Stereospecific Synthesis of the C-9—C-16 Segment of Carbonolide B, the Aglycon of Carbomycin B†

Kuniaki Tatsuta,* Toyoki Yamauchi, and Mitsuhiro Kinoshita
Department of Applied Chemistry, Faculty of Engineering, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223
(Received March 24, 1978)

Stereospecific synthetic routes to methyl (R)-7-hydroxy-(2E,4E)-octadienoate (9) and its (2E,4Z)-isomer (16), the former which can be a useful chemical precursor to the 16-membered-ring aglycon of carbomycin B (carbonolide B), are discussed. Compound 9, corresponding to its C-9—C-16 segment, was synthesized starting with methyl 2-deoxy-α-p-arabino-hexopyranoside (2). The deoxysugar 2 was converted to the masked 2,4,6-trideoxy-α-d-threo-hexopyranoside (6) via the 4,6-dichloro-2,4,6-trideoxy-α-p-lxyo-hexopyranoside derivative. Treatment of 6 with p-toluenesulfonyl chloride and triethylamine afforded 3-O-acetyl,5-anhydro-2,4,6-trideoxy-α-d-threo-hex-1-enitol, which by reaction with mercury(II) acetate was converted to (R)-5-hydroxy-(2E)-hexenal (8). Reaction of 8 with Wittig reagent gave the (2E,4E)-isomer 9. Compound 16 was prepared by the Wittig reaction with the 2,3-unsaturated deoxysugar, 2,3,4,6-tetrahydro-p-glycero-hex-2-enopyranoside, which was derived from methyl 2,3-anhydro-4,6-dideoxy-α-p-lxyo-hexopyranoside by treatment with potassium selenocyanate followed by acid hydrolysis.

In the course of studies directed toward the total synthesis of 16-membered macrolide antibiotics, the regio- and stereoselective introduction of an aminodiisasccharide onto the 16-membered aglycon has been reported.1 Carbomycin B2 is a representative antibiotic of the 16-membered-ring macrolides, and the structure of the aglycon, carbomycin B (1a), can be divided into two segments of C-1—C-8 and C-9—C-16. The latter is stereochemically related to methyl (R)-7-hydroxy-(2E,4E)-octadienoate (9), where the C-1 and C-8 carbon atoms correspond to the C-9 and C-16 of carbonolide B. This paper reports the stereospecific synthesis of 9 as an intermediate in the synthesis of carbonolide B using carbohydrates. Recently, a variety of carbohydrates have been used as chiral intermediate in the total synthesis of and/or in the synthetic approach to natural products.

The key process was the conversion of 3-O-acetyl-1,5-anhydro-2,4,6-trideoxy-p-threo-hex-1-enitol (7) by mercury(II) acetate to (R)-5-hydroxy-(2E)-hexenal (8), which reacted with Wittig reagent to give 9. Methyl (R)-7-hydroxy-(2E,4Z)-octadienoate (16) was prepared by the Wittig reaction with 2,3,4,6-tetrahydro-p-glycero-hex-2-enopyranoside (15) in order to provide a reference for 9.

Results and Discussion

The starting methyl 2-deoxy-α-p-arabino-hexopyranoside (2) was treated with sulfuryl chloride in pyridine followed by treatment with sodium iodide in aqueous methanol, to give methyl 4,6-dichloro-2,4,6-trideoxy-α-p-lxyo-hexopyranoside (3). The corresponding 3-O-chlorosulfate, which could not be isolated, was considered to be an intermediate.7 Acetylation of 3 gave a syrupy product 4, which was dechlorinated with tributylstannane and successively hydrolyzed with dilute hydrochloric acid to give 3-O-acetyl-2,4,6-trideoxy-p-threo-hexopyranoside (6). The intermediate methyl 3-O-acetyl-2,4,6-trideoxy-α,p-threo-hexopyranoside (5) was intractable because of its volatility. Conversion of the 2-deoxysugars to the corresponding glycols was achieved by treatment with p-toluenesulfonyl chloride in the presence of triethylamine.1,4 The method was effectively applied to the preparation of 3-O-acetyl-1,5-anhydro-2,4,6-trideoxy-p-threo-hex-1-enitol (7) from 6. Attempts were unsuccessful to prepare 7 from 2,3-di-O-acetyl-4,6-dideoxy-α-p-xlyo-hexopyranosyl bromide by the usual manner. As 7 was too labile to be purified, it was, without isolation, treated with mercury(II) acetate. This was followed by the addition of dilute sulfuric acid, which gave the syrupy (R)-5-hydroxy-(2E)-hexenal (8).

