A Concise and General Method for Doubly Attaching 2-Ketosugars to Aglycon Diols: Synthesis of the Gomphosides and of Spectinomycin

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Experimental Section

General. Melting points, determined with a Bock hot-stage microscope, are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20 °C using a cell of 1 dm path length; concentration (c) in g/100 mL and solvent are given in parentheses. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ARX-300 spectrometer in the solvents given. Mass spectra were acquired on Varian MAT 311 and MAT 212 spectrometers. Microanalyses were determined on a Perkin-Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F$_{254}$) with detection by UV (254 nm) and/or spraying with H$_2$SO$_4$ (50 %) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70-230 mesh) using the specified eluents. Donor 10 was prepared from hydroxyglucal ester 9 either by the 3-step procedure previously reported,[11] or by the modified version thereof given below, combining the first two steps into one continuous operation.

(1,3-di-O-benzoyl-4,6-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) [(2S,6R)-2,4-Bis(benzoyl oxy)-6-methyl-2H-pyran-3(6H)-one] (10a). Dry chlorine gas was slowly passed through a stirred and cooled (-20 °C) solution of 10.0 g (22 mmol) of 3,4-di-O-benzoyl-2-benzoyloxy-6-deoxy-D-glucal (9) in toluene (200 mL) that contained 3 mL of water. Upon reaching a pale yellow solution (5 – 10 min), stirring was continued at room temp. (20 min) followed by evaporation to dryness in vacuo. The resulting amorphous residue, consisting of the anomeric ulose hydrates (9a, majorily the β-anomer, $R_f = 0.12 – 0.24$ in CHCl$_3$/CH$_2$Cl$_2$, 5:1) and about 10 % of the manno-1,2-dichloride ($R_f = 0.77$), from which 9a may be secured in crystalline form as the monohydrate (47 %). For a more straightforward acquisition of donor 10, the mixture as such was subjected to elimination of benzoic acid by dissolution in benzene (200 mL), addition of NaHCO$_3$ (15 g) and water (5 mL), and heating under reflux with stirring for 1.5 h. After cooling, MgSO$_4$ was stirred into the mixture (30 min) and the inorganic salts were filtered off. Evaporation to dryness in vacuo followed by two co-evaporations from ethanol left a syrup which crystallized from ethanol (30 mL) on standing for ca. 12 h in a refrigerator: 3.95 g (51 %) of enolone dibenzoate 10a as colorless needles with m.p. 82 – 83 °C, and $[\alpha]_{D}^{22} = -89$ (c = 1, CHCl$_3$). A second crop (0.78 g, 10 %) was secured from the mother liquor, which also contained the well soluble manno-dichloride. $^1$H NMR data for 10a:[11].

