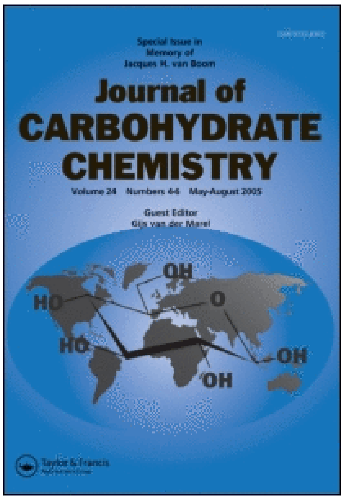


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of D- and L-Galactose Derivatives from Quebrachitol

Noritaka Chida[a]; Minoru Suzuki[a]; Masami Suwama[a]; Seichiro Ogawa[a]
[a] Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Yokohama, Japan

To cite this Article Chida, Noritaka , Suzuki, Minoru , Suwama, Masami and Ogawa, Seichiro(1989) 'Synthesis of D- and L-Galactose Derivatives from Quebrachitol', Journal of Carbohydrate Chemistry, 8: 3, 319 — 332
To link to this Article: DOI: 10.1080/07328308908048562
URL: http://dx.doi.org/10.1080/07328308908048562

J. CARBOHYDRATE CHEMISTRY, 8(3), 319-332 (1989)

SYNTHESIS OF D- AND L-GALACTOSE DERIVATIVES FROM QUEBRACHITOL

Noritaka Chida, Minoru Suzuki, Masami Suwama, and Seiichiro Ogawa*

Department of Applied Chemistry, Faculty of Science and Technology,
Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223 Japan

Received July 1, 1988 - Final Form November 15, 1988

ABSTRACT

Quebrachitol [1L-(-)-2-O-methyl-chiro-inositol] was converted into D- and L-galactose derivatives via the common intermediate, the 7-membered hemiacetal-lactone (9), which was obtained by regioselective Baeyer-Villiger oxidation of the inosose (8).

INTRODUCTION

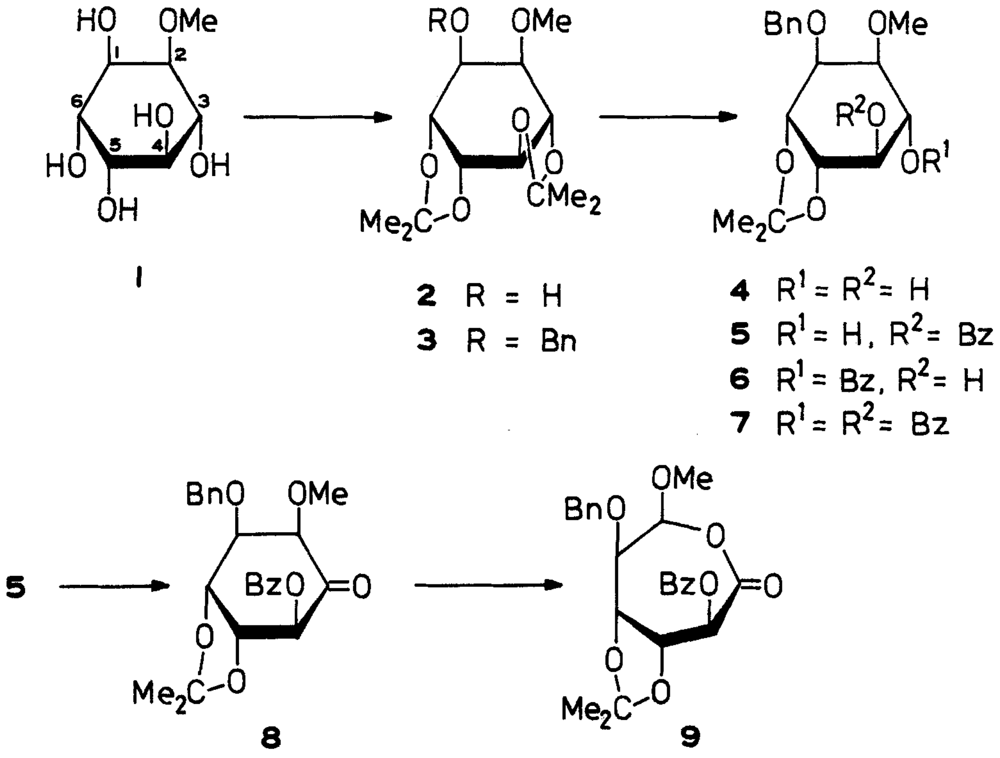
Quebrachitol [1L-(-)-2-O-methyl-chiro-inositol, 1] is one of the naturally occurring optically active inositols and is known to constitute 1-1.5% of the aqueous phase of the latex produced by the rubber tree, Hevea brasiliensis.[1] It has been reported that quebrachitol is readily prepared without difficulty from the serum of the rubber tree,[2] however, to our best knowledge, quebrachitol has not been commercially available, and thousands of tons of quebrachitol are lost each year since the serum obtained after coagulation of the rubber is a waste product. Although Paulsen and his co-workers have reported the synthesis of some optically active cyclitol and branched-chain cyclitol derivatives starting from 1,[3] only a few reports have appeared concerned with the synthesis of other natural products from 1.[4] Our interest in utilizing quebrachitol as a useful starting material for synthesis of natural products in optically active forms and as a valuable resource led us to study chemical conversion of 1 to other important compounds. In this communication, we wish to report the synthesis of D- and L-galactose derivatives starting from 1 via the 7-membered hemiacetal-lactone (9) which was obtained by regioselective Baeyer-Villiger oxidation of the inosose (8).

