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Synthesis and Optical Resolution of 4,6-Dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-DL-glucitol

YOSHIO TAKEUCHI, MUTSUMI FURUMURA, and EIICHI YOSHII*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930–01, Japan

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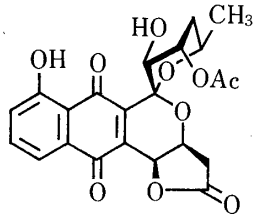
4,6-Dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-DL-glucitol (**3**) was conveniently prepared from (±)-parasorbic acid (**4**). Resolution of the racemate **3** into the D- and L-isomers, each of which serves as a synthetic building block for the sugar moiety of naturally occurring (−)-griseusin A (**2**) or its enantiomer (**1**), was effected by high-performance liquid chromatography of its benzoate (**12**) on a column packed with (+)-poly(triphenylmethylmethacrylate) on macroporous silica gel [Chiralpak OT(+)®].

Keywords——parasorbic acid; *cis*-dihydroxylation; selective acylation; dideoxyhexose; optical resolution; HPLC; chiral polymer packing

As a part of our synthetic studies on pyranonaphthoquinone antibiotics, we have recently reported the total synthesis of (+)-griseusin A (**1**),[1] leading to the correction of the absolute configuration assigned to naturally occurring griseusin A to its enantiomer **2**.[2] In this chiral synthesis of **1**, an appropriately protected 4,6-dideoxy-L-glucitol (**3**) prepared from D-glucuronolactone in 9 steps was employed as a precursor of the dideoxyhexose moiety.[3] This paper describes a convenient synthetic route to this particular sugar derivative, obtainable in D- and L-forms through resolution of its racemic benzoate prepared from readily available (±)-parasorbic acid (**4**)[4] in a straightforward manner.



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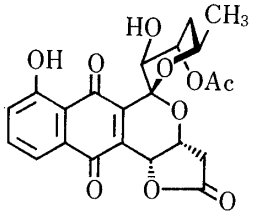

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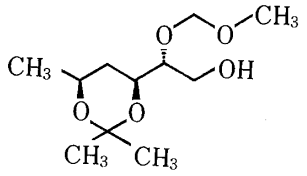

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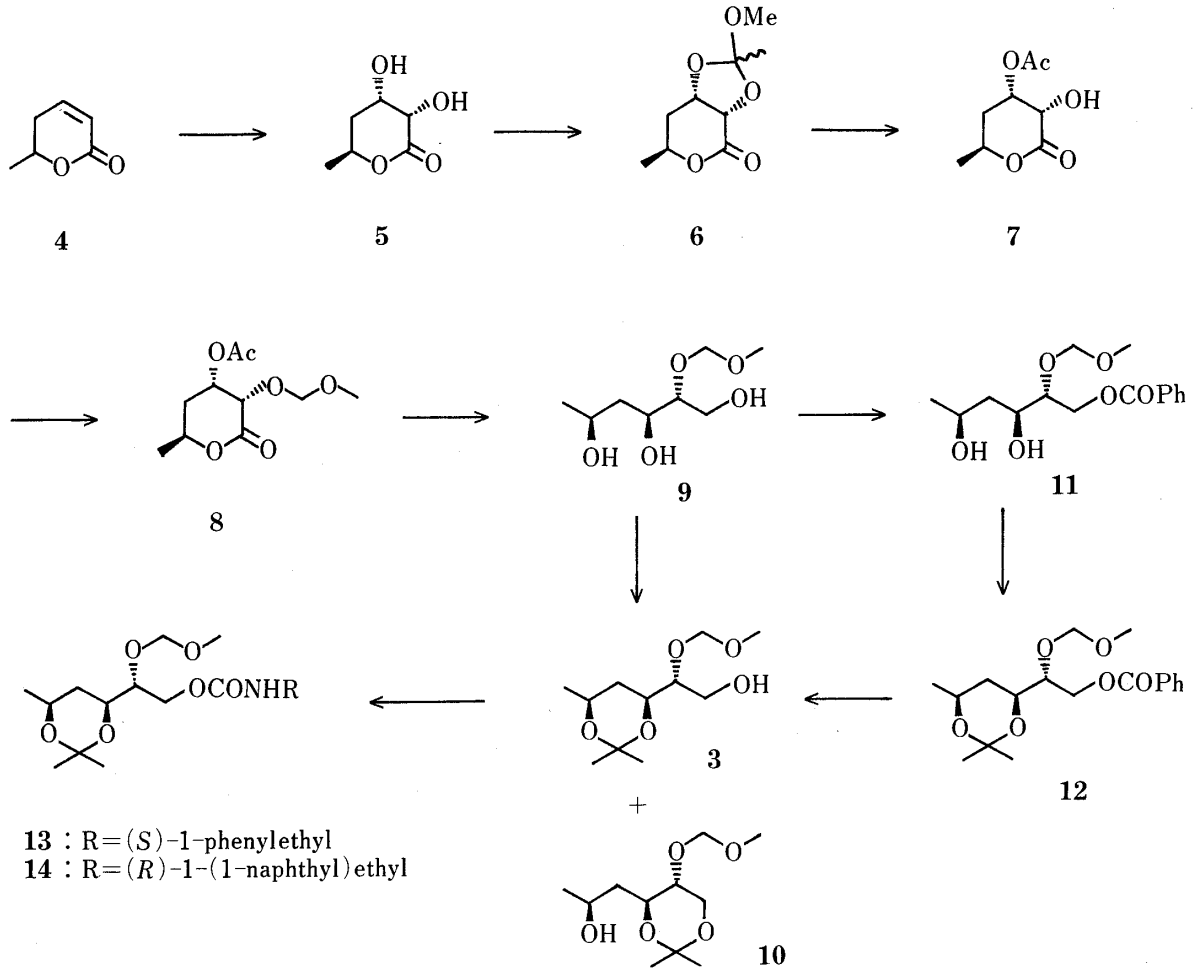
Chart 1