3-O-Benzoyl-4,6-dideoxy-α-D-glycero-hex-3-enopyranosyl-chloride [(2R,6R)-2-Chloro-4-benzoyloxy-6-methyl-2H-pyran-3(6H)-one] (10). Enolone dibenzoate 10 (2.40 g, 6.8 mmol) was gradually added with stirring to 65 mL of acetyl chloride presaturated with HCl gas and the mixture was stood at room temp. for 12 h followed by evaporation in vacuo. The resulting syrup was co-evaporated twice from benzene for removal of traces of acetyl chloride and subsequently crystallized by dissolution in ether and addition of n-pentane to turbidity. After standing at 0 – 5 °C for 1 d the colorless crystals were collected: 1.15 g (63 %) of 10 with m.p. 90 – 92 °C and $[\alpha]_{D}^{22} = +151$ (c = 1, CHCl$_3$). A second crop (600 mg, 11 %) was similarly isolated from the mother liquor. $^1$H NMR data cf. ref. [11].
(2R,3R,4S,4aS,5aR,9aR,10aS)-3,4-Bis(benzoyloxy)-4a-hydroxy-2-methyl-decahydro-2H-pyrano[2,3-b][1,4]benzodioxin (14): A mixture of [R,R]-1,2-cyclohexanediol (232 mg, 2 mmol), Ag₂CO₃ (552 mg, 2 mmol), freshly desiccated molecular sieves (4 Å) and CH₂Cl₂ (50 mL) was stirred for 15 min at ambient temperature, followed by addition of ulosyl bromide 11[12] (867 mg, 2 mmol). Stirring was continued for 18 h with the exclusion of light and moisture, followed by filtration through kieselgur and evaporation of the filtrate to dryness in vacuo to afford 14 as uniform (TLC) syrup (810 mg, 87 %), suitably pure for its conversion into 16. Further purification by elution from a silica gel column (2 x 15 cm) with toluene/EtOAc (4:1) and trituration of the syrup obtained on evaporation of the eluate to dryness with ether n-hexane gave 14 as colorless crystals. M.p. 167-168 °C; [α]₂₀°D = −79.9 (c = 0.7, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.38 (d, J = 6.1 Hz, 3H, CH₃), 3.90 (3H-m, 2-H, 5a-H, 9a-H), 4.84 (s, 1H, 10a-H), 5.14 (d, 1H, J₃,₄ = 9.7, 4-H), 5.27 (s, 1H, OH), 5.50 (dd, J₂,₃ = 9.8, J₃,₄ = 9.7 Hz, 1H, 3-H), 7.2-8.1 (m, 10H, 2 C₆H₅). ¹³C NMR (75.5 MHz, CDCl₃): δ = 17.5 (CH₃), 21.7 (C-7, C-8), 29.7, 29.8 (C-6, C-9), 70.1 (C-2), 72.2, 72.3, 72.5 (C-3, C-5a, C-9a), 79.0 (C-4), 92.1 (C-4a), 96.2 (C-10a), 165.6, 168.3 (BzCO). MS (FD, 15 mA): m/z (%) = 468 (100 [M⁺]). C₂₆H₂₈O₈ (468.48): calcd. C 66.65, H 6.02; found C 66.58, H 5.93.
(2R,4aS,5aR,9aR,10aS)-4a-Benzoyloxy-2-methyl-decahydro-2H-pyrano[2,3-b][1,4]benzodioxin-4-one (15)

A. Glycosylation of (R,R)-1,2-cyclohexanediol with actinospectosyl chloride (10). A slurry of 12 (87 mg, 0.75 mmol), Ag₂CO₃ (210 mg, 0.75 mmol), freshly desiccated molecular sieve and CH₂Cl₂ (25 mL) was stirred for 15 min at 25 °C, followed by the addition of chloride 10 (215 mg, 0.8 mmol) and subsequent gentle reflux (40 °C) for 8 h. Filtration, removal of the solvent in vacuo and elution of the syrup residue from a silica gel column with toluene/EtOAc (8:1) and evaporation of the eluate to dryness afforded 210 mg of 15 (81 %, based on diol 12) as a colorless foam. Rf 0.54 (toluene/EtOAc, 8:1). [α]₂⁰D = −9.7 (c = 0.9, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.43 (d, J = 6.1 Hz, 3H, CH₃), 2.62 (dd, J = 10.0, 16.6 Hz, 1H, 3-H₃), 2.69 (dd, J = 4.0, 16.6 Hz, 1H, 3-He), 3.99 (m, 2H, 5a-H, 9a-H), 4.26 (m, 1H, 2-H), 5.45 (s, 1H, 10a-H). ¹³C NMR 75.5 MHz, CDCl₃): δ = 21.3 (CH₃), 23.9, 24.1 (C-7, C-8), 29.6, 29.7 (C-6-C-9), 45.8 (C-3), 67.1 (C-2), 71.7, 75.0 (C-5a, C-9a), 94.4, 95.7 (C-10a, C-4a), 166.1 (BzCO), 196.7 (C-4). MS (FD, 10 mA): m/z = 346 (100 %, M⁺). C₁₉H₂₂O₆ (346.37): calcd. C 65.88, H 6.40; found C 65.73, H 6.35.