RESULTS AND DISCUSSION

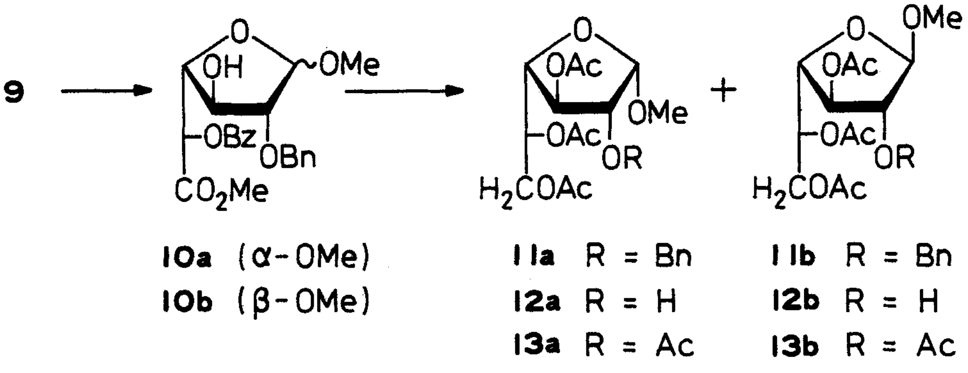
In previous paper,[5] we have reported the Baeyer-Villiger oxidation of inosose derivatives proceeded quite regioselectively, and was a useful method for the regioselective opening of the cyclohexane ring of inositols, which culminated in the synthesis of methyl (methyl idopyranosid)uronate from *myo*-inositol. Therefore, we first tried to apply this Baeyer-Villiger methodology for the regioselective ring opening of quebrachitol (1).

Quebrachitol (1), prepared from the spray-dried serum of the rubber tree by crystallization from water-ethanol, was converted into the known di-*O*-isopropylidene derivative (2) by the procedure reported by Paulsen.[3a] Benzylation of the hydroxyl group of 2 and subsequent selective hydrolysis gave the diol (4) in 86% yield. Treatment of 4 with a slight excess of benzoyl chloride in pyridine afforded the 4-benzoate (5) as a main product (41%) along with the 3-benzoate (6, 6%) and the dibenzoate (7, 35%). The structures of compounds 5 and 6 were established from their ^{1}H NMR spectra. In compound 5, no couplings were observed between H-2 (δ 3.58, dd, J = 3.0 and 5.8 Hz) and a proton attached to a carbon bearing a benzoyloxy group (δ 4.96, dd, J = 7.6 and 8.9 Hz), indicating that the C-3 hydroxyl group was not located at C-3. Whereas in compound 6, a signal attributable to a proton attached to a carbon possessing a benzoyloxy group was coupled to H-2 (J = 4.2 Hz), indicating that the C-3 hydroxyl group was esterified. Oxidation of compound 5 with pyridinium chlorochromate afforded the inosose (8) in 94% yield. Since the inosose (8) possessed a methoxy group at C-2, which is more electron-rich than C-6 bearing an electron withdrawing benzyloxy group, it was highly anticipated from our previous observations[5] that Baeyer-Villiger oxidation of compound 8 would proceed regiospecifically and the C-C bond attached to the methoxy group (C-2) would migrate to oxygen atom.

Baeyer-Villiger oxidation of 8 with *m*-chloroperbenzoic acid in the presence of potassium hydrogencarbonate proceeded regiospecifically, and, as expected, the hemiacetal-lactone (9) was obtained as crystals



