5$: 278.1154. Found: *m*/*z* 278.1151.

2,5-Anhydro-4-*O*-benzoyl-3,6-dideoxy-L-*xylo*-hexitol (31). *(Procedure A)* A solution of **29** (0.193 g, 0.69 mmol) in trifluoroacetic acid (2 mL) and 6 M HCl (0.5 mL) was stored at +4°C for 24 h. The mixture was evaporated by co-distillation with toluene, and the remaining crude aldehyde **30** (0.2 g) was reduced with $NaBH_4$ (0.06 g, 1.59 mmol) in MeOH (5 mL) following the procedure for preparation of **26**. Column chromatography (20 g; 4:1 toluene–Me_2CO) afforded pure **31** (0.097 g, 59%) as colorless syrup.

Procedure B: treatment of **22** (0.54 g, 3.1 mmol) with benzoyl chloride (1.5 mL, 12.91 mmol) in dry pyridine (6 mL) under the same reaction conditions as described above (preparation of **29**) afforded crude **29** (1.6 g). Hydrolysis of the crude **29** with a mixture of trifluoroacetic acid (8 mL) and 6 M HCl (1 mL) at +4°C for 24 h gave the unstable aldehyde **30**, which was subsequently reduced with $NaBH_4$ (0.5 g, 13.22 mmol) in MeOH (15 mL). After workup as described in the procedure for preparation of **26**, followed by flash column chromatography (4:1 toluene–Me_2CO), pure **31** (0.385 g, 53%) was obtained as a colorless syrup: $[\alpha]_D$=+25.2 (*c*, 0.92 in $CHCl_3$); R_f 0.16 (4:1 toluene–Me_2CO). ν_{max} (film): 3450 (broad), 3000, 2960, 2890, 1740, 1610, 1460, 1300, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 3H, $J_{5,6}$=6.7 Hz, 3×H-6), 1.98 (ddd, 1H, $J_{3a,3b}$=14.6 Hz, $J_{2,3a}$=6.1 Hz, $J_{3a,4}$=1.8 Hz, H-3a), 2.17 (bs, 1H, exchangeable with D_2O, OH), 2.52 (ddd, 1H, $J_{2,3b}$=8.5 Hz, $J_{3b,4}$=6.5 Hz, H-3b), 3.65 (dd, 1H, $J_{1a,1b}$ 11.3 $J_{1a,2}$=5.6 Hz, H-1a), 3.8 (dd, 1H, $J_{1b,2}$=2.8 Hz, H-1b), 4.09 (m, 1H, $J_{4,5}$=3.9 Hz, H-5), 4.15 (m, 1H, H-2), 5.49 (m, 1H, H-4), 7.4–8.09 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 14.48 (C-6), 35.08 (C-3), 64.94 (C-1), 75.92 (C-4), 78.01 (C-2), 78.24 (C-5), 128.53, 129.62, 130.01, and 133.24 (Ph), 165.98 (C=O). CI-MS: *m*/*z* 237 (M^++1). HR-MS: Calcd for $C_{13}H_{16}O_4$: 236.1049. Found: *m*/*z* 236.1045.

