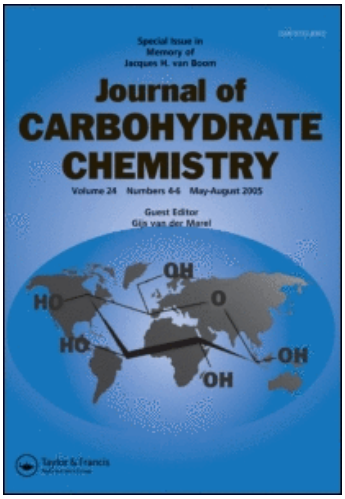

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SYNTHESIS OF METHYL (METHYL D- AND L-IDOPYRANOSID)URONATES FROM myo-INOSITOL

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ABSTRACT

Methyl (methyl α-D- (**9a**), α-L- (**9b**), β-D- (**10a**), and β-L- (**10b**) idopyranosid)uronates were synthesized from myo-inositol. Baeyer-Villiger oxidation of the optically resolved inosose derivatives (**3a** and **3b**) proceeded regioselectively to afford **4a** and **4b** in high yields, respectively. Ring-opening of the 7-membered hemiacetal-lactones (**4a** and **4b**) with acid and subsequent deprotection gave the title compounds.

INTRODUCTION

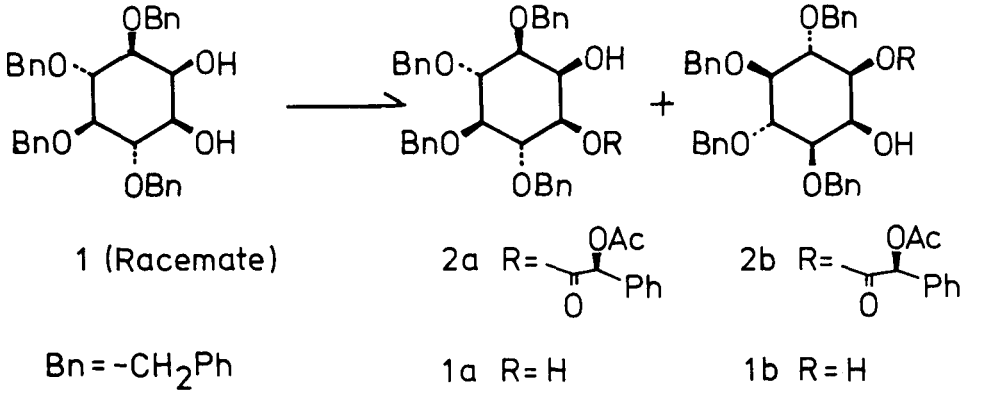
myo-Inositol is one of the most abundant inositols[1] and is considered to play significant rolls in biological systems, for example, cellular second messenger.[2] Although readily available myo-inositol has been frequently used as the starting material for syntheses of cyclitol[3] and aminocyclitol derivatives,[4] only a few reports have appeared so far concerning the synthesis of other natural products from myo-inositol.[5] Our initial interest in utilizing myo-inositol as a useful starting material for synthesis of unaccessible natural products led us to develop a selective total synthesis of hexoses: L-Idopyranosiduronic acid known as a component of heparin and other biologically important mucopolysaccharides.[6] We wish to report herein the synthesis of D- and L-idopyranosiduronic acid derivatives (**9a**, **9b**, **10a**, and **10b**) via the 7-membered hemiacetal-lactones (**4a** and **4b**) which were obtained by

regioselective Baeyer-Villiger oxidation of optically active inososes (**3a** and **3b**). The structures of **9a** and **9b** were further confirmed by conversion to known methyl 2,3,4,6-tetra-O-acetyl-α-D-idopyranoside (**12a**) and its enantiomer (**12b**), respectively.