Scheme 1



Bn = $-CH_2Ph$ Bz = $-CO_2Ph$

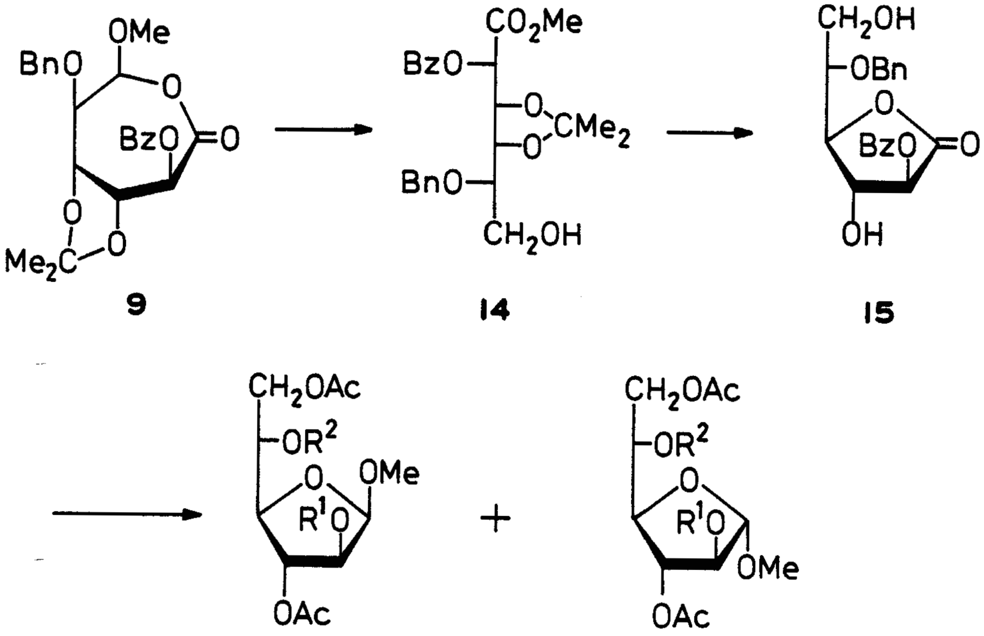
Scheme 2

in 95% yield. The ^{1}H NMR spectrum of 9 showed signals attributable to H-2 and H-6 at δ 5.55-5.72 as a multiplet, which strongly suggested that the C-C bond bearing a methoxy group migrated to oxygen atom (SCHEME 1).

The 7-membered hemiacetal-lactone (9) was first treated with p-toluenesulfonic acid in methanol and trimethyl orthoformate to give methyl (methyl 5-O-benzoyl-2-O-benzyl-D-galactofuranosid)uronate (10a and 10b) as an anomeric mixture (α:β = 7:3) in 89% yield. Treatment of the mixture of 10a and 10b with lithium aluminum hydride and subsequent acetylation afforded methyl 3,5,6-tri-O-acetyl-2-O-benzyl-α-D-galactofuranoside (11a) and its β-anomer (11b) in 35% and 24% isolated yields, respectively, after separation by silica gel chromatography. Removal of the benzyl group in 11a by hydrogenolysis and acetylation provided methyl 2,3,5,6-tetra-O-acetyl-α-D-galactofuranoside (13a) as crystals: mp 75-77 °C, $[\alpha]_D^{22}$ +82° (c 0.7, chloroform). The physical and spectral data were in good accordance with the authentic sample[6] prepared from natural D-galactose: the authentic sample, mp 75-77 °C, $[\alpha]_D^{23}$ +77° (c 1.3, chloroform). Similar treatment of 10b gave methyl 2,3,5,6-tetra-O-acetyl-β-D-galactofuranoside (13b) as a syrup: $[\alpha]_D^{23}$ -46° (c 0.9, chloroform); lit.[7] $[\alpha]_D^{25}$ -44.4° (c 0.5, methanol). The ^{1}H NMR and IR were identical with those of the authentic sample[6] prepared from natural D-galactose (SCHEME 2).

Since the synthesis of D-galactose derivatives from quebrachitol was achieved, we then turned our attention to the conversion of the 7-membered hemiacetal-lactone (9) to L-galactose derivatives (SCHEME 3).

Treatment of the hemiacetal-lactone (9) with excess sodium borohydride in methanol caused reduction of the hemiacetal group as well as methanolysis of the lactone moiety to give the methyl L-galactonate derivative (14) in 78% yield. Acid treatment of 14 gave 2-O-benzoyl-5-O-benzyl-α-L-galactofuranoside (16a) and its β-anomer (16b) as an inseparable mixture in 33% yield (16a:16b = 2:5). Finally, the benzyl and benzoyl groups in 16a and 16b were removed, and acetylation of the products gave mainly 2,3,5,6-tetra-O-acetyl-α-L-galactofuranoside (17a) and its β-anomer (17b) in 88% yield. The ^{1}H NMR (400 MHz) of the product showed that the mixture consisted of 17a and 17b in a ratio of 2:5. Careful separation of the mixture with silica gel chromatography



16a R^1 = Bz, R^2 = Bn **16b** R^1 = Bz, R^2 = Bn

17a R^1 = R^2 = Ac **17b** R^1 = R^2 = Ac

Scheme 3

afforded pure methyl 2,3,5,6-tetra-O-acetyl-β-L-galactofuranoside (17b): $[\alpha]_D^{22}$ +42° (*c* 0.58, chloroform), and the 1:1 mixture of 17a and 17b. The ^{1}H NMR spectra of 17b and the mixture of 17a and 17b were superimposable on those of compounds 13b and 13a.

These results showed that quebrachitol (1) was effectively converted into D- and L-galactose derivatives via the common intermediate, the 7-membered hemiacetal-lactone (9).

The synthesis of other natural products utilizing quebrachitol 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 Chemical, 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, ^1H NMR spectra were recorded for solution in $CDCl_3$ (internal Me_4Si) with a Varian EM-390 spectrometer. Spectra at 400 MHz were recorded with a Jeol JNM-GX 400 FT spectrometer. Mass spectra (EI mode) were taken on a Hitachi M-80 mass spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <45 °C under diminished pressure.

ISOLATION OF QUEBRACHITOL. The spray-dried serum[8] (brown solid, 100 g) of the rubber tree was suspended in methanol (500 mL) with stirring and an insoluble material was removed by filtration. The filtrate was concentrated to give a crystalline residue, which was filtered and washed with 1:10 water-ethanol to give crude quebrachitol (18 g, mp 177-181 °C). This crude compound was dissolved in hot water (50 mL), and ethanol (200 mL) was added to this solution after cooling. After standing at 5 °C overnight, crystals were collected and washed with 1:10 water-ethanol to provide 11.8 g of almost pure quebrachitol: mp 186-188 °C, $[\alpha]_D^{25}$ -77° (c 1, water), lit.[9] mp 192-193 °C, $[\alpha]_D^{20}$ -81.2° (c 5, water).