B. By benzoic acid elimination in 14. To a solution of 14 (100 mg, 0.21 mmol) in dry CH₂Cl₂ (5 mL) was added tetrabutylammonium acetate (180 mg, 0.6 mmol) and the mixture was stirred for 20 h at ambient temperature. Dilution with CH₂Cl₂ (50 mL), washing with water (3 x 25 mL), drying (Na₂SO₄), evaporation to dryness in vacuo, elution of the residue from a short silica gel column with toluene/EtOAc (4:1) gave 62 mg (85 %) of 15 as a chromatographically uniform syrup, identical with the product described above.
(2R,4aR,5aR,9aR,10aS)-4a-Hydroxy-2-methyl-decahydro-2H-pyano[2,3-b][1,4]benzodioxin-4-one (16)

A. Exposure of 14 to nBu₄NOAc in moist acetonitrile. To a solution of 14 (250 mg, 0.53 mmol) in acetonitrile (20 mL) was added tetrabutylammonium acetate (490 mg, 1.6 mmol) and 5 drops of water and the mixture was stirred for 20 h at ambient temperature. Dilution with CH₂Cl₂ (100 mL), washing with water (3 x 30 mL), drying (Na₂SO₄), evaporation to dryness in vacuo, and purification of the syrupy residue by elution from a silica gel column (0.5 x 15 cm) with toluene/EtOAc (4:1) afforded 105 mg (81 %) of 16 in the form of colorless crystals. M.p. 92-94 °C. [α]D²⁰ = −28.4 (c = 1.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 1.43 (d, J = 6.1 Hz, 3H, CH₃), 2.46 (dd, J = 2.0, 14.2 Hz, 1H, 3-H_e), 2.84 (dd, J = 11.8, 14.2 Hz, 1H, 3-H_a), 3.75 (ddd, J = 2.0, 6.1, 11.8 Hz, 1H, 2-H), 4.42 (4a-OH), 4.65 (s, 1H, 10a-H). ¹³C NMR (75.5 MHz, CDCl₃): δ = 21.5 (C-H₃), 24.1, 24.3 (C-7, C-8), 29.8 (C-6, C-9), 44.7 (C-3), 67.6 (C-2), 72.6, 72.8 (C-5a, C-9a), 91.0 (C-4a), 97.3 (C-10a), 202.0 (C-4). MS (FD, 20 mA): m/z = 242 (100 %) [M⁺]. C₁₂H₁₈O₅ (242.26): calcd. C 59.49, H 7.49; found C 59.39, H 7.45.

Racemic 16 has previously been obtained in non-crystalline form (11 mg) via elaboration of the pyranoid portion through an aldehyde/diene cycloaddition approach. While the ¹H NMR chemical shifts reported correlate well with ours, the coupling constants show distinct differences, i.e. J₂,Me = 7.5, J₂,3e = 3.3, J₂,3a = 12.1, J₃e,3a = 14.6 Hz (numbering used by us) versus 6.1, 2.8, 11.8 and 14.2 Hz found by us.

B. De-O-benzoylation of 15. K₂CO₃ (28 mg, 0.2 mmol) was added to a solution of benzoate 15 (70 mg, 0.2 mmol) in MeOH (2.5 mL) followed by stirring for 15 min at ambient
temperature. Dilution with CH$_2$Cl$_2$, and processing as described under A gave 43 mg (87 %) of 16.

Glycosylation of gomphogenin (17) with ulosyl bromide 11. Ag$_2$CO$_3$ (220 mg, 0.8 mmol) and freshly desiccated molecular sieve 4 Å (300 mg) was added to a solution of 17$^{[15]}$ (156 mg, 0.4 mmol) in CH$_2$Cl$_2$ (15 mL) and the mixture was stirred for 15 min at ambient temperature, followed by the addition of ulosyl bromide 11 (175 mg, 0.4 mmol). After continued stirring for 16 h under exclusion of light and moisture, the mixture was filtered through kieselgur. Evaporation of the filtrate in vacuo gave a solid residue consisting of an approximate 3:1 mixture of 18 and 19 ($^1$H NMR, including small amounts of unreacted 17), which was subjected to separation by preparative HPLC (Lichrosorb RP-C$_{18}$, 5 µm, 25 x 2.5 cm, acetonitrile/water 50:50, 1 mL/min).