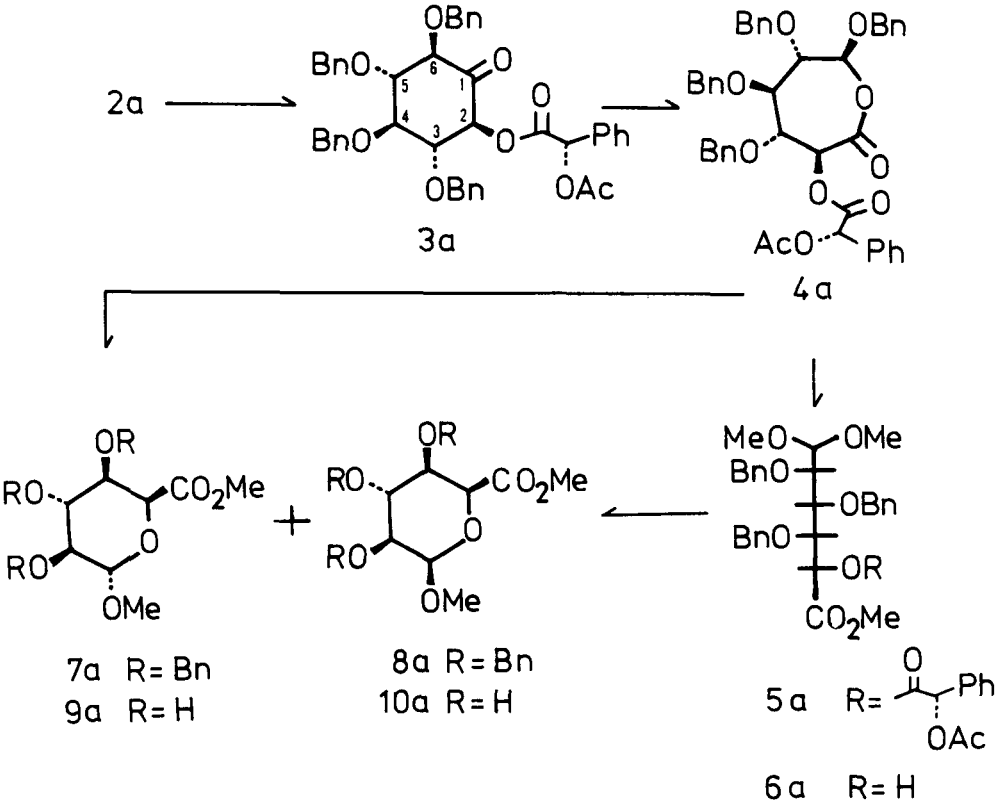
RESULTS AND DISCUSSION

In 1968, Nakajima and co-workers found that Baeyer-Villiger oxidation of some inosose derivatives proceeded quite regioselectively, and they successfully carried out a synthesis of DL-allose and DL-ribose derivatives from myo-inositol using Baeyer-Villiger oxidation as the key reaction.[5] On Baeyer-Villiger oxidation, it is known that the more electron-rich bond migrates to oxygen atom if there is no special steric factor.[7] We therefore anticipated that Baeyer-Villiger oxidation of an inosose derivative possessing an acyloxy and an alkoxy groups at C-2 and C-6, respectively, would proceed regioselectively, and expected that the C-C bond attached to an alkoxy group (ether-type protecting group), which is considered to be more electron-rich than that of an acyloxy group (ester-type protecting group), would migrate to the oxygen atom exclusively. For this purpose, racemic 1,4,5,6-tetra-O-benzyl-myo-inositol (**1**),[8] easily accessible from myo-inositol, was employed as the starting material. L-(+)-O-Acetylmandelic acid was chosen as an ester-type protecting group[9] to control the direction of the Baeyer-Villiger oxidation, and also to get optically active substances.

Reaction of (**1**) with L-(+)-O-acetylmandelic acid[10] in the presence of DCC and a catalytic amount of 4-dimethylaminopyridine afforded the ester (**2a**) and (**2b**) in 32 and 35% yields, respectively. These two diastereoisomers were cleanly separated by chromatography on silica gel and their structures were unambiguously confirmed from their 400 MHz ^1H NMR spectra. The signals of H-1 attributable to **2a** and **2b** were observed at δ 4.81 and 4.83 as doublet of doublets (J=2.7 and 9.7 Hz for **2a**, and 2.4 and 9.5 Hz for **2b**), respectively, indicating that the equatorial hydroxy group was esterified. Base catalyzed deacylation of **2a** and **2b** gave optically active **1a** {$[\alpha]_D^{25}$ - 18.5° (c 1.3, $CHCl_3$)} and **1b** {$[\alpha]_D^{20}$ + 19.5° (c 0.96, $CHCl_3$)}, respectively. Judging from the optical rotation, compound **1a** and **1b** were assumed to possess the 1L- and 1D-configuration, respectively {reported value for 1D-1,4,5,6-tetra-O-



SCHEME 1



SCHEME 2

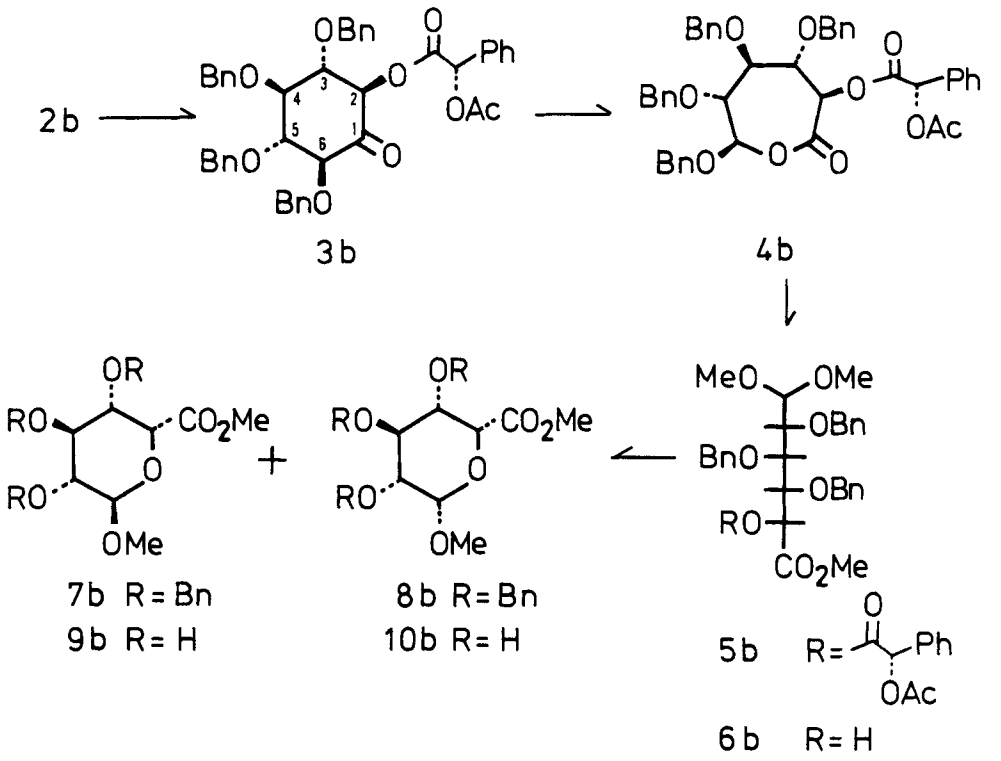
benzyl-myo-inositol; $[\alpha]_D^{20}$ +18.8° (c 0.99, $CHCl_3$)[11] and +25.0° (c 0.18, $CHCl_3$)[12]} (Scheme 1).

Compound **2a** was oxidized with Jones reagent to give the 1-inosose derivative (**3a**). Baeyer-Villiger oxidation of **3a** with 1.2 equivalent of m-chloroperbenzoic acid (mCPBA) in the presence of potassium hydrogen carbonate proceeded regiospecifically and, as anticipated, the hemiacetal-lactone (**4a**) was obtained quanititatively. The ^1H NMR spectrum of **4a** showed two doublets at δ 5.70 (J=5 Hz) and 5.84 (J=8 Hz), attributable to H-2 and H-6, which strongly suggested that the C-C bond bearing a benzyloxy group migrated to oxygen atom. The isomeric product was not found in the reaction mixture. The 7-membered hemiacetal-lactone (**4a**) was then treated with methanol and trimethyl orthoformate in the presence of a catalytic amount of p-TsOH to afford the dimethyl acetal (**5a**) in 66% yield. Removal of the acetylmandelyl group was effected by methanolic sodium methoxide and subsequent acid treatment gave methyl (methyl α-D-2,3,4-tri-O-benzyl-idopyranosid)uronate (**7a**) and its β-anomer (**8a**) in 62 and 38% yields, respectively, based on **5a**. Alternatively, treatment of **4a** with 3% methanolic hydrogen chloride gave **7a** directly in 61% yield, traces of the β-anomer (**8a**) could be detected on TLC, but not isolated.