1L-1-O-Benzyl-3,4:5,6-di-O-isopropylidene-2-O-methyl-chiro-inositol (3). To a solution of 1L-1,2:3,4-di-O-isopropylidene-5-O-methyl-chiro-inositol, prepared from quebrachitol (1) by the procedure reported by Paulsen[3a] (2, 7 g, 15.9 mmol) in N,N-dimethylformamide (DMF, 40 mL) was added sodium hydride (60% in oil, 1.27 g, 31.9 mmol) at 0 °C. After stirring at 0 °C for 30 min, benzyl chloride (3.67 mL, 31.9 mmol) was added and the mixture was further stirred at room temperature for 1 h. The reaction was quenched by adding methanol (5 mL), and the mixture was concentrated to give a residue, which was dissolved in ethyl acetate and washed successively with water and brine, and dried. Evaporation of the solvent gave 5.80 g (100%) of analytically pure compound 3 as a colorless syrup: $[\alpha]_D^{22}$ -12° (c 1.5, chloroform); ^1H NMR δ 1.32, 1.43, 1.47 (3s, 12H, $2CMe_2$), 3.46 (s, 3H, MeO), 3.52-4.42 (m, 6H, H-1,2,3,4,5,6), 4.55 (d, 1H, J = 12 Hz, benzyl), 4.85 (d, 1H, J = 12 Hz, benzyl), and 7.32 (s, 5H, phenyl). High resolution mass spectrum, calcd for $C_{20}H_{28}O_6$: m/z 364.1886, found: M, 364.1890.

1L-1-*O*-Benzyl-5,6-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol (**4**). To a stirred solution of **3** (5.80 g, 13.7 mmol) in methanol (40 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (260 mg, 1.37 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized with triethylamine and concentrated to give a residue, which was chromatographed on a column of silica gel (50 g) with 5:1 chloroform-methanol to afford 4.45 g (86%) of compound **4** as a colorless syrup: $[\alpha]_D^{23}$ -73° (*c* 1.2, chloroform); IR (neat) 3450 cm^{-1} (OH); ^1H NMR δ 1.32, 1.46 (2s, 6H, CMe_2), 3.37 (s, 3H, MeO), 3.44-4.34 (m, 8H, H-1,2,3,4,5,6 and 2 OH), 4.68 (s, 2H, benzyl), and 7.30 (s, 5H, phenyl). High resolution mass spectrum, calcd for $C_{17}H_{24}O_6$: m/z 324.1573, found: M, 324.1555.

1L-3-*O*-Benzoyl-6-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-methyl-*chiro*-inositol (**5**). To a solution of **4** (1.35 g, 4.16 mmol) in pyridine (5 mL) at 0 °C was added dropwise a solution of benzoyl chloride (0.572 mL, 4.93 mmol) in pyridine (2 mL) over 15 min. After stirring at room temperature for 30 min, the reaction mixture was concentrated to give a residue, which was dissolved in ethyl acetate and washed successively with 0.5M HCl, saturated aqueous sodium hydrogencarbonate, water, and brine, and dried. Evaporation of the solvent left a syrup, which was chromatographed on a column of silica gel (50 g) with 1:25 ethyl acetate-toluene to give, first, 782 mg (35%) of 1L-3,4-di-*O*-benzoyl-1-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol (**7**, R_f = 0.80, 1:3 ethyl acetate-toluene) as a syrup: ^1H NMR δ 1.37, 1.60 (2s, 6H, CMe_2), 3.55 (s, 3H, MeO), 3.63-4.64 (m, 4H, H-1,2,5,6), 4.78 (s, 2H, benzyl), 5.41-5.80 (m, 2H, H-3,4), and 7.10-8.26 (m, 15H, phenyl).

Second elution gave 724 mg (41%) of compound **5** (R_f = 0.51, 1:3 ethyl acetate-toluene): mp 88-90 °C (from ethanol-hexane), $[\alpha]_D^{23}$ -82° (*c* 1.2, chloroform); IR ($CHCl_3$) 3470 (OH) and 1730 cm^{-1} (ester); ^1H NMR δ 1.40, 1.54 (2s, 6H, CMe_2), 3.48 (s, 3H, MeO), 3.58 (dd, 1H, $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 3.6 (b, 1H, OH), 3.95 (dd, 1H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 7.6 Hz, H-3), 4.00-4.64 (m, 3H, H-1,5,6), 4.76 (s, 2H, benzyl), 4.96 (dd, 1H, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 8.9 Hz, H-4) and 7.18-8.22 (m, 10H, phenyl). High resolution mass spectrum, calcd for $C_{24}H_{29}O_7$: m/z 429.1913, found: M+H, 429.1892.

Further elution gave 103 mg (6%) of 1*L*-3-*O*-benzoyl-1-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol (6, R_f = 0.41, 1:3 ethyl acetate-toluene) as a colorless syrup: $[\alpha]_D^{23}$ -55° (*c* 0.77, chloroform); IR (neat) 3470 (OH) and 1730 cm^{-1} (ester); ^{1}H NMR δ 1.38, 1.51 (2s, 6H, CMe_2), 2.7 (b, 1H, OH), 3.54 (dd, 1H, $J_{1,2}$ = 2.4 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 3.81-4.60 (m, 4H, H-1,4,5,6), 4.77 (bs, 2H, benzyl), 5.22 (dd, 1H, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 6.0 Hz, H-3), and 7.16-8.15 (m, 10H, phenyl). High resolution mass spectrum, calcd for $C_{24}H_{28}O_7$: m/z 428.1835, found: M, 428.1821.