The main fraction with $R_f = 0.43$ (toluene/EtOAc, 1:1) upon evaporation to dryness afforded 180 mg (61 %) of the naturally linked isomer 18. M.p. 183-185 °C (CHCl$_3$), $[\alpha]_D^{20} = -37.3$ (c
= 1.2, CHCl₃). ¹H NMR (500 MHz, CDCl₃), sugar portion: δ = 1.36 (d, J = 6.1 Hz, 3H, 6'-H₃), 3.81 (sx, J₄,₅ = 9.8, J₅,₆ = 6.1 Hz, 1H, 5'-H). 4.82 (s, 1H, 1'-H), 5.12 (d, J₃,₄ = 9.8 Hz, 1H, 3'-H), 5.35 (s, 1H, 2'-OH), 5.45 (dd, J₃,₄ = 9.7, J₄,₅ = 9.8 Hz, 1H, 4'-H); steroid portion: δ = 0.84 and 0.86 (two 3H-s, 18-H₃, 19-H₃), 2.77 (m, 1H, 17-H), 3.99 (ddd, J₂,₃ = 10.4, J₃,₄ = 4.7, 10.9 Hz, 1H 3-H), 4.12 (ddd, J₁,₂ = 4.3, 11.7, J₂,₃ = 10.4 Hz, 1H, 2-H), 4.77 and 4.97 (two 1H-dd, J = 1.4 and 18.1 Hz, 21-H₂), 5.85 (s, 1H, 22-H). ¹³C NMR (75.5 MHz, CDCl₃), sugar portion: δ = 17.7 (6'-CH₃), 70.3 (C-5'), 72.5 (C-4'), 79.7 (C-3'), 92.5 (C-2'), 96.7 (C-1'); steroid portion: 13.9 (C-18), 16.0 (C-19), 21.6 (C-11), 27.1, 27.6, 27.9 (C-6, C-7, C-16), 32.3, 33.3 (C-4, C-15), 38.2 (C-10), 40.0 (C-12), 41.2 (C-8), 42.3 (C-1), 45.1 (C-5), 49.7 (C-13), 50.0 (C-9), 51.0 (C-17), 69.3 (C-2), 73.2, 73.6 (C-3, C-21), 85.6 (C-14), 117.9 (C-22), 165.8, 168.8 (BzCO), 174.7 (C-23). MS (FD, 25 mA): m/z = 743 (100 %, M⁺). C₄₃H₅₀O₁₁ (742.8): calcd. C 69.52, H 6.78; found C 69.49, H 6.88.

The minor fraction, Rᵣ = 0.47 (toluene/EtOAc, 1:1) gave upon removal of the solvents a solid residue which crystallized on trituration with CHCl₃: 42 mg (14 %) of 19 as colorless crystals. M.p. 204-206 °C. [α]₂₀ D = −44.2 (c = 1.3, CHCl₃). ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR data were identical within 0.1-0.2 ppm with those obtained for 18, the only notable difference being the chemical shift for 3-H (3.94 in 19 vs. 3.99 in 18). MS (FD, 25 mA): m/z = 743 (100 %, M⁺). C₄₃H₅₀O₁₁ (742.8): calcd. C 69.52, H 6.78; found C 69.61; H 6.85.

3'-Didehydrogomphoside (3)

A. From 18 via elimination of benzoic acid and hydrolysis:

To a solution of 18 (75 mg, 0.1 mmol) in acetonitrile (10 mL) was added tetrabutylammonium acetate (100 mg, 0.33 mmol) and 1 drop of water, and the mixture was stirred for 15 h at ambient temperature, whereafter complete conversion into 3 had occurred (Rᵣ = 0.43 → 0.30,
toluene/EtOAc, 1:1). Evaporation to dryness in vacuo (bath temperature < 30 °C), filtration through a short silica gel column with toluene/EtOAc (1:1), removal of the solvents, trituration of the residue with EtOAc (5 mL) and standing in the open overnight gave 46 mg (89 %) of 3 as colorless needles. M.p. 300-301 °C (partial dec.); [α]_D^20 = 8.7 (c = 0.5, CDCl₃).