Catalytic *cis*-dihydroxylation of (±)-parasorbic acid (**4**) with the OsO_4–$NaClO_3$ combination[5] afforded the diol **5** in 75% yield as the only isolable stereoisomer and the stereochemistry of **5** (as depicted in Chart 2) was confirmed by 200 MHz proton nuclear magnetic resonance (^{1}H NMR) spectral analysis of the coupling constants of the vicinal protons: 3-H_{ax}, 4-H_{eq} = 3 Hz; 4-H_{eq}, 5-H_{ax} = 1.5 Hz; 5-H_{ax}, 6-H_{ax} = 11 Hz. Selective *O*-acetylation of the axial 4-hydroxyl group of **5** for temporary protection was readily performed by acid-catalyzed condensation with trimethyl orthoacetate, followed by immediate treatment of the resulting dioxolane **6** with aqueous acetic acid.[6] The monoacetate **7** obtained in 57% yield was then reacted with bromomethyl methyl ether in the presence of *N*,*N*-diethylaniline

to give the methoxymethyl (MOM) derivative **8** in 87% yield. Compound **8** was subjected to reduction with lithium aluminum hydride, providing 4,6-dideoxy-DL-glucitol 2-MOM ether (**9**).



13 : R=(*S*)-1-phenylethyl
14 : R=(*R*)-1-(1-naphthyl)ethyl

Chart 2

With the facile synthesis of the dideoxy sugar **9** established, the feasibility of selective 3,5-*O*-isopropylidenation was investigated. Treatment of **9** with 2,2-dimethoxypropane and camphorsulfonic acid (CSA) in acetone at room temperature resulted in the formation of an equilibrium mixture of two 1,3-dioxanes **3** and **10** (ratio, *ca.* 4 : 1). Although this direct isopropylidenation afforded the desired compound DL-**3** as a major product, separable from the unwanted isomer **10** by silica gel chromatography, we sought a more reliable access to **3** which involved prior protection of the primary 1-hydroxyl group. Thus, the monobenzoate **11** obtained from **9** in 72% yield by a conventional method was subjected to isopropylidenation to give compound **12**, which on treatment with methanolic potassium hydroxide produced **3** in nearly quantitative yield.

Optical resolution of DL-**3** was initially attempted by leading it to the *N*-(1-phenylethyl)carbamate diastereomers **13**. However, they could not be separated by high-performance liquid chromatography (HPLC). Switching to the *N*-1-[(1-naphthyl)ethyl]-carbamate **14**[7] did improve the result, but failed to give satisfactory separation on a preparative scale. However, the serious problem encountered here was overcome by HPLC of the racemic benzoate **12** employing a chiral packing, (+)-poly(triphenylmethyl-methacrylate) coated on macroporous silica gel[8] [Chiralpak OT(+)®]. The DL-**12** was completely resolved by this column, and the D- and L-isomers could be isolated readily.

4,6-Dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-D-glucitol obtainable by saponification of the corresponding benzoate is applicable to the synthesis of the naturally occurring griseusin A (**2**).