† Presented at the 37th National Meeting of the Chemical Society of Japan, Yokohama, April 2, 1978.
in a moderate overall yield. The structure was supported by the characteristic, intense IR absorption at 1695 cm⁻¹ and a weak absorption (shoulder) at 1650 cm⁻¹, complemented by a maximum at 223 nm in the UV spectrum. The NMR spectrum provided independent evidence for the open-chain structure of 8, namely, the doublet at extremely low field (Δ 9.62) for H-1, the well-resolved multiplets (Δ 6.19 and 6.93) for H-2 and H-3, and the presence of a hydroxyl group (signal at Δ 1.80, that disappeared upon addition of D₂O); the large value for ²J₇₈ (15.5 Hz) indicated the trans position of the olefinic protons. This transformation agrees with expectations based on the reaction of 3,4,6-tri-O-acetyl-d-glucal with acidic mercury(II) sulfate. The Wittig reaction of 8 with methoxy carbonylmethyl ester phosphorane provided an 80% yield of the dienoate 9. The UV and NMR spectra of 9 were very similar to those of ethyl (2E,4E)-hexadienoate,¹¹ showing that 9 was a desired (2E,4E)-isomer implying not only the stereospecific synthesis of the C₉-C₁₆ segment of carbonyl B but also the utility of the key intermediate, the trans-unsaturated aldehyde 8.

\[
\text{Chart 3.}
\]

The (2E,4Z)-isomer 16 was directly synthesized from the reducing sugar 15 by the Wittig reaction. Selective tosylation of the starting methyl 4,6-dideoxy-α-D-xylono-hexopyranoside⁷ (10) gave predominantly the corresponding 2-O-p-toluenesulfonate 11 in 72% yield. Treatment of the crude p-toluenesulfonate 11, containing a small amount of the 3-O-p-toluenesulfonate, with sodium methoxide gave a ca. 50:1 mixture of methyl 2,3-anhydro-4,6-dideoxy-α-D-lyxo- and ribo-hexopyranosides (12 and 13), suggesting that the 3-O-p-toluenesulfonate was a very minor component. The product 12 could configurationally be a precursor of the C₁₁-C₁₆ segment of carbonyl B (1b), an aglycon of carbomycin A.¹⁴ Compound 12, which was isolated as needles, was treated with a boiling solution of potassium selenocyanate in aqueous 2-methoxyethanol for twenty minutes to give methyl 2,3,4,6-tetrahydroxy-α-D-glycero-hex-2-enopyranoside (14). The syrupy product 13, however, required two hours for the complete reaction to give 14 in the same conditions as described above. Acid hydrolysis of 14 gave a syrupy compound 15, which was subsequently treated with the Wittig reagent to give the (2E,4Z)-isomer 16 in 77% overall yield. The structure of 16 was confirmed by UV and NMR spectra in comparison with those of 9 and ethyl (2E,4Z)-hexadienoate.¹¹ It appears reasonable on the basis of the above results to suppose that, during the Wittig reaction, the trans and cis unsaturated aldehydo-forms 8 and 15, the latter of which is considered to take part in the reaction of 15 as an intermediate, do not suffer the trans-cis and cis-trans isomerizations, and the newly produced olefin groups possess the trans configuration in both cases.

The utility of the deoxy unsaturated carbohydrates 8 and 15 is thus demonstrated for stereospecific synthesis of α:β; γ:β-unsaturated esters.

**Experimental**

Melting points were determined on a micro hot-stage Yanaco MP-S3 and are uncorrected. Specific rotations were measured (0.2-dm tube) with a Carl Zeiss Photodiconlectric Precision Polarimeter. The NMR spectra were determined with Varian A60, EM-390 or XL100 spectrometers. Unless otherwise stated, chloroform-d was used as a solvent and internal tetramethylsilane as a standard. Coupling constants were obtained by measuring spacings of spectra judged to be first-order. TLC and column chromatography were performed on silica gel Wakogel B-5 and Wakogel C-300, respectively. In general, concentration was carried out under reduced pressure below 30 °C.

The starting materials, methyl 2-deoxy-α-D-arabino-hexopyranoside⁷ (2), which was recrystallized from ethyl acetate to give cubics; mp 94–95 °C; [α]10º = +160° (c 1.0, CH₃OH) and methyl 4,6-dideoxy-α-D-xyl-o-hexopyranoside (10) which was purified by sublimation at 47 °C at 1 Torr; mp 108–109 °C; [α]10º = +179° (c 1.0, CH₃OH) were prepared according to the published procedures.