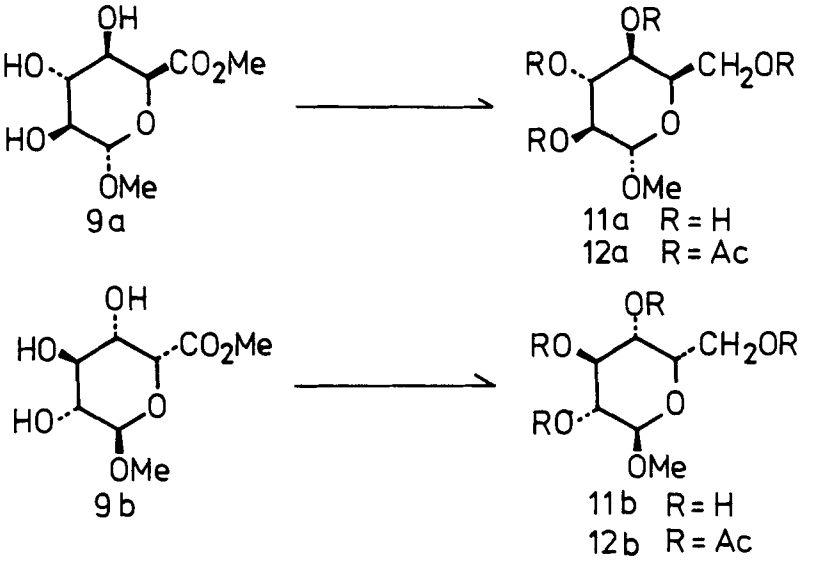
Compound **7a** was then O-debenzylated by hydrogenolysis ($Pd(OH)_2$, atmospheric H_2) to give methyl (methyl α-D-idopyranosid)uronate (**9a**) in a quantitative yield. From **8a**, the β-D-isomer (**10a**) was obtained quantitatively (Scheme 2).

Similar treatment of compound **4b**, which was obtained from **2b** by Jones oxidation, followed by regiospecific Baeyer-Villiger oxidation, afforded methyl (methyl α-L-idopyranosid)uronate (**9b**) and its β-L-anomer (**10b**) (Scheme 3).

Some physical properties of compounds **9a**, **9b**, **10a**, and **10b** are listed in Table 1. The patterns of the ^1H NMR spectra of compounds **9** and **10** were quite similar to those of methyl α- and β-D-idopyranosid-uronic acids reported by Perlin et al.[13] The small coupling constants (< 4.4 Hz) observed in compounds **9** and **10** suggested that both α- and β-anomers mainly adopt a conformation with equatorially orientated methoxycarbonyl group (C1 form for the D-sugar and 1C form for the L-sugar). The presence of long-range couplings (< 1 Hz) between H-2 and



SCHEME 3



SCHEME 4

TABLE 1. Physical and Spectral Data for Compounds 9a, 9b, 10a, and 10b.

	9a	9b	10a	10b
mp	syrup	syrup	168-170°	170-172°
$[\alpha]_D$[a]	+61° (c 1.5)	-59° (c 1.4)	-86° (c 1.1)	+90° (c 0.5)
^{1}H NMR[b,c]	δ 4.78 bd H-1 $J_{1,2}$ 2.9		δ 4.68 d H-1 $J_{1,2}$ 1.0	
	4.67 d H-5 $J_{2,3}$ 4.4		4.55 d H-5 $J_{2,3}$ 3.4	
	3.87 bdd H-4 $J_{3,4}$ 4.4		4.00 t H-3 $J_{3,4}$ 3.4	
	3.81 t H-3 $J_{4,5}$ 3.2		3.80 ddd H-4 $J_{4,5}$ 1.5	
	3.50 ddd H-2 $J_{2,4}$ 0.9		3.60 dt H-2 $J_{2,4}$ 1.0	
	3.41 s OMe $J_{1,3}$<0.9		3.56 s OMe	
	3.78 s CO_2Me		3.78 s CO_2Me	
^{13}C NMR[b]	δ 172.2, 103.8, 71.5, 71.2, 70.6, 69.9, 56.3, 52.5.		δ 171.8, 101.6, 75.2, 71.6, 71.2, 70.7, 57.4, 52.6.	

a. Measuared in MeOH at 22°C.
b. Measuared in MeOH-d_4 solution. Chemical shifts are relative to Me_4Si (0 ppm).
c. Coupling constants (J) are expressed in Hz.

H-4 observed both in compounds **9** and **10**, and between H-1 and H-3 in compound **9**, are ascribed to a "W" arrangement of bonds, also supporting this consideration.[13]

For further confirmation of the structures of **9a** and **9b**, the methoxycarbonyl group of each was reduced with sodium borohydride in methanol-water. The reduction proceeded smoothly to give syrupy methyl α-**D**- (**11a**) and α-**L**-idopyranoside (**11b**), respectively. Acetylation of these compounds in the usual way gave crystalline methyl 2,3,4,6-tetra-O-acetyl-α-**D**-idopyranoside (**12a**), mp 104 °C, $[\alpha]_D^{25}$ +43° (c 1.4, $CHCl_3$); lit.[14] mp 107-108 °C, $[\alpha]_D$ +55°, and the enantiomer (**12b**), mp 104 °C, $[\alpha]_D^{25}$ -45° (c 0.82, $CHCl_3$); lit.[15] mp 107-108 °C, $[\alpha]_D$ -53° (Scheme 4).

These results showed that **D**- and **L**-idose derivatives were prepared in optically active forms from myo-inositol.

The synthesis of other natural products utilizing inositol derivatives is under investigation in our laboratory.