Lit.[¹] m.p. 302-304 °C; no rotational data. \(^1\)H NMR (500 MHz, CDCl₃) sugar portion: \(\delta = 1.41 \) (d, \(J_{5',6'} = 6.1\) Hz, 3H, 6'-H₃), 2.46 (dd, \(J_{4'e,5'} = 1.9, J_{4',4'} = 14.2\) Hz, 1H, 4'-He), 2.78 (dd, \(J_{4'a,5'} = 11.8, J_{4',4'} = 14.2\) Hz, 1H, 4'-Ha), 3.74 (ddd, \(J_{4',5'} = 1.9\) and \(J_{5',6'} = 6.1\), 1H, 5'-H), 4.11 (m, 2H, 2-H, 3-H), 4.39 (s, 1H, 2'-OH), 4.64 (s, 1H, 1'-H); other data in the steroid portion correlated closely to those observed in 18 (vide supra). The \(^{13}\)C NMR data obtained matched those previously reported for the Asclepia fruticosa-derived product[¹] within 0.1-0.2 ppm. MS (EI): \(m/z = 516.2721\); calcd. for C₂₉H₄₀O₈: 516.2722.

B. Glycosylation of gomphogenine (17) with ene-ulosyl chloride 10 and subsequent de-O-benzoylation:

\[\begin{align*}
10 & \quad 17 \\
\text{Ag}_2\text{CO}_3 & \text{CH}_2\text{Cl}_2
\end{align*}\]

\[\begin{align*}
20 & \quad 28 \\
3 & \quad 29
\end{align*}\]

R = Bz  \quad R = H
A mixture of 17 (115 mg, 0.3 mmol), Ag₂CO₃ (220 mg, 0.8 mmol), and freshly desiccated molecular sieve 4 Å (200 mg) and CH₂Cl₂ (10 mL) was stirred for 20 min at ambient temperature, followed by the addition of ene-ulosyl chloride 10 (190 mg, 0.7 mmol) and gentle refluxing (bath temp. 40 °C) for 3 h. Filtration, evaporation of the filtrate to dryness and elution of the residue from a short silica gel column with toluene/EtOAc (1:1) gave upon removal of the solvents an amorphous solid (160 mg, 90 % based on 17), consisting of an approximate 3:1 mixture of 20 and its unnaturally linked isomer 28. Separation of 20/28 on silica gel being capricious and unfavourable due to partial de-O-benzoylation on the column, the mixture was dissolved in MeOH (5 mL) and stirred with K₂CO₃ (35 mg) for 20 min for saponification of the benzoate. The reaction mixture was partitioned between CH₂Cl₂ (10 mL) and water (10 mL), the aqueous layer was extracted twice with 10 mL portions of CH₂Cl₂, the combined organic phases were dried (Na₂SO₄) and evaporated to dryness. The amorphous residue was subjected to reversed phase column chromatography (Lichrosorb RP-C₁₈, 5 µm, 2.5 x 25 cm column) with 1 mL/min acetonitrile/water (1:1) as the eluant. Collection of the main fraction (RF = 0.48, toluene/EtOAc 1:1), removal of the solvents in vacuo and slurrying the residue with EtOAc gave well filtrable crystals: 84 mg of 3 (55 %, based on 17), identical in all respects with the product described under A.

Gomphoside (1): A solution of 3′-didehydrogomphoside 3 (52 mg, 0.1 mmol) in a mixture of MeOH-water-acetic acid (90:5:5) was hydrogenated over 500 mg of 5 % Rh-C catalyst at 3 atm for 24 h. The catalyst was removed by filtration, the filtrate was taken to dryness in vacuo, and the residue was chromatographed on silica gel (1.6 x 20 cm column) with EtOAc/toluene (2:1) to afford 1 as colorless crystals (42 mg, 67 %) of m.p. 235-238 °C and [α]₂₀ D = 15.9 (c = 1, MeOH); lit.[¹⁷] m.p. 234-242 °C and [α]₂¹ D = 16.3 ± 2 (c = 1.09, MeOH).