2D-(2,3,6/4,5)-6-O-Benzoyl-3-O-benzyl-4,5-O-isopropyliene-2-O-methyl-pentahydroxycyclohexanone (8). To a stirred mixture of pyridinium chlorochromate (6.36 g, 29.5 mmol) and powdered molecular sieves 4A (6.3 g) in dichloromethane (30 mL) at 0 °C was added dropwise a solution of compound 5 (2.81 g, 6.56 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 1 h, and then partially concentrated. The mixture was diluted with ether and passed through a column of silica gel (70 g) with ether. Concentration of the eluent gave 2.62 g (94%) of compound 8 as a colorless syrup. This compound showed a single spot on TLC and was used in subsequent steps without purification: $[\alpha]_D^{23}$ 0° (*c* 6, chloroform); IR (neat) 1755 (ester) and 1720 cm^{-1} (ketone); ^{1}H NMR δ 1.36, 1.58 (2s, 6H, CMe_2), 3.49 (s, 3H, MeO), 4.29-4.80 (m, 4H, H-2,3,4,5), 4.70 (d, 1H, J = 15 H, benzyl), 5.60 (d, 1H, $J_{5,6}$ = 6.0 Hz, H-6), and 7.23-8.21 (m, 10H, phenyl). High resolution mass spectrum, calcd for $C_{24}H_{26}O_7$: m/z 426.1679, found: 426.1644.

(2S,3R,4R,5R,6S)-2-Benzoyloxy-5-benzyloxy-3,4-isopropylidenedioxy-6-methoxy-6-hexanolide (9). A mixture of 8 (2.20 g, 5.16 mmol), potassium hydrogencarbonate (619 mg, 6.19 mmol) and *m*-chloroperbenzoic acid (1.07 g, 6.19 mmol) in 1,2-dichloromethane (25 mL) was stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane and washed with 10% aqueous sodium bisulfite solution, saturated aqueous sodium hydrogencarbonate, and water, and dried. Evaporation of the solvent afforded a residue, which was recrystallized from ethyl acetate-hexane to give 2.17 g (95%) of compound 9: mp 165-166 °C, $[\alpha]_D^{27}$ +44° (*c* 1.0, chloroform); IR (neat) 1760 (lactone) and 1720 cm^{-1} (ester); ^{1}H NMR δ 1.34, 1.45 (2s, 6H,

CMe$_2$), 3.62 (s, 3H, MeO), 4.03-4.60 (m, 3H, H-3,4,5), 4.56 (d, 1H, J = 12 Hz, benzyl), 5.04 (d, 1H, J = 12 Hz, benzyl), 5.55-5.72 (m, 2H, H-2,6), and 7.23-8.25 (m, 10H, phenyl).

Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.08; H, 5.85.

Methyl (methyl 5-O-benzoyl-2-O-benzyl-α-D-galactofuranosid)uronate (10a) and its β-Anomer (10b). A mixture of compound 9 (2.55 g, 5.76 mmol) in trimethyl orthoformate (30 mL) and methanol (30 mL) was heated at 50 °C for 20 h. The reaction mixture was concentrated to give a residue, which was extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogencarbonate water, and brine, and dried. Evaporation of the solvent afforded a residue, which was chromatographed on a column of silica gel (50 g) with 1:8 ethyl acetate-toluene to give an inseparable mixture of compounds 10a and 10b (2.15 g, 89%, 10a:10b = 7:3) as a syrup: IR (neat) 1755 and 1725 cm^{-1} (ester); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.48 (d, 1H, J = 3.9 Hz, OH), 3.39 (s, 0.3 × 3H, MeO of 10b), 3.40 (s, 0.7 × 3H, MeO of 10a), 3.79 (s, 3H, CO$_2$Me), 3.95 (dd, 0.7H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 7.3 Hz, H-2 of 10a), 3.96 (d, 0.3H, $J_{2,3}$ = 8.3 Hz, H-2 of 10b), 4.27 (ddd, 0.3H, $J_{2,3}$ = 8.3 Hz, $J_{3,4}$ = 5.8 Hz, $J_{3,OH}$ = 3.9 Hz, H-3 of 10b), 4.33 (dd, 0.7H, $J_{3,4}$ = 7.3 Hz, $J_{4,5}$ = 4.9 Hz, H-4 of 10a), 4.49 (dd, 0.3H, $J_{3,4}$ = 5.8 Hz, $J_{4,5}$ = 4.4 Hz, H-4 of 10b), 4.60 (td, 0.7H, $J_{2,3}$ = $J_{3,4}$ = 7.3 Hz, $J_{3,OH}$ = 3.9 Hz, H-3 of 10a), 4.68 (d, 1H, J = 11.7 Hz, benzyl), 4.69 (d, 0.7H, $J_{1,2}$ = 4.4 Hz, H-1 of 10a), 4.74 (d, 1H, J = 11.7 Hz, benzyl), 5.03 (bs, 0.3H, H-1 of 10b), 5.44 (d, 0.7H, $J_{4,5}$ = 4.9 Hz, H-5 of 10a), 5.53 (d, 0.3H, $J_{4,5}$ =4.4 Hz, H-5 of 10b), and 7.27-8.16 (m, 10H, phenyl). High resolution mass spectrum, calcd for $C_{22}H_{25}O_8$: m/z 417.1549, found: M+H, 417.1560.