EXPERIMENTAL

General Procedures. Melting points were determined in capillary tubes and are uncorrected. Specific rotations were measured in a 0.1 dm tube with a JEOL DIP-4 polarimeter. Column chromatography was performed with Wakogel C-300 (Wako Pure Chemicals, Osaka, Japan), and TLC was carried out on glass plates coated with Wakogel B-5F with detection by UV light or/and by charring with 10% sulfuric acid. Unless otherwise noted, ^{1}H NMR spectra were recorded for solution in $CDCl_3$ (internal tetramethylsilane) with a Varian EM-390 spectrometer. Spectra at 400 MHz and ^{13}C NMR spectra were recorded with a JEOL JNM-GX 400 FT Spectrometer. Mass spectra were taken on a Hitachi M-80 mass spectrometer. IR spectra were recorded with a Hitachi Model-225 or a Jasco Model A-202 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <45°C under diminished pressure.

1D- (2a) and 1L-1-O-(L-(+)-O-Acetylmandelyl)-3,4,5,6-tetra-O-benzyl-myo-inositol (2b). To a solution of **DL**-1,4,5,6-tetra-O-benzyl-myo-inositol[8] (1, 3.01 g, 5.57 mmol), **L**-(+)-O-acetylmandelic acid[9] (1.10 g, 5.66 mmol) and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in dichloromethane (10 mL) was added a solution of 1,3-dicyclohexylcarbodiimide (DCC, 1.25 g, 6.06 mmol) in dichloromethane (2 mL) at -10°C dropwise over 80 min. After stirring at -10°C for 30 min, the reaction mixture was filtered through a short column of silica gel. The filtrate was successively washed with 1M HCl, saturated aqueous sodium hydrogen carbonate, water and brine, and dried. Evaporation of the solvent left a solid, which was chromatographed on a column of silica gel (90 g) with 1:15 ethyl acetate-toluene to give, first, 1.25 g (32%) of compound **2a** (Rf=0.63, 1:3 ethyl acetate-toluene): mp 96-97.5 °C (from ethanol); $[\alpha]_D^{28}$ -154° (c 0.71, chloroform); IR (KBr) 3530 (OH) and 1745 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (b, 1H, OH), 2.21 (s, 3H, AcO), 3.47 (dd, 1H, $J_{2,3}$ = 2.9 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.50 (t, 1H, $J_{4,5}$ = $J_{5,6}$ = 9.5 Hz, H-5), 3.93 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 4.07 (t, 1H, $J_{1,6}$ = $J_{5,6}$ = 9.7 Hz, H-6), 4.16 (bddd, 1H, $J_{1,2}$ = 2.7 Hz, $J_{2,3}$ = 2.9 Hz, $J_{2,OH}$ < 1.5 Hz, H-2), 4.65 (s, 2H, benzyl), 4.72 (d, 1H, J = 11.0 Hz, benzyl), 4.77 (d, 1H, J = 11.0 Hz, benzyl), 4.81 (dd, 1H, $J_{1,2}$ = 2.7 Hz, $J_{1,6}$ = 9.5 Hz, H-1), 4.81 (d, 1H, J = 10.5 Hz, benzyl), 4.83

(s, 2H, benzyl), 4.87 (d, 1H, J = 10.5 Hz, benzyl), 5.95 (s, 1H, PhCH(OAc)), and 7.20-7.45 (m, 25H, phenyl).

Anal. Calcd for $C_{44}H_{44}O_9$: C, 73.73; H, 6.19. Found: C, 73.75; H, 6.24.

Further elution gave 1.39g (35%) of compound **2b** (Rf= 0.53, 1:3 ethyl acetate-toluene) as an amorphous solid: mp 140-144 °C, $[\alpha]_D^{28}$ +24° (c 0.49, chloroform); IR (KBr) 3500 (OH) and 1745 cm^{-1} (ester); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H, AcO), 2.64 (b, 1H, OH), 3.45 (t, 1H, $J_{4,5} = J_{5,6}$ = 9.5 Hz, H-5), 3.52 (dd, 1H, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.95 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 4.03 (t, 1H, $J_{1,6} = J_{5,6}$ = 9.5 Hz, H-6), 4.12 (d, 1H, J = 10.8 Hz, benzyl), 4.41 (q, 1H, $J_{1,2} = J_{2,3} = J_{2,OH}$ = 2.4 Hz, H-2), 4.47 (d, 1H, J = 10.8 Hz, benzyl), 4.67 (d, 1H, J = 11.2 Hz, benzyl), 4.69 (d, 1H, J = 10.7 Hz, benzyl), 4.72 (d, 1H, J = 11.2 Hz, benzyl), 4.77 (d, 1H, J = 10.7 Hz, benzyl), 4.82 (d, 1H, J = 10.7 Hz, benzyl), 4.83 (dd, 1H, $J_{1,6}$ = 9.5 Hz, $J_{1,2}$ = 2.4 Hz, H-1), 4.88 (d, 1H, J = 10.7 Hz, benzyl), 5.97 (s, 1H, PhCH(OAc)), and 6.81-7.48 (m, 25 H, phenyl).

Anal. Found: C, 73.62; H, 6.24.

Deacylation of compound 2a and 2b. To a stirred solution of **2a** (176 mg, 0.25 mmol) in methanol (1.5 mL) was added 1M sodium methoxide in methanol (0.25 mL, 0.25 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was neutralized with Amberlite IR 120B resin (H^+ form). The resin was removed by filtration and washed with methanol. Evaporation of the solvent gave a solid, which was purified by preparative TLC (1:3 ethyl acetate-toluene) to give 105 mg (79 %) of 1L-1,4,5,6-tetra-O-benzyl-myo-inositol (**1a**): mp 144-145 °C (from methanol), $[\alpha]_D^{25}$ - 18.5° (c 0.84, chloroform). (lit.[12] mp 141-143 °C, $[\alpha]_D^{20}$ -24.3° (c 1.3, chloroform)).

Similar treatment of **2b** (50 mg, 0.07 mmol) with 1M sodium methoxide in methanol (0.07 mL, 0.07 mmol) afforded 37 mg (99%) of 1D-isomer (**1b**): mp 146-146.5 °C (from methanol), $[\alpha]_D^{25}$ + 19.5° (c 0.96, chloroform). (lit.[12] mp 140.2-142.1 °C, $[\alpha]_D^{20}$ +25.0° (c 0.18, chloroform), + 18.8° (c 0.99, chloroform)[11]).