³¹H NMR (300 MHz, CDCl₃/DMSO-d₆ 10:1): δ = 1.24 (d, J = 6.1 Hz, 3H, 6′-Me), 3.69 (t, J₃′,₄′ = 3.1 Hz, 1H, 3′-H), 3.94 (m, 1H, 2-H), 4.08 (m, 2H, 3-H, 5′-H), 4.78 (s, 1H, 1′-H), other aglycon protons as in 18. ³¹C NMR data correlated closely (deviations within 0.2 ppm) with
those reported for the *Asclepias fruticosa*-derived product.\textsuperscript{[2b]} MS (FD, 25 mA): \textit{m/z} = 519 (M$^+$+1).

\begin{center}
\includegraphics[width=\textwidth]{structure.png}
\end{center}

\textbf{3'-epi-Gomphoside (2):} NaBH$_4$ (10 mg, 0.25 mmol) was added to an ice-cooled solution of 3 (50 mg, 0.097 mmol) in carefully dried\textsuperscript{[4]} MeOH (5 mL), the mixture was stirred for 5 min at ambient temperature, then poured into water (25 mL) and extracted with CH$_2$Cl$_2$ (2 x 15 mL). The combined extracts were dried (Na$_2$SO$_4$), freed of the solvent in vacuo, and the residue was purified on silica gel (1.5 x 20 cm column) by elution with EtOAc/toluene (2:1). The appropriate eluates ($R_f$ = 0.41, EtOAc) were evaporated in vacuo, followed by trituration of the residue with CH$_2$Cl$_2$/MeOH: 39 mg (79 \%) of 2 as colorless crystals. M.p. 189-191 °C;\textsuperscript{[17]} [$\alpha$]$_D^{20}$ = +37.2 (c = 0.5, MeOH). $^1$H NMR (300 MHz, CDCl$_3$): \(\delta = 1.28\) (d, J = 6.2 Hz, 3H, 6'-H$_3$), 3.60-3.72 (m, 2H, 3'-H, 5'-H), 3.95, 4.11 (two 1H-m, 2-H, 3-H), 4.60 (s, 1H, 1'-H), other aglycon protons as in 18. $^{13}$C NMR (75.5 MHz, CDCl$_3$) correlated within 0.2-0.3 ppm deviations with those reported\textsuperscript{[4]} for natural 2 in 10:1 CDCl$_3$/CD$_3$OD. C$_{29}$H$_{42}$O$_8$: CH$_2$Cl$_2$ (603.59): calcd. C 59.70, H 7.35; found C 58.99, H 7.08.

Crystals suitable for X-ray analysis were obtained by addition of ether to a CH$_2$Cl$_2$/MeOH solution and standing overnight, allowing for slow evaporation at ambient temperature. Crystal size: 0.55 x 0.08 x 0.05 mm; $M_r$= 603.62; orthorhombic, space group P212121; \(a = 12.234\) (3), \(b = 13.002\) (2), \(c = 18.619\) (2) Å, \(\alpha = \beta = \gamma = 90^\circ\), \(V = 2961.7\) (9) Å$^3$; $\zeta_{\text{calc}}$ = 1.349 Mgm$^{-3}$; MoK$_\alpha$ radiation. \(\lambda = 0.71069\) Å; \(T = 293\) K; 3706 independent of 3508 measured

\begin{footnotesize}
\textsuperscript{*} Aqueous MeOH gives rise to substantial further reduction involving the 2'-carbonyl due to base-induced hemiketal opening.
\end{footnotesize}
reflections $R_{int} = 0.0363$; refinement method: full matrix leastsquares on $F^2$. For a stereoplot see Figure 2; for crystal packing clearly revealing the presence of 1 mole of $\text{CH}_2\text{Cl}_2$: Figure 3.
Figure 3. Unit cell ($Z = 4$) and anisotropic thermal ellipsoids with and without hydrogen atoms of 3’-epi-gomphoside (2). The lactone ring and the solvent of crystallization (CH$_2$Cl$_2$) are disordered.

These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).