2,5-Anhydro-4-*O*-benzoyl-1-iodo-1,3,6-trideoxy-L-*xylo*-hexitol (32). Treatment of **31** (0.359 g, 1.52 mmol) with imidazole (0.237 g, 3.48 mmol), Ph_3P (0.888 g, 3.38 mmol) and iodine (0.68 g, 2.68 mmol) in dry toluene (25 mL), according to the procedure described above for **27**, yielded crude **32**. Column chromatography on silica gel (150 g; 49:1 toluene–Me_2CO) afforded pure **32** (0.475 g, 90%) as a colorless syrup: $[\alpha]_D$=+31.2 (*c*, 0.96 in $CHCl_3$); R_f 0.74 (4:1 toluene–Me_2CO). ν_{max} (film): 3000, 2950, 2870, 1730, 1610, 1290, 1120, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 3H, $J_{5,6}$=6.1 Hz, 3×H-6), 2.02 (ddd, 1H, $J_{3a,3b}$=14.6 Hz, $J_{2,3a}$=5.8 Hz, $J_{3a,4}$=1.8 Hz, H-3a), 2.64 (ddd, 1H, $J_{2,3b}$=8.2 Hz, $J_{3b,4}$=6.4 Hz, H-3b), 3.31 (dd, 1H, $J_{1a,1b}$ 9.8 $J_{1a,2}$=7.2 Hz, H-1a), 3.39 (dd, 1H, $J_{1b,2}$=5.4 Hz, H-1b), 4.08–4.22 (m, 2H, $J_{4,5}$=4.0 Hz, H-2 and H-5), 5.51 (ddd, 1H, H-4), 7.42–8.11 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 9.18 (C-1), 14.75 (C-6), 39.34 (C-3), 75.68 (C-4), 77.51 (C-2), 78.92 (C-5), 128.5, 129.61, 129.89 and 133.22 (Ph), 165.87 (C=O). CI-MS: *m*/*z* 347 (M^++1). HR-MS: Calcd for $C_{13}H_{15}IO_3$: 346.0066. Found: *m*/*z* 346.0072.

2,5-Anhydro-1-iodo-1,3,6-trideoxy-L-*xylo*-hexitol (33). A solution of **32** (0.44 g, 1.27 mmol) in dry THF (5 mL) was treated with saturated methanolic K_2CO_3 solution (1 mL), as described above (procedure for **28**), to afford crude **33**. Flash chromatography (9:1 toluene–Me_2CO) yielded pure **33** (0.201 g, 65%) as an oil. Crystallization from hexane gave colorless needless: mp 63.5°C, $[\alpha]_D$=−1.5 (*c*, 1.13 in $CHCl_3$); lit.[8] mp 62°C, $[\alpha]_D$=−0.34 (*c*, 0.16 in $CHCl_3$); R_f 0.4 (4:1 toluene–Me_2CO). ^{1}H NMR ($CDCl_3$): δ 1.28 (d, 3H, $J_{5,6}$=6.4 Hz, 3×H-6), 1.77 (ddd, 1H, $J_{3a,3b}$ 14.3 $J_{2,3a}$=5.2 Hz, $J_{3a,4}$=1.3 Hz, H-3a), 1.97 (bs, 1H, exchangeable with D_2O, OH), 2.4 (ddd, 1H, $J_{2,3b}$=8.4 Hz, $J_{3b,4}$=6.0 Hz, H-3b), 3.31 (dd, 1H, $J_{1a,1b}$ 10.0 $J_{1a,2}$=4.7 Hz, H-1a), 3.4 (dd, 1H, $J_{1b,2}$=6.3 Hz, H-1b), 3.86 (m, 1H, $J_{4,5}$=3.4 Hz, H-5), 3.94 (m, 1H, H-2), 4.17 (bs, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 11.69 (C-1), 14.07 (C-6), 41.34 (C-3), 73.27 (C-4), 76.69 (C-2), 79.82 (C-5), CI-MS: *m*/*z* 243 (M^++1).

(+)-*epi*-Muscarine iodide (2). Iodo alcohol **33** (0.16 g, 0.66 mmol) was treated with a 40% ethanolic solution of Me_3N (15 mL) according to the same procedure as described for **1**. The usual workup gave pure alkaloid **2** (0.19 g, 95%) as a yellow syrup. (For ^{1}H and ^{13}C spectral data see Table 1). Crystallization from 2-propanol gave pale yellow needles: mp 172–173°C, $[\alpha]_D$=+31.7 (*c*, 0.4 in H_2O); lit.[8] mp 175°C, $[\alpha]_D$=+32 (*c*, 0.55 in H_2O).

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