2L-(2,4,6/3,5)-2-O-(L-(+)-O-Acetylmandelyl)-3,4,5,6-tetra-O-benzyl-pentahydroxycyclohexanone (3a). To a stirred solution of **2a** (1.15 g, 1.60 mmol) in acetone (11 mL) at 0 °C was added Jones reagent (2.67

mol/l solution of CrO_3 in aqueous sulfuric acid; 1.8 mL, 4.8 mmol). The reaction mixture was stirred overnight at 5 °C. After addition of 2-propanol, the mixture was concentrated and the resultant residue was extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogen carbonate, water and brine, and dried. Evaporation of the solvent afforded the residue, which was purified on a column of silica gel (45 g) with 1:30 ethyl acetate-toluene to give 874 mg (76%) of compound **3a**: mp 134.5-136.5 °C (from ethanol), $[\alpha]_D^{29}$ +29° (c 1.1, chloroform); IR (neat) 1745 (ester) and 1720 cm^{-1} (shoulder, ketone); ^1H NMR δ 2.18 (s, 3H, AcO), 3.4-4.1 (m, 3H, H-3,4,5), 4.2-5.0 (m, 9H, 4 benzyl and H-2), 5.33 (d, 1H, $J_{2,3}$ = 10.5 Hz, H-2), 6.07 (s, 1H, PhCHOAc), and 7.2-7.6 (m, 25 H, phenyl).

Anal. Calcd for $C_{44}H_{42}O_9$: C, 73.93; H, 5.92. Found: C, 73.50; H, 5.88.

(2S,3R,4R,5S,6S)-2-(L-(+)-O-Acetylmandelyloxy)-3,4,5,6-tetrakis-(benzyloxy)-7-heptanolide (4a). A mixture of **3a** (660 mg, 0.923 mmol), potassium hydrogen carbonate (111 mg, 1.11 mmol) and m-chloroperbenzoic acid (191 mg, 1.11 mmol) in 1,2-dichloroethane (4 mL) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with dichloromethane and washed with 10% aqueous sodium bisulfite solution, saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation of the solvent gave 692 mg (100%) of compound **4a** as a colorless syrup. This compound showed one spot on TLC and was used in subsequent steps without further purification: $[\alpha]_D^{26}$ +61° (c 1.4, chloroform); IR (neat) 1750 cm^{-1} (ester and lactone); ^1H NMR δ 2.20 (s, 3H, AcO), 3.6-4.1 (m, 3H, H-3,4,5), 4.28-5.00 (m, 8H, 4 benzyl), 5.48 (d, 1H, $J_{5,6}$ = 5 Hz, H-6), 5.63 (d, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 6.00 (s, 1H, PhCH(OAc), and 7.0-7.6 (m, 25H, phenyl); mass spectrum (EI mode) m/z 731 (M+H) and 623 (M-$PhCH_2O$).

Methyl [5-O-(L-(+)-O-Acetylmandelyl)-2,3,4-tri-O-benzyl-D-idose dimethyl acetal]uronate (5a). A solution of **4a** (586 mg, 0.80 mmol) and p-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) in trimethyl orthoformate (6 mL) and methanol (6 mL) was heated at 90 °C for 50 min. The mixture was concentrated to give a residue, which was then dissolved in dichloromethane and treated with excess diazomethane at 0 °C. Evaporation of the solvent and subsequent purification on a column of

silica gel (20 g) with 1:15 ethyl acetate-toluene gave 372 mg (66%) of compound (**5a**) as a colorless syrup: $[\alpha]_D^{28}$ +34° (c 1.9, chloroform); IR (neat) 1740 and 1750 cm^{-1} (ester); ^1H NMR δ 2.17 (s, 3H, AcO), 3.26 (s, 3H, MeO), 3.35 (s, 3H, MeO), 3.40 (s, 3H, MeO), 3.3-4.0 (m, 3H, H-2,3,4), 4.3-5.0 (m, 9H, 4 benzyl and H-1), 5.10 (d, 1H, $J_{4,5}$ = 2.5 Hz, H-5), 6.03 (s, 1H, PhCH(OAc)), and 7.0-7.7 (m, 20H, phenyl).

Anal. Calcd for $C_{40}H_{44}O_{11}$: C, 68.56; H, 6.33. Found: C, 68.68; H, 6.33.

Methyl (2,3,4-tri-O-Benzyl-D-idose dimethyl acetal)uronate (6a). To a stirred solution of **5a** (336 mg, 0.48 mmol) in methanol (5 mL) at 0 °C was added 1M sodium methoxide in methanol (0.48 mL, 0.48 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with Amberlite IR 120B resin (H^+ form), and the resin was removed by filtration. The filtrate was concentrated to give a syrup, which was chromatographed on a column of silica gel (10 g) with 1:15 ethyl acetate-toluene to afford 186 mg (76%) of compound **6a** as a colorless syrup: $[\alpha]_D^{26}$ +26.2° (c 1.3, chloroform); IR (neat) 3470 (OH) and 1740 (ester) cm^{-1}; ^1H NMR δ 2.99 (d, 1H, $J_{5,OH}$ = 7.5 Hz, OH), 3.28 (s, 3H, MeO), 3.50 (s, 3H, MeO), 3.60 (s, 3H, MeO), 3.5-4.2 (m, 4H, H-2,3,4,5), 4.34-5.00 (m, 7H, 3 benzyl and H-1), and 7.1-7.5 (m, 15H, phenyl). High resolution mass spectrum, calcd for $C_{30}H_{34}O_7$: m/z 506.2305, found: M-H_2O, 506.2298; calcd for $C_{29}H_{33}O_7$: m/z 493.2226, found: M-OMe, 493.2200.