1) Methyl 4,6-Dichloro-2,4,6-trideoxy-α-D-lyxo-hexopyranoside (3).

To a stirred solution of 2 (8.91 g) in a dry mixture of pyridine (33 ml) and chloroform (82 ml), cooled in a Dry-Ice-acetone bath, was added sulfuryl chloride (21.3 ml) drop by drop over 30 min. Cooling was continued for a further 2 h, after which the reaction mixture was allowed to stand at room temperature overnight. The resulting precipitate, possibly of pyridine salts, was filtered from the chloroform solution. The filtrate was washed successively with 10% sulfuric acid, saturated NaHCO₃ solution and water, dried (Na₂SO₄), and evaporated to give an oil. To a methanolic solution (200 ml) of the oil was added a solution of sodium iodide (6.60 g) in 50%aq methanol (16 ml). The mixture was vigorously stirred for 2 h at room temperature and then neutralized with NaHCO₃ (11.7 g). The resulting precipitate was removed by filtration, the filtrate evaporated, and the residue chromatographed on a column of silica gel (500 g) with benzene-ethyl acetate (3:1). The eluate containing the major product (Rf 0.40 by TLC with the same solvent system) was evaporated to give a solid which was further purified by recrystallization from hexane, followed by sublimation at 67 °C under reduced pressure (12 Torr), to give crystals of 3 (4.4 g, 41%): mp 114–115 °C; [α]10º = 175° (c 1.0, CH₃OH); NMR δ 1.6–2.6 (3H, m, CH₃-2 and OH-3), 3.39 (3H, s, OCH₃), 3.67 (2H, m, CH₂-5), 3.9–4.3 (2H, m, H-3 and 5), 4.45 (1H, m, H-4) and 4.85 (1H, t, J₁₂₃ = 2.5 Hz, H-1).

Found: C, 39.15; H, 5.44; Cl, 32.72%. Caled for C₁₁H₁₈Cl₂

†† Throughout this paper 1 Torr = 133.322 Pa.
OCl₂; C, 39.09; H, 5.62; Cl, 32.97%.

2) Methyl 3-O-Acetyl-4,6-dichloro-2,4,6-trideoxy-α-D-lyxo-hexopyranoside
A solution of 3 (121 mg) in a mixture of acetic anhydride (0.11 ml) and pyridine (0.61 ml) was kept overnight at room temperature and, after addition of ethanol (0.11 ml), was concentrated in vacuo to give a residue that was chromatographed on a column of silica gel (10 g) with hexane–ethyl acetate (6:1) to give an oil of 4 (143 mg, 93%).

Micro-distillation of 4 at 35 °C at 1 Torr gave an analytically pure oil: [α]D²⁰ = +153° (c 2.0, CHCl₃); IR (CCl₄) 3450 (OH), 1695 and 1650 cm⁻¹ (C=C-CHO); UV max (CH₂Cl₂) 223 nm (ε 11,000); NMR δ = 1.6-2.6 (2H, m, CH₂-2), 2.08 (3H, s, OAc), 3.37 (3H, s, OCH₃), 3.64 (2H, d, J₆,₆ = 7 Hz, CH₂-5), 4.15 (1H, dt, J₆,₅ = 1 Hz, H-5), 4.59 (1H, m, H-4), 4.87 (1H, dd, J = 1 and 3 Hz, H-1) and 5.30 (1H, m, H-3).

Found: C, 42.34; H, 5.41; Cl, 27.27%. Calcd for C₃H₅Cl₂O₃: C, 42.04; H, 5.49; Cl, 27.50%.

3) 3-O-Acetyl-2,4,6-trideoxy-α-D-xylo-hexopyranose (6).
To a solution of 4 (318 mg) in dry toluene (3.2 ml) under an argon atmosphere was added tributylstannane (792 mg) and azobisisobutyronitrile (20 mg). The solution was stirred overnight at 100 °C and then concentrated to afford a residue, which was chromatographed on a column of silica gel with benzene–ethyl acetate (7:1). The eluate containing the product (Rf 0.42 on TLC with the same solvent system) was carefully concentrated with an aspirator to give an oil 5, which contained a little solvent: NMR δ = 0.7-2.4 (4H, m, CH₂-4'), 1.29 (3H, d, J = 6.5 Hz, CH₃-5'), 2.02 (3H, s, OAc), 3.34 (3H, s, OCH₃), 3.97 (1H, m, H-5), 4.86 (1H, dd, J = 1 and 3 Hz, H-1) and 6.21 (1H, d, J₆,₅ = 7 Hz, H-5) and 6.93 (1H, dt, J₆,₅ = 7 Hz, H-3) and 9.62 (1H, d, CH-1). Found: C, 62.92; H, 8.74%. Calcd for C₃H₅Cl₂O₃: C, 63.13; H, 8.83%.