Experimental

Infrared spectra (IR) were recorded on a Jasco IRA-1 grating spectrometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Proton nuclear magnetic resonance spectra (^1H NMR) were taken on a Varian XL-200 (200 MHz) spectrometer in deuteriochloroform. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Resonance patterns were reported as s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. EI mass spectra (MS) were obtained on a JEOL JMS-D300 spectrometer. Optical rotations were measured on a Jasco DIP automatic polarimeter. Elemental analyses were performed by the Microanalytical Laboratory of this university. For chromatography, the following adsorbents were used: Merck Silica gel 60, 70—230 mesh for column chromatography and 230—400 mesh for flash chromatography; Merck precoated Silica gel 60 F_{254} plates for analytical thin layer chromatography (TLC). HPLC was carried out on a Waters model 6000A equipped with a ultraviolet (UV) detector (254 nm). Dry solvents were obtained by using standard procedures. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in work-up, and removal of the solvents was performed with a rotary evaporator.

3(*R),4(*R**)-Dihydroxy-6(*R**)-methyltetrahydropyran-2-one (5)**——Osmium tetroxide (340 mg) and $NaClO_3$ (6.3 g) in water (28 ml) were added to a stirred mixture of **4** (8.78 g) and water (14 ml) at room temperature, and stirring in a water bath at 45 °C was continued until disappearance of the starting material on TLC (*ca.* 5 h). The reaction mixture was concentrated under reduced pressure below 45 °C, and the oily residue was dried by azeotropic distillation with benzene containing a small amount of dry ethanol, then extracted with dry ethanol (100 ml). The ethanol extract was concentrated under reduced pressure to give a viscous oil (15 g), which was subjected to column chromatography in two portions (silica gel, 75 g; acetone/dichloromethane = 1/4) affording colorless needles (total yield, 8.48 g; 74.8%). An analytical sample was obtained by recrystallization from benzene–ethyl acetate: mp 85—86 °C. *Anal.* Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.89. Found: C, 49.24; H, 6.61. IR (KBr): 3400, 1700 cm^{-1}. ^1H NMR δ: 1.39 (3H, d, J=6 Hz, 6-Me), 1.83 (1H, ddd, J=15, 11, 1.5 Hz, 5-H_{ax}), 2.22 (1H, ddd, J=15, 4.5, 3.5 Hz, 5-H_{eq}), 4.18 (1H, d, J=3 Hz, 3-H_{ax}), 4.34 (1H, br s, 4-H_{eq}), 4.90 (1H, m, 6-H_{ax}).

4(*R)-Acetoxy-3(*R**)-methoxymethoxy-6(*R**)-methyltetrahydropyran-2-one (8)**——Trimethyl orthoacetate (10 ml) and CSA (*ca.* 20 mg) were added to a suspension of **5** (3.51 g) in dry benzene (60 ml) under Ar. The mixture was stirred at room temperature for 1 h to give a homogeneous solution, which after treatment with triethylamine (0.6 ml) was washed with water and concentrated under reduced pressure to give **6** as a colorless oil (4.85 g). The ^1H NMR of the product showed it to be a *ca.* 2:1 mixture of the diastereomers **6**: Me on the 1,3-dioxane ring, δ 1.61 (minor), 1.64 (major); OMe δ 3.29 (minor), 3.35 (major). Crude **6** was dissolved in 80% acetic acid (40 ml) and set aside at room temperature for 30 min. The solution was concentrated under reduced pressure, and the residue was extracted with dichloromethane (100 ml). The organic extract was washed with water, dried, and concentrated to give a pale yellow oil (3.2 g), which was purified by column chromatography (silica gel, 40 g; solvent, ethyl acetate/dichloromethane = 1/5) to afford the monoacetate (**7**) as an oil (2.39 g, 57.4%). MS *m/e*: 189 (M^++1), 102 (base peak).