Methyl (Methyl-2,3,4-tri-O-benzyl-α-D-idopyranosid)uronate (7a) and Its β-Anomer (8a). A mixture of **6a** (159 mg, 0.3 mmol) and p-toluenesulfonic acid monohydrate (29 mg, 0.15 mmol) in trimethyl orthoformate (3 mL) and methanol (3 mL) was heated at 60-70 °C for 3 h. The reaction mixture was concentrated to give a residue, which was dissolved in ethyl acetate and washed succsessively with saturated aqueous sodium hydrogen carbonate, water and brine, and dried. Evaporation of the solvent left an oil, which was chromatographed on a column of silica gel (5 g) with 1:15 ethyl acetate-toluene. The first fraction, Rf=0.68 (2:1:10 chloroform-ethanol-toluene), gave 93 mg (62%) of compound **7a** as a colorless syrup: $[\alpha]_D^{27}$ +27° (c 1.1, chloroform); IR (neat) 1735 cm^{-1} (ester) ; ^1H NMR δ 3.42 (m, 1H, H-2), 3.46 (s, 3H, MeO), 3.71 (s, 3H, MeO), 3.74-3.94 (m, 2H, H-3,4), 4.37-4.77 (m, 7H, 3 benzyl and H-5), 4.98 (d, $J_{1,2}$ = 4.4 Hz, H-1), and 7.1-7.5 (m, 15H, phenyl).

Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.99; H, 6.54.

The second fraction, Rf=0.51 (2:1:10 chloroform-ethanol-toluene), gave 58 mg (38%) of compound **8a** as a colorless syrup: $[\alpha]_D^{24}$ -50° (c 1.3, chloroform); IR (neat) 1735 cm^{-1} (ester) ; ^1H NMR δ 3.4-4.2 (m, 3H, H-2,3,4), 3.48 (s, 3H, MeO), 3.68 (s, 3H, MeO_2C), 4.27 (d, 1H, $J_{4,5}$ = 4 Hz, H-5), 4.34-4.82 (m, 7H, 3 benzyl and H-1), and 7.0-7.4 (m, 15H, phenyl). High resolution mass spectrum, calcd for $C_{29}H_{33}O_7$: m/z 493.2222, found: M+H, 493.2226.

Treatment of Compound 4a with Methanolic Hydrogen Chloride. Compound **4a** (99 mg, 0.14 mmol) was dissolved in 3% methanolic hydrogen chloride (7 mL), and the mixture was heated under reflux for 2 h. The reaction mixture was neutralized with sodium hydrogen carbonate at 0 °C, and carefully concentrated to give a residue. This residue was dissolved in ethyl acetate and the organic layer was washed with water and brine, and dried. Evaporation of the solvent afforded a syrup, which was purified on preparative TLC (1:3 ethyl acetate-toluene) to give 44 mg (61%) of compound **7a**. The ^1H NMR spectrum of this compound was identical with that of compound **7a** prepared *via* another route (*vide supra*).

Methyl (Methyl-α-D-idopyranosid)uronate (9a). Compound **7a** (91 mg, 0.18 mmol) in ethanol (1.5 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (20 mg) under an atmospheric pressure of H_2 at room temperature for 3 h. The catalyst was removed by filtration through a short column of celite and the filtrate was concentrated to give 41 mg (100%) of analytically pure **9a** as a colorless syrup: $[\alpha]_D^{22}$ +61° (c 1.5, methanol); IR (neat) 3350 (OH) and 1740 cm^{-1} (ester) ; ^1H and ^{13}C NMR data are given in Table 1. High resolution mass spectrum, calcd for $C_8H_{14}O_7$: m/z 222.0739, found: M, 222.0718.

Methyl (Methyl-β-D-idopyranosid)uronate (10a). Compound **8a** (57 mg, 0.12 mmol) in ethanol (1 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (20 mg) under an atmospheric pressure of H_2 at room temperature for 6 h. The catalyst was removed by filtration through a short column of silica gel, and the filtrate was concentrated to give 28 mg (100%) of compound **10a**: mp 168-170 °C (from ethanol-*n*-hexane), $[\alpha]_D^{22}$

-86° (c 1.1, methanol); IR (KBr) 3350 (OH) and 1745 cm^{-1} (ester); ^{1}H and ^{13}C NMR data are given in Table 1.

Anal. Calcd for $C_8H_{14}O_7$: C, 43.25; H, 6.35. Found: C, 43.06; H, 6.22.

2D-(2,4,6/3,5)-2-O-(L-(+)-O-Acetylmandelyl)-3,4,5,6-tetra-O-benzyl-pentahydroxycyclohexanone (3b). To a stirred solution of **2b** (896 mg, 1.25 mmol) in acetone (20 mL) at 0 °C was added Jones reagent (1.4 mL, 3.74 mmol). After stirring at 5 °C overnight, the reaction mixture was treated as described for the preparation of **3a**. Purification by chromatography on silica gel (35 g) with 1:30 ethyl acetate-toluene afforded 545 mg (61%) of compound **3b** as an amorphous solid: mp 87-90 °C, $[\alpha]_D^{24}$ +23.5° (c 0.92, chloroform); IR (neat) 1745 (ester) and 1720 cm^{-1} (shoulder, ketone); ^{1}H NMR δ 2.14 (s, 3H, AcO), 3.52-3.93 (m, 3H, H-3,4,5), 4.03-4.99 (m, 9H, 4 benzyl and H-6), 5.29 (d, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 6.25 (s, 1H, PhCH(OAc)), and 7.0-7.5 (m, 25H, phenyl).

Anal. Calcd for $C_{44}H_{42}O_9$: C, 73.93; H, 5.92. Found: C, 73.95; H, 6.05.

(2R,3S,4S,5R,6R)-2-(L-(+)-O-Acetylmandelyl)-3,4,5,6-tetrakis-(benzyloxy)-7-heptanolide (4b). A mixture of **3b** (149 mg, 0.21 mmol), potassium hydrogen carbonate (25 mg, 0.25 mmol) and m-chloroperbenzoic acid (43 mg, 0.25 mmol) in 1,2-dichloroethane (1.5 mL) was stirred at room temperature for 1.5 h. The reaction mixture was worked up as described for the preparation of **4a** to give 154 mg (100%) of compound **4b** as a colorless syrup. This compound showed one spot on TLC and was used in subsequent steps without further purification: $[\alpha]_D^{26}$ -3° (c 1.4, chloroform); IR (neat) 1750 cm^{-1} (ester and lactone); ^{1}H NMR δ 2.11 (s, 3H, AcO), 3.57-3.87 (m, 3H, H-3,4,5), 3.99-5.07 (m, 8H, 4benzyl), 5.42 (d, 1H, $J_{5,6}$ = 4 Hz, H-6), 5.61 (d, 1H, $J_{2,3}$ = 8 Hz, H-2), 6.21 (s, 1H, PhCH(OAc)), and 7.0-7.6 (m, 25H, phenyl); mass spectrum (EI mode) m/z 731 (M+H) and 623 (M-$PhCH_2O$).