Methyl 3,5,6-Tri-O-acetyl-2-O-benzyl-α-D-galactofuranoside (11a) and its β-anomer (11b). To a suspension of lithium aluminum hydride (183 mg, 4.84 mmol) in THF (7.5 mL) at 0 °C was added a solution of the mixture of compounds 10a and 10b (1.00 g, 2.42 mmol, 10a:10b = 7:3), and the mixture was stirred at 0 °C for 7 h. The excess reagent was destroyed with water, and the mixture was neutralized with 2M HCl, and concentrated. The resultant residue was treated with acetic anhydride (10 mL) and pyridine (10 mL) at room temperature overnight. The mixture was concentrated to give a residue, which was extracted with ethyl acetate. The extract was washed successively with 1M HCl, saturated aqueous sodium hydrogencarbonate, water, and brine, and dried. Evaporation of the solvent afforded a syrup, which was chromatographed on column of silica gel (40 g) with 1:15 ethyl acetate-toluene to give, first, 246 mg (24%) of compound 11b (R_f = 0.50, 1:3 ethyl acetate-toluene) as a syrup: $[\alpha]_D^{24}$ $-62°$ (*c* 1.0, chloroform); IR (neat) 1740 cm^{-1} (ester); ^{1}H NMR δ 2.03, 2.05, 2.08 (3s, 9H, 3AcO), 3.36 (s, 3H, MeO), 3.86 (d, 1H, $J_{2,3}$ = 2.0 Hz, H-2), 4.08-4.42 (m, 3H, H-4,6,6'), 4.56 (d, 1H, J = 12 Hz, benzyl), 4.70 (d, 1H, J = 12 Hz, benzyl), 4.98 (s, 1H, H-1), 5.09 (dd, 1H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 4.7 Hz, H-3), 5.36 (m, 1H, H-5), and 7.32 (s, 5H, phenyl). High resolution mass spectrum, calcd for $C_{20}H_{26}O_9$: m/z 410.1577, found: M, 410.1583.

Further elution gave 357 mg (35%) of compound 11a (R_f = 0.38, 1:3 ethyl acetate-toluene) as a syrup: $[\alpha]_D^{24}$ +46° (*c* 1.0, chloroform); IR (neat) 1740 cm^{-1} (ester); ^{1}H NMR δ 2.02, 2.10 (2s, 9H, 3AcO), 3.36 (s, 3H, MeO), 3.88-4.46 (m, 4H, H-2,4,6,6'), 4.61 (s, 2H, benzyl), 4.68 (d, $J_{1,2}$ = 4.5 Hz, H-1), 5.18 (bq, 1H, J = 5.5 Hz, H-5), 5.50 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 7.5 Hz, H-3), and 7.34 (s, 5H, phenyl).

Anal. Calcd for $C_{20}H_{26}O_9$: C, 58.53; H, 6.39. Found: C, 58.24; H, 6.35.

Methyl 3,5,6-Tri-O-acetyl-α-D-galactofuranoside (12a). Compound 11a (102 mg, 0.25 mmol) in ethanol (1 mL) and ethyl acetate (1 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (30 mg) under an atmospheric pressure of H_2 at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated to give 81 mg (100%) of analytically pure 12a as a colorless syrup: $[\alpha]_D^{23}$ +84° (*c* 1.2, chloroform); IR (neat) 3500 (OH) and 1740 cm^{-1} (ester); ^{1}H NMR δ 2.03, 2.11 (2s, 9H, 3AcO), 3.14 (s, 1H, OH), 3.47 (s, 3H, MeO), 3.98-4.42 (m, 4H, H-2,4,6,6'), 4.83 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), and 5.10-5.31 (m, 2H, H-3,5).

Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.40; H, 6.16.

Methyl 3,5,6-Tri-O-acetyl-β-D-galactofuranoside (12b). Compound 11b (216 mg, 0.53 mmol) was hydrogenolyzed and processed as described for the preparation of 12a to give 176 mg (100%) of analytically pure

12b as a colorless syrup: $[\alpha]_D^{24}$ -62° (c 1.0, chlorofomr); IR (neat) 3480 (OH) and 1745 cm^{-1} (ester); ^1H NMR δ 2.03, 2.09, 2.11 (3s, 9H, 3AcO), 3.34 (bs, 1H, OH), 3.36 (s, 3H, MeO), 4.00-4.48 (m, 4H, H-2,4,6, 6'), 4.66 (dd, 1H, $J_{2,3}$ = 2.7 Hz, $J_{3,4}$ = 6.5 Hz, H-3), 4.90 (s, 1H, H-1), and 5.38 (dt, J = 4.5 and 7.5 Hz, H-5). High resolution mass spectrum, calcd for $C_{13}H_{20}O_9$: m/z 320.1107, found: M, 320.1097.