5) Methyl (R)-7-Hydroxy-(2E,4E)-octadec-9-enoate (9). To a solution of 8 (16 mg) in dry benzene (1 ml) was added methoxy carbonyl methyl methylenetriphosphonate (52 mg), and the mixture refluxed for 1 h and then evaporated in vacuo. The residue was chromatographed on a column of alumina (Woelm neutral, 3.5 g) with chloroform–acetone (5:1), followed by chromatography on a column of silica gel (2 g) with hexane–ethyl acetate (1:1) to give an oil of 9 (20 mg, 83%). TLC (hexane–ethyl acetate 1:1) Rf 0.50; [α]D²⁰ = +17° (c 2.0, CHCl₃); IR (CHCl₃) 3406 (OH), 1720, 1705 (C=O), 1645, 1620 cm⁻¹ (C=C-C=C); UV max (CH₂Cl₂) 260 nm (ε 27,800); NMR δ = 1.23 (3H, d, J = 6.5 Hz, CH₃-7'), 1.97 (1H, broad s, OH-7), 2.34 (2H, m, CH₂-6), 3.74 (3H, s, COOCH₃), 3.91 (1H, m, H-7), 5.83 (1H, d, J₆,₅ = 15 Hz, H-2), 6.0-6.4 (2H, m, H-4 and 5) and 7.27 (1H, m, H-3).

Found: C, 63.46; H, 8.17%. Calcd for C₃H₅O₃C: 63.51; H, 8.29%.

6) Methyl 4,6-Dideoxy-2-O-p-toluenesulfonyl-α-D-xylo-hexopyranoside (11). To an ice-cold, stirred solution of 10 (2.46 g) in pyridine (24 ml) was added p-toluenesulfonyl chloride (3.76 g), and the mixture allowed to stand at room temperature for 1 day. The mixture was then poured into agitated ice-water (70 ml), and the product extracted with chloroform (80 ml x 2). The extracts were combined, washed successively with an ice-cold, saturated KHSO₄ solution, saturated NaHCO₃ solution and water, dried (Na₂SO₄), and evaporated. The residue was chromatographed on a column of silica gel (200 mg) with benzene–ethyl acetate (3:1) to give an oil of 11 (34.6 g, 72%): [α]D²⁰ = +99° (c 2.0, CH₂Cl₂); IR (CCl₄) 11.18 (3H, d, J = 6.5 Hz, CH₃-5'), 1.3-2.5 (3H, m, CH₂-4 and 3), 2.46 (3H, s, Ts-CH₃), 3.28 (3H, s, OCH₃), 3.5-4.3 (2H, m, H-3 and 5), 4.21 (1H, dd, J₆,₅ = 3 Hz and J₆,₅ = 1.5 Hz, H-2), 4.67 (1H, d, J = 1, H-1), 7.37 and 7.87 (each 2H, AB quartet, J = 8.5 Hz, Ts).

Found: C, 52.91; H, 6.38%. Calcd for C₃H₅O₃C: 53.15; H, 6.37%.

7) Methyl 3,5-Anhydro-4,6-dideoxy-α-L-ribopyranoside (12 and 13).
To a methanolic solution (2.8 ml) of a crude sample of 11 (817 mg) was added a 28% methanolic sodium methoxide solution (0.70 ml), and the solution refluxed for 1 h. After cooling, the solution was poured into ice-water (30 ml) and the product extracted with dichloromethane (35 ml x 3). The combined extracts were washed with water, dried (Na₂SO₄), and evaporated. The residue was chromatographed on a column of silica gel (40 g) with benzene–ethyl acetate (7:1) to give 12 (286 mg) and 13 (8 mg), which on TLC with the same solvent gave Rf 0.48 and 0.31 respectively, in 79% total yield. Micro-distillation of 12 at 45-80 °C at 16 Torr gave analytically pure needles: mp 28-30 °C; [α]D²⁰ = +70° (c 1.0, CH₂Cl₂); NMR δ = 1.15 (3H, d, J = 6.5 Hz, CH₃-5'), 1.5-2.1 (2H, m, CH₂-4'), 2.98 (1H, d, J₆,₅ = 4 Hz, H-2'), 3.40 (1H, m, H-3'), 3.48 (3H, s, OCH₃), 3.88 (1H, s, H-5') and 4.91 (1H, s, H-1').
Found: C, 58.35; H, 8.31%. Caled for C₉H₁₅O₂: C, 58.31; H, 8.39%. Compound 13 was an oil: NMR δ = 1.15 (3H, d, J = 6.5 Hz, CH₃-5), 1.4–2.3 (2H, m, CH₂-4), 3.2–3.5 (2H, m, H-2 and 3), 3.46 (3H, s, OCH₃), 3.85 (1H, m, H-5) and 4.92 (1H, d, J₆,₇ = 3 Hz, H-1).