Methyl [5-O-(L-(+)-O-Acetylmandelyl)-2,3,4-tri-O-benzyl-L-idose dimethyl acetal]uronate (5b). A solution of **4b** (806 mg, 1.1 mmol) and p-toluenesulfonic acid monohydrate (63 mg, 0.33 mmol) in trimethyl orthoformate (4 mL) and methanol (4 mL) was heated at 55 °C for 1 h. The mixture was concentrated and the residue was dissolved in dichloromethane and treated with excess diazomethane at 0 °C.

Evaporation of the solvent and subsequent purification on a column of silica gel (28 g) with 1:15 ethyl acetate-toluene gave 612 mg (79%) of compound **5b** as a colorless syrup: $[\alpha]_D^{24}$ -7° (c 1.2, chloroform); IR (neat) 1750 cm^{-1} (ester); ^1H NMR δ 2.17 (s, 3H, AcO), 3.1-3.5 (m, 2H, H-3,4), 3.13 (s, 3H, MeO), 3.42 (s, 3H, MeO), 3.55 (s, 3H, MeO), 4.22-4.90 (m, 8H, 3benzyl and H-1,2), 5.05 (d, 1H, $J_{4,5}$ = 2.5 Hz, H-5), 6.15 (s, 1H, PhCH(OAc)), and 7.1-7.7 (m, 20H, phenyl).

Anal. Calcd for $C_{40}H_{44}O_{11}$: C, 68.56; H, 6.33. Found: C, 68.43; H, 6.28.

Methyl (2,3,4-tri-O-Benzyl-L-idose dimethyl acetal)uronate (6b). To a stirred solution of **5b** (494 mg, 0.71 mmol) in methanol (3 mL) at 0 °C was added 1M sodium methoxide in methanol (0.71 mL, 0.71 mmol), and the mixture was treated as described for the preparation of **6a**. Purification on a column of silica gel (15 g) with 1:15 ethyl acetate-toluene gave 367 mg (99%) of compound **6b** as a colorless syrup: $[\alpha]_D^{26}$ -23° (c 1.2, chloroform); IR and NMR spectra were identical with those of compound **6a**. High resolution mass spectrum, calcd for $C_{30}H_{35}O_7$: m/z 507.2383, found: M-OH, 507.2382; calcd for $C_{29}H_{33}O_7$: m/z 493.2226, found: M-OMe, 493.2240.

Methyl (Methyl-2,3,4-tri-O-benzyl-α-L-idopyranosid)uronate (7b) and Its β-Anomer (8b). A mixture of **6b** (367 mg, 0.70 mmol) and p-toluenesulfonic acid monohydrate (67 mg, 0.35 mmol) in trimethyl orthoformate (4 mL) and methanol (4 mL) was heated at 60-70 °C for 3 h. The reaction mixture was worked up as described for the preparation of **7a** and **8a**. Chromatography on silica gel (11 g) with 1:15 ethyl acetate-toluene gave, first, 182 mg (53%) of compound **7b** as a colorless syrup: $[\alpha]_D^{21}$ -29° (c 1.2, chloroform); IR and NMR data were identical with those of **7a**.

Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.34; H, 6.49.

The second fraction, gave 106 mg (31%) of compound **8b** as a colorless syrup: $[\alpha]_D^{23}$ +44° (c 0.66, chloroform); IR and NMR data were identical with those of **8a**.

Anal. Found: C, 70.33; H, 6.49.

Methyl (Methyl-α-L-idopyranosid)uronate (9b). Compound **7b** (133 mg, 0.27 mmol) in ethanol (3 mL) was hydrogenolyzed in the presence of 20%

$Pd(OH)_2$ on carbon (40 mg) under an atmospheric pressure of H_2 at room temperature for 3 h. Filtration of the mixture through celite and concentration of the filtrate gave 63 mg (100%) of analytically pure **9b** as a colorless syrup: $[\alpha]_D^{22}$ -59^0 (c 1.4, methanol); IR and NMR data were identical with those of **9a**. High resolution mass spectrum, calcd for $C_8H_{14}O_7$: m/z 222.0739, found: M, 222.0711; calcd for $C_7H_{11}O_6$: m/z 191.0556, found: M-OMe, 191.0554.

Methyl (Methyl-β-L-idopyranosid)uronate (10b). Compound **8b** (80 mg, 0.16 mmol) in ethanol (2 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (20 mg) under an atmospheric pressure of H_2 at room temperature for 4 h. The catalyst was removed by filtration through a short column of celite, and the filtrate was concentrated to give 37 mg (100%) of compound **10b**: mp 170-172 °C (from ethanol), $[\alpha]_D^{22}$ $+90^0$ (c 0.46, methanol); IR and NMR data were identical with those of **10a**.

Anal. Calcd for $C_8H_{14}O_7$: C, 43.25; H, 6.35. Found: C, 43.06; H, 6.22.

Methyl 2,3,4,6-Tetra-O-acetyl-α-D-idopyranoside (12a). To a stirred solution of **9a** (36 mg, 0.16 mmol) in methanol-water (1:1, 1 mL) at 0 °C was added sodium borohydride (19 mg, 0.50 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was neutralized with Amberlite IR 120B (H^+ form), and the resin was removed by filtration. Concentration of the filtrate gave 30 mg of methyl α-D-idopyranoside (**11a**) as a colorless syrup: ^1H NMR (400 MHz, in D_2O, acetone as an internal standard, δ=2.09) δ 3.34 (s, 3H, MeO), 3.41 (ddd, 1H, $J_{1,2}$ = 4.1 Hz, $J_{2,3}$ = 5.0 Hz, $J_{2,4}$ = 0.9 Hz, H-2), 3.6-3.75 (m, 4H, H-3,4,6,6'), 3.98 (dt, 1H, $J_{4,5}$ = $J_{5,6}$ = 4.4 Hz, $J_{5,6'}$ = 7.8 Hz, H-5), and 4.58 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1); ^{13}C NMR (D_2O, acetone as an internal standard, δ=30.7 ppm) δ 56.2, 60.3, 70.4, 71.0, 71.4, 71.7, and 101.7. (lit.[16] 56.3, 60.7, 70.7, 71.2, 71.5, 72.0, and 102.0).