Methyl 2,3,5,6-Tetra-O-acetyl-α-D-galactofuranoside (13a). Compound 12a (80 mg, 0.25 mmol) was treated with acetic anhydride (1 mL) and pyridine (1 mL) at room temperature overnight. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (2 g) with 1:7 ethyl acetate-toluene to afford 90 mg (99%) of compound 13a: mp 75-77 °C (from ethanol); $[\alpha]_D^{22}$ +82° (c 0.7, chloroform); IR ($CHCl_3$) 1740 cm^{-1} (ester); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05, 2.08, 2.11, 2.13 (4s, 12H, 4AcO), 3.38 (s, 3H, MeO), 4.11 (dd, 1H, $J_{3,4}$ = 6.5 Hz, $J_{4,5}$ = 5.6 Hz, H-4), 4.16 (dd, 1H, $J_{5,6}$ = 5.6 Hz, $J_{6,6'}$ = 12.2 Hz, H-6), 4.33 (dd, 1H, $J_{5,6'}$ = 4.4 Hz, $J_{6,6'}$ = 12.2 Hz, H-6'), 5.04 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 5.06 (dd, 1H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 6.5 Hz, H-2), 5.22 (td, 1H, $J_{4,5}$ = $J_{5,6}$ = 5.6 Hz, $J_{5,6'}$ = 4.4 Hz, H-5), and 5.57 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 6.5 Hz, H-3).

Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.65; H, 5.96.

The authentic sample[6] prepared from methyl α-D-galactofuranoside by acetylation had mp 75-77 °C (from ethanol) and $[\alpha]_D^{23}$ +77° (c 1.3, chloroform). The IR and ^1H NMR spectra of 13a were superimposable on those of the authentic sample.

Methyl 2,3,5,6-Tetra-O-acetyl-β-D-galactofuranoside (13b). Compound 12b (170 mg, 0.53 mmol) was treated with acetic anhydride (2 mL) and pyridine (2 mL) at room temperature overnight. The reaction mixture was worked up and purified as described for the preparation of 13a to give 189 mg (98%) of compound 13b as a colorless syrup: $[\alpha]_D^{23}$ -46° (c 0.9, chloroform), [lit.[7] $[\alpha]_D^{25}$ -44.4° (c 0.5, methanol)]; IR (neat) 1745 cm^{-1} (ester); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07, 2.09, 2.11, 2.14 (4s, 12H, 4AcO), 3.39 (s, 3H, MeO), 4.23 (dd, 1H, $J_{5,6}$ = 7.1 Hz, $J_{6,6'}$ = 12.0 Hz, H-6), 4.24 (dd, 1H, $J_{3,4}$ = 5.9 Hz, $J_{4,5}$ = 3.9 Hz, H-4), 4.36 (dd, 1H, $J_{5,6'}$ = 3.9 Hz, $J_{6,6'}$ = 12.0 Hz, H-6'), 4.92 (s, 1H, H-1), 5.01 (dd, 1H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 5.9 Hz, H-3), 5.04 (d, 1H,

$J_{2,3}$ = 2.0 Hz, H-2), and 5.39 (dt, 1H, $J_{4,5}$ = $J_{5,6'}$ = 3.9 Hz, $J_{5,6}$ = 7.1 Hz, H-5).

The IR and ^{1}H NMR spectra of 13b were superimposable on those of the authentic sample[6] prepared from methyl β-D-galactofuranoside by acetylation.

Methyl 2-O-Benzoyl-5-O-benzyl-3,4-O-isopropylidene-L-galactonate (14). To a solution of compound 9 (500 mg, 1.14 mmol) in methanol (10 mL) was added at 0 °C sodium borohydride (43 mg, 1.14 mmol). After stirring at 0 °C for 3 h, additional sodium borohydride (43 mg, 1.14 mmol) was added, and the mixture was further stirred at 0 °C for 30 min. The reaction mixture was neutralized with acetic acid and concentrated to give a residue. The residue was extracted with ethyl acetate and the extract was washed with water and brine, and dried. Evaporation of the solvent afforded a syrup, which was chromatographed on a column of silica gel (6 g) with 1:5 ethyl acetate-toluene to give 390 mg (78%) of compound 14 as a colorless syrup: $[\alpha]_D^{21}$ -62° (c 1.6, chloroform); IR (neat) 3500 (OH), 1760 and 1725 cm^{-1} (ester); ^{1}H NMR δ 1.44, 1.74 (2s, 6H, CMe_2), 2.25 (b, 1H, OH), 3.59-3.73 (m, 3H, h-5,6,6'), 3.74 (s, 3H, CO_2Me), 4.39-4.80 (m, 4H, H-3,4 and benzyl), 5.45 (d, 1H, $J_{2,3}$ = 3.3 Hz, H-2), 7.21 (s, 5H, phenyl), and 7.30-8.21 (m, 5H, phenyl). High resolution mass spectrum, calcd for $C_{24}H_{28}O_8$: m/z 444.1784, found: M, 444.1802.