Bromomethyl methyl ether (6 ml) was added over a 2 min period to a stirred solution of **7** (4.57 g) and *N,N*-diethylaniline (16 ml) in dry dichloromethane (60 ml) at room temperature. After continued stirring for 24 h, the reaction mixture was successively washed with 3% sulfuric acid and water, dried, and concentrated to give a brown oil (5.93 g). The product was purified in two portions by column chromatography (silica gel, 40 g; solvent, ethyl acetate/hexane = 1/1) to give **8** as a pale yellow oil (4.92 g, 87.2%). IR (film): 1740 cm^{-1}. ^1H NMR δ: 1.41 (3H, d, J=6.5 Hz, 6-Me), 1.93 (1H, ddd, J=15, 12, 2 Hz, 5-H_{ax}), 2.14 (3H, s, OAc), 2.28 (1H, ddd, J=15, 3.5, 3 Hz, 5-H_{eq}), 3.44 (3H, s, OMe), 4.27 (1H, d, J=3.5 Hz, 3-H), 4.7—4.84 (1H, m, 6-H), 4.77 (1H, d, J=7 Hz, OCH_2O), 4.95 (1H, d, J=7 Hz, OCH_2O), 5.53 (1H, m, 3-H).

4,6-Dideoxy-2-*O*-(methoxymethyl)-DL-glucitol (9)——Lithium aluminum hydride (68 mg) was added to a stirred solution of **8** (112 mg) in dry tetrahydrofuran (THF) (10 ml) at room temperature. After 3.5 h, excess hydride was decomposed by addition of saturated Na_2SO_4 and the mixture was filtered through a layer of Celite. The filtrate was dried and concentrated to give essentially pure **9** as a colorless oil (49 mg, 52%). ^1H NMR δ: 1.21 (3H, d, J=7 Hz, 6-H), 1.56 (1H, ddd, J=19, 12, 9 Hz, 4-H), 1.72 (1H, dt, J=19, 3 Hz, 4-H), 3.45 (3H, s, OMe), 3.48 (1H, q, J=6 Hz, 2-H), 3.65 (1H, d, J=4 Hz, 5-OH), 3.76 (2H, dd, J=7, 6 Hz, 1-H), 3.92—4.16 (2H, m, 3-H and 5-H), 4.06 (1H, br s, 1-OH), 4.46 (1H, d, J=4 Hz, 3-OH), 4.73 (1H, d, J=7 Hz, OCH_2O), 4.79 (1H, d, J=7 Hz, OCH_2O).

1-Benzoate (**11**): A stirred solution of **9** (495 mg) and pyridine (0.4 ml) in dry dichloromethane (20 ml) was cooled in an ice-water bath, and benzoyl chloride (0.3 ml) was added to it. After 2.5 h, the cooling bath was removed and stirring at room temperature was continued for 1 h. The reaction mixture was washed successively with cold 3% H_2SO_4, 5% $NaHCO_3$ and brine, then dried, and concentrated. The residue was subjected to flash chromatography (silica gel, 30 g; solvent, acetone/ethyl acetate = 3/7) to give analytically pure **11** as a colorless oil (518 mg, 72%). *Anal.*

Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.19; H, 7.25. IR (film): 3400, 1720 cm^{-1}. MS *m/e*: 297 ($M^+ - 1$), 167, 105, 101 (base peak), 77, 45. ^1H NMR δ: 1.22 (3H, d, J=6.5 Hz, 6-H), 1.60 (1H, dd, J=14, 10 Hz, 4-H), 1.77 (1H, dt, J=14, 2.5 Hz, 4-H), 3.43 (3H, s, OMe), 3.83 (1H, ddd, J=5.5, 5, 4 Hz, 2-H), 3.95—4.20 (2H, m, 3-H and 5-H), 4.49 (1H, dd, J=12.5, 4 Hz, 1-H), 4.56 (1H, dd, J=12.5, 5.5 Hz, 1-H), 4.77 (1H, d, J=7 Hz, OCH_2O), 4.82 (1H, d, J=7 Hz, OCH_2O), 7.48 (2H, t, J=8 Hz, ArH), 7.61 (1H, t, J=8 Hz, ArH), 8.07 (2H, dd, J=8, 1.5 Hz, ArH).