This crude syrup was dissolved in pyridine (1 mL) and acetic anhydride (1 mL), and the mixture was stirred at room temperature overnight. After addition of methanol at 0 °C, the reaction mixture was concentrated to give a residue, which was purified by passing through a short column of silica gel with ethyl acetate to afford 53 mg (89%) of compound **12a**: mp 104 °C (from ethanol); $[\alpha]_D^{20}$ $+43^0$ (c 1.4, chloroform) (lit.[14] mp 107-108 °C, $[\alpha]_D$ $+55^0$); IR (neat) 1740 cm^{-1} (ester); ^1H

NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H AcO), 2.10 (s, 3H, AcO), 2.11 (s, 3H, AcO), 2.13 (s, 3H AcO), 3.41 (s, 3H, MeO), 4.18 (dd, 1H, $J_{6,6'}$ = 11.5 Hz, $J_{5,6}$ = 5.4 Hz, H-6), 4.24 (dd, 1H, $J_{6,6'}$ = 11.5 Hz, $J_{5,6'}$ = 7.3 Hz, H-6'), 4.40 (ddd, 1H, $J_{5,6'}$ = 7.3 Hz, $J_{5,6}$ = 5.4 Hz, $J_{4,5}$ = 2.0 Hz, H-5), 4.71 (bd, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.82 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.89 (bdd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 2.0 Hz, H-4), and 5.00 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 3.4 Hz, H-3); ^{13}C NMR ($CDCl_3$, tetramethylsilane as an internal standard, δ=0 ppm) δ 20.7, 20.8, 20.8, 20.9, 55.5, 62.4, 64.3, 66.8, 67.3, 67.4, 98.9, 169.2, 169.3, 169.8, and 170.5.

Methyl 2,3,4,6-Tetra-O-acetyl-α-L-idopyranoside (12b). To a stirred solution of **9b** (49 mg, 0.22 mmol) in methanol-water (1:1, 1 mL) at 0 °C was added sodium borohydride (25 mg, 0.66 mmol), and the mixture was stirred at 0 °C for 7 h. The reaction mixture was neutralized with Amberlite IR 120B resin (H^+ form), and the resin was removed by filtration. The filtrate was concentrated to give 40 mg of methyl α-L-idopyranoside (**11b**) as a colorless syrup. This crude product was dissolved in pyridine (0.5 mL) and acetic anhydride (0.5 mL), and the mixture was stirred at room temperature overnight. After addition of methanol, the reaction mixture was concentrated to give a residue, which was purified by a column of silica gel (1 g) with 1:7 ethyl acetate-toluene to give 42 mg (53%) of compound **12b**: mp 103.5-104 °C (from ethanol), $[\alpha]_D^{25}$ -45° (c 0.82, chloroform) (lit.[15] mp 107-108 °C, $[\alpha]_D$ -53°); IR and NMR data were identical with those of **12a**.

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REFERENCES AND FOOTNOTES

1. L. Anderson in The Carbohydrates, Vol. 1A; W. Pigman and D. Horton, Eds.; Academic Press: New York, 1972, p 519.

2. H. Streb, R. F. Irvine, M. J. Berridge, and I. Schulz, Nature, **306**, 67 (1983); M. J. Berridge and R. F. Irvine, ibid., **312**, 315 (1984).

3. For example, see T. Suami, S. Ogawa, T. Ishibashi, and I. Kasahara, Bull. Chem. Soc. Jpn., **49**, 1388 (1976).

4. T. Suami, S. Ogawa, S. Oki, and H. Kunitomo, ibid., **47**, 1737 (1974) and references therein.

5. H. Fukami, H. -S. Koh, T. Sakata, and M. Nakajima, Tetrahedron Lett., 4771 (1967); Idem, ibid., 1701 (1968).

6. R. W. Jeanloz in The Carbohydrates, Vol. 2B; W. Pigman and D. Horton, Eds.; Academin Press: New York, 1970, p 589.

7. M. F. Hawthone, W. D. Emmons, and K. S. McCallum, J. Am. Chem. Soc., **80**, 6369 (1958); W. E. Doering and L. Speers, ibid., **72**, 5515 (1950).

8. R. Gigg and C. D. Warren, J. Chem. Soc., (C), 2367 (1969).

9. P. J. Garegg, B. Lindberg, I. Kvarnstrom, and S. C. T. Svensson, Carbohydr. Res., **139**, 209 (1985).

10. L-(+)-O-Acetylmandelic acid was prepared from L-(+)-mandelic acid (purchased from Tokyo Chemical Industry Co., Tokyo, Japan) by the procedure reported in Organic Synthesis, Coll. Vol. 1, A. H. Blatt Eds.; John Wiley and Sons: New York, 1956, p 11. It had $[\alpha]_D^{29}$ +147° (c 1.1, chloroform) [lit.[17] $[\alpha]_D^{21}$ +158° (c 1.4, ethanol)].

11. C. B. Reese and J. G. Ward, Tetrahedron Lett., **28**, 2309 (1987).

12. V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeva, Tetrahedron, **29**, 331 (1973).

13. A. S. Perlin, B. Casu, G. R. Sanderson, and J. Tse, Carbohydr. Res., **21**, 123 (1972).

14. C. Pedersen, Acta Chem. Scand., **17**, 673 (1963).

15. R. J. Ferrier and P. C. Tyler, J. Chem. Soc., Perkin I, 1528 (1981).

16. R. Helleur, V. S. Rao, and A. S. Perlin, Carbohydr. Res., **89**, 83 (1981).

17. G. Pracejus, Liegigs Ann. Chem., **622**, 10 (1959).