2-O-Benzoyl-5-O-benzyl-L-galactono-1,4-lactone (15). A mixture of 14 (390 mg, 0.88 mmol) and p-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol) in methanol (7 mL) was stirred at room temperature overnight, The reaction mixture was concentrated to give a residue, which was dissolved in benzene (7 mL) and the mixture was heated under reflux for 3 h. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous sodium hydrogencarbonate, water, and brine, and dried. Evaporation of the solvent afforded a residue, which was crystallized from chloroform-hexane to give 171 mg (52%) of compound 15: mp 105.5-107 °C; $[\alpha]_D^{23}$ +8° (c 1.5, acetone); IR (KBr) 3400 (OH), 1780 (γ-lactone), and 1720 cm^{-1} (ester); ^{1}H NMR (acetone-d_6) δ 3.0 (bs, 2H, 2OH), 3.80-4.00 (m, 3H, H-5,6,6'), 4.62-4.95 (m, 4H, H-3,4 and benzyl), 5.98 (d, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 7.28-8.10 (m, 10H, phenyl). High resolution mass spectrum, calcd for $C_{20}H_{20}O_7$: m/z 372.1209, found: M, 372.1212.

Methyl 2-O-Benzoyl-5-O-benzyl-α-L-galactofuranoside (16a) and its β-Anomer (16b). To a solution of 15 (168 mg, 0.45 mmol) in THF (5 mL) under Ar at -78 °C was added 1.5M solution of diisobutylaluminum hydride in THF (1.8 mL, 2.70 mmol). After stirring at -78 °C for 3 h, the reacton was quenched by adding 2M HCl (1.6 mL) at -78 °C for 3 h, the mixture was concentrated to give a residue, which was extracted with ethyl acetate. The extract was washed twice with brine and dried. Evaporation of the solvent left crude 2-O-benzoyl-5-O-benzyl-L-galactose as a syrup (120 mg). This crude syrup was dissolved in methanol (1 mL) and trimethyl orthformate (1 mL). To this solution was added p-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with triethylamine and then concentrated to give a residue, which was extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogencarbonate, water, and brine, and dried. Evaporation of the solvent afforded a residue, which was purified on preparative TLC (1:1 ethyl acetate-toluene) to give 58 mg (33%) of compounds 16a and 16b as an inseparable mixture: IR (neat) 3500 (OH) and 1730 cm^{-1} (ester); ^1H NMR δ 2.69 (b, 2H, OH), 3.38 (s, 3 × 2/7H, MeO of α-anomer), 3.47 (s, 3 × 5/7H, MeO of β-anomer), 3.69-4.66 (m, 5H, H-3,4,5,6,6'), 4.78 (bs, 2H, benzyl), 5.04-5.30 (m, 2H, H-1,2). High resolution mass spectrum, calcd for $C_{21}H_{25}O_7$: m/z 389.1600, found: M+H, 389.1591.

Methyl 2,3,5,6-Tetra-O-acetyl-α-L-galactofuranoside (17a) and its β-Anomer (17b). A mixture of compounds 16a and 16b (36 mg, 0.09 mmol) in methanol (2 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (15 mg) under an atmospheric pressure of H_2 at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated to give 27 mg (100%) of a mixture of methyl 2-O-benzoyl-α-L-galactofuranoside and its β-anomer as a syrup. This syrup was then dissolved in methanol (1 mL). To this solution was added 1M sodium methoxide in methanol (1 mL) and the mixture was stirred at room temperature overnight. 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 residue, which was treated with acetic anhydride (1 mL) and pyridine (1 mL). The mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel

(2 g) with 1:15 ethyl acetate-toluene to give 11.5 mg (35%) of compound 17b as a syrup: $[\alpha]_D^{22}$ +42° (c 0.58, chloroform); IR and ^{1}H NMR data were identical with those of 13b.

Further elution gave a mixture of 17a and 17b (17.5 mg, 53%) as a syrup. The ^{1}H NMR spectrum (400 MHz) revealed that the syrup was a mixture consisting of 17a and 17b in a ratio of 1:1.

ACKNOWLEDGMENT

The authors thank Mr. Hisao Arita for the elemental analyses. This work was supported in part by the Yokohama Rubber Co., Ltd. (Tokyo, Japan).

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. J. van Alphen, Ind. Eng. Chem., 43, 141 (1951).

3. a) H. Paulsen and F. R. Heiker, Liebigs Ann. Chem., 2180 (1981). b) H. Paulsen and W. von Deyn, Ibid., 133 (1987).

4. S. J. Angyal and R. M. Hoskinson in Method in Carbohydr. Chem., Vol. 2; R. Whistler and M. L. Wolfrom, Eds.; Academic Press: New York, 1963, p 87.

5. N. Chida, E. Yamada, and S. Ogawa, J. Carbohydr. Chem., 7, 555 (1988).

6. The authentic samples of methyl 2,3,4,6-tetra-O-acetyl-α-D-galactofuranoside and its β-anomer were prepared from methyl α- and β-D-galactofuranoside by acetylation (pyridine-acetic anhydride, rt), respectively. Methyl α- and β-D-galactofuranoside were prepared from D-galactose by the procedures described by Augestad and Berner[10], followed by chromatography on a column of silica gel with 1:10 methanol-chloroform.

7. I. Dyong, L. Baumeister, and H. Bendlin, Chem. Ber., 112, 161 (1979).

8. The spray-dried serum of the rubber tree was provided by the Yokohama Rubber Co., Ltd. (Tokyo, Japan).

9. F. K. Beilstein, "Handbuch der organischen Chemie," 4th ed. Suppl. III, Vol VI, 1967; p 6927; E. P. Clark, J. Am. Chem. Soc., 58, 1009 (1936).

10. I. Augestad and E. Berner, Acta Chem. Scand., 8, 251 (1954).