# Preparation of 2-Deoxy-β-C-arylglycosides and C-Arylglycals from Carbohydrate Lactones

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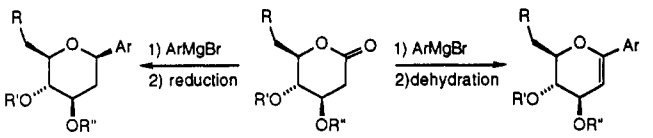
A common structural feature to several groups of antitumor antibiotics such as the rubiflavins,[1,2] gilvocarcins,[1,3] and the urdamycins[1,4] is the C-arylglycosidic linkage. These classes of natural products display significant biological activity; consequently, an assortment of methods have been developed for the preparation of a carbon–carbon bond between the anomeric center of a carbohydrate unit and an aromatic ring. These synthetic strategies can be divided into two catagories based upon (i) construction of C-arylglycals[5] and (ii) the stereoselective preparation of β-C-arylglycosides.[6] The advantage of the former approach is the potential for further synthetic manipulation of the resultant enol ether, whereas the latter approach is more direct.

As part of a program directed toward the preparation of structural analogues of the angucycline antibiotics, we became interested in developing a method which would allow accessibility to either C-arylglycals or C-arylglycosides depending upon the choice of reaction conditions. Herein we report a procedure which can be adjusted to give C-arylglycosides or C-arylglycals. Specifically, addition of an aryl Grignard reagent to a sugar lactone followed by reduction provides 2-deoxy-β-C-arylglycosides, while Grignard addition–dehydration yields C-arylglycals.

It has been demonstrated previously that aryl organometallic reagents add to sugar lactones in high yield.[7] Furthermore, Kraus[6f] has reported that the reduction of




hemiketals resulting from the addition of organometallic reagents to tetrabenzylgluconolactone with $BF_3$·$OEt_2$/$Et_3$SiH provides the corresponding C-glycoside in good yield. When this procedure was applied to hemiketals produced from 2-deoxysugars, Tius and co-workers[5d] observed exclusive formation of the corresponding C-arylglycal. Subsequent reduction of this glycal with $Na(CN)BH_3$ at pH 4.5 provided the corresponding β-C-arylglycoside in good yield. We anticipated, based upon these observations, that direct reduction of the intermediate hemiketal would afford the corresponding β-C-arylglycoside. Indeed, treatment of 2,6-dideoxy-3,4-dibenzylgluconolactone[8] (entry a) with phenylmagnesium chloride (2 M in THF, 5 equiv) in THF at −78 °C for 0.5 h provided the corresponding addition product as a 1.7:1 mixture of hemiketal and its open-chain tautomer. Without purification, the crude product was treated with sodium cyanoborohydride in ethanol at 50 °C for 1 h while the pH of the reaction mixture was maintained at 4.5.[9] This two-step procedure provided β-C-phenylglycoside 1 in 91% overall yield after purification. The assignment of a β configuration was based upon the observed 11.2- and 1.8-Hz coupling constants of the C1 proton to the C2 axial and equatorial protons, respectively.

As part of our synthetic effort directed toward the urdamycin antibiotics, we required the preparation of a β-C-naphthylglycoside 3. First, bromonaphthalene 8 was prepared according to the procedure outlined in Scheme I. Next, metal–halogen exchange of the bromonaphthalene 8 followed by the addition of 2,6-dideoxy-3,4-dibenzylgluconolactone provided hemiketal 9. Reduction of hemiketal 9 under the previously described conditions provided the desired naphthylglycoside 3 in 70% yield (entry c).

Alternatively, dehydration of the intermediate hemiketal provides the corresponding C-arylglycal. We examined several dehydration protocols and found Martin sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$) to be the reagent of choice.[10] In general, the aryl Grignard addition product was treated with 5 equiv of Martin sulfurane in dichloromethane. After 30 min, the reaction mixture was concentrated and purified by flash chromatography. This simple procedure provided the corresponding C-arylglycal in good overall yield (entries d and e). The yield of this process compares favorably to that of palladium-mediated coupling reactions.[5a,d] In summary, we have developed two simple two-step procedures for the preparation of β-C-arylglycosides and C-arylglycals starting from readily available sugar lactones.

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