8) Methyl 2,3,4,6-Tetrahydroxy-a-d-glycerohex-2-ene-napynoside (14).

To a solution of 12 (57 mg) in 90%aq. 2-methoxyethanol (1.1 ml) was added 80% potassium selenocyanate (150 mg), and the mixture refluxed for 20 min. After cooling, the mixture was poured into water (5 ml) and the product extracted with dichloromethane (6 ml x 3). The combined extracts were washed with water, dried (MgSO₄), and evaporated.

The residue was chromatographed on a column of silica gel (3 g) with dichloromethane-chloroform (4:1) to give an oil of 14 (21 mg, 42%); [α]D = 48° (c 2.0, CHCl₃); NMR δ = 1.25 (3H, d, J = 6.5 Hz, CH₃-5), 1.7–2.2 (2H, m, CH₂-4), 3.45 (3H, s, OCH₃), 4.00 (1H, m, H-5), 4.87 (1H, dd, J = 1 and 3 Hz, H-1), 5.74 (1H, m, H-2) and 6.01 (1H, dt, J₆,₇ = 10 Hz, J₆,₇ = 4 Hz, H-3).

Found: C, 65.42; H, 9.25%. Caled for C₉H₁₅O₂: C, 65.59; H, 9.44%. Compound 13 was treated with potassium selenocyanate in a similar manner as above, except for a 2-h reaction time, to give 14 in 23% yield.

9) Methyl (R)-7-Hydroxy-4Z-2-oxo-4Z-acteolide (16).

A suspension of 14 (69 mg) in a mixture of 1 M hydrochloric acid (0.38 ml) and 50% acq acetone (3.4 ml) was stirred at room temperature for 2 min. The resulting solution was then neutralized with NaHCO₃ (90 mg) and extracted with dichloromethane (2 ml x 6). The combined extracts were dried (Na₂SO₄) and evaporated to give a crude oil of 15 (56 mg), which on TLC with chloroform–acetone (9:1) gave an Rf of 0.54: NMR δ = 1.23 and 1.24 (3H in total, d, J = 6.5 Hz, CH₃-5), 1.58 (1H, sharp m, OH), 1.6–2.3 (2H, m, CH₂-4), 3.7–4.3 (1H, m, H-5), ~5.4 (1H, m, H-1) and 5.5–6.2 (2H, m, H-2 and 3).

To a solution of the oil (56 mg) in benzene (1.0 mg) was added methoxycarbonylmethylenetriphenylphosphorane (180 mg), and the mixture was refluxed for 3 h, after which time TLC (chloroform–acetone = 9:1) indicated that the Wittig reaction was complete to give a single product (Rf 0.46). The solvent was evaporated, and the residue extracted with pentane (5 ml) under reflux for 30 min. After cooling, the pentane solution was decanted and evaporated. The residue was chromatographed on a column of silica gel (3 g) with chloroform–acetone (9:1), followed by chromatography on a column of alumina (Woelm neutral, 10 g) with chloroform, to give an oil of 16 (71 mg, 77%): [α]D = +5.2° (c 2.0, CHCl₃); IR (CHCl₃) 3420 (OH), 1720, 1710 (C=O), 1640, 1605 cm⁻¹ (C=C=O=C); UV max (CH₃OH) 265 nm (ε 20,600); NMR δ = 1.24 (3H, d, J = 6.5 Hz, CH₃-7), 1.84 (1H, s, OH), 2.50 (2H, t with a little long-range coupling, J = 6.5 Hz, CH₆-1), 3.79 (3H, s, COOCH₃), 3.95 (1H, sextet, H-7), 5.7–6.2 (1H, m, H-5), 5.95 (1H, d, J₆,₇ = 15 Hz, H-2), 6.32 (1H, t, J₆,₇ = 10.5 Hz, H-4) and 7.65 (1H, dd, H-3).

Found: C, 63.39; H, 8.10%. Caled for C₉H₁₅O₂: C, 63.51; H, 8.29%.

The authors are grateful to Emeritus Professor Sumio Umezawa for his helpful discussions and Mr. Saburo Nakada for the elemental analyses. This investigation was assisted in part financially by the Naito Research Grant for 1977.

References