1-*O*-Benzoyl-4,6-dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-DL-glucitol (12)——2,2-Dimethoxypropane (0.9 ml) and CSA (*ca.* 10 mg) were added to a stirred solution of **11** (518 mg) in dry acetone (20 ml). After continued stirring for 1 h, the reaction mixture was treated with $CdCO_3$ for 30 min and diluted with benzene. The resulting suspension was washed with 5% $NaHCO_3$ and brine, then dried, and concentrated under reduced pressure to give essentially pure **12** as a colorless oil (810 mg). An analytical sample was obtained by distillation, bp 150—151 °C (bath temperature) at 0.07 Torr. *Anal.* Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 63.72; H, 7.85. IR (film): 1725 cm^{-1}. MS *m/e*: 339 ($M^+ + 1$), 323, 281, 249, 219, 129, 105, 59, 45 (base peak). ^1H NMR δ: 1.21 (3H, d, J=6 Hz, 6-H), 1.28 (1H, d, J=13 Hz, 4-H), 1.39 (3H, s, C–Me), 1.43 (3H, s, C–Me), 1.72 (1H, dt, J=13, 2.5 Hz, 4-H), 3.39 (3H, s, OMe), 3.83 (1H, m, 5-H), 3.94—4.14 (2H, m, 2-H and 3-H), 4.40 (1H, dd, J=12, 5.5 Hz, 1-H), 4.63 (1H, dd, J=12, 3 Hz, 1-H), 4.75 (1H, d, J=6.5 Hz, OCH_2O), 4.83 (1H, d, J=6.5 Hz, OCH_2O), 7.46 (2H, t, J=8 Hz, ArH), 7.60 (1H, t, J=8 Hz, ArH), 8.08 (2H, d, J=8 Hz, ArH).

Optical resolution of DL-**12** was performed by HPLC using a Chiralpak OT(+)® column (4.6 × 500 mm) with MeOH solvent at a flow rate of 0.5 ml/min. The L-isomer was eluted first giving separation factor (α) = 1.39 and resolution factor (Rs) = 1.93. The ^1H NMR spectra of the isolated D- and L-isomers were both identical with that of the racemate. D-**12**: $[\alpha]_D^{23}$ −11.2° (c=0.18, $CHCl_3$); L-**12**: $[\alpha]_D^{23}$ +11.1° (c=0.14, $CHCl_3$).

4,6-Dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-DL-glucitol (3)——A solution of **12** (740 mg) in MeOH (15 ml) and 5% KOH (4 ml) was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure to *ca.* 1/3 volume and extracted with ethyl acetate. The extract was washed with brine, then dried, and concentrated to give DL-**3** as a colorless oil (327 mg). The ^1H NMR spectrum of the product was identical with that of L-**3**: δ 1.19 (3H, d, J=6 Hz, 6-H), 1.27 (1H, d, J=13 Hz, 4-H), 1.40 (3H, s, C–Me), 1.45 (3H, s, C–Me), 1.65 (1H, dt, J=13, 2.5 Hz, 4-H), 2.83 (1H, t, J=2.5 Hz, OH), 3.44 (3H, s, OMe), 3.40—3.52 (1H, m, 1-H), 3.62—3.86 (2H, m, 1-H and 5-H), 3.90—4.10 (2H, m, 2-H and 3-H), 4.71 (1H, d, J=7 Hz, OCH_2O), 4.78 (1H, d, J=7 Hz, OCH_2O).

Diastereomeric (*S*)-*N*-(1-phenylethyl)carbamates (**13**) were obtained as an oil by reaction with (*S*)-(−)-1-phenylethyl isocyanate in refluxing benzene in the presence of triethylamine. HPLC (μ-Porasil column) showed a single peak with various solvent systems. MS *m/e*: 366 ($M^+ - 15$), 261, 129, 105, 86, 84 (base peak), 59, 45. ^1H NMR δ (prominent common peak): 1.17 (d, J=6 Hz, Me), 1.48 (d, J=7 Hz, Me), 3.37 (s, OMe).

Diastereomeric (*R*)-*N*-1-[(1-naphthyl)ethyl]carbamates (**14**) were obtained as an oil by reaction with (*R*)-(−)-1-[(1-naphthyl)ethyl]isocyanate as described above for the phenyl analog. MS *m/e*: 431 (M^+), 416, 342, 328, 215, 156, 129, 59 (base peak), 45. ^1H NMR δ (prominent common peak): 1.16 (d, J=6 Hz, Me), 1.39 (d, J=8 Hz, Me), 3.35 (s, OMe).

Acetonization of DL-9——2,2-Dimethoxypropane (100 μl) and CSA (*ca.* 4 mg) were added to a stirred solution of **9** (51.7 mg) in dry acetone (2 ml). After continued stirring for 22 h, the reaction mixture was treated with $CdCO_3$ for 30 min and then filtered. Concentration of the filtrate afforded a mixture of **3** and **10** (ratio, 3.9 : 1 by ^1H NMR). Characteristic ^1H NMR signals due to **10**: δ 1.18 (d, J=6 Hz, 6-H), 1.50 (s, C–Me), 1.90 (dt, J=14, 2.5 Hz, 4-H), 3.36 (s, OMe), 4.62 (d, J=7 Hz, OCH_2O), 4.67 (d, J=7 Hz, OCH_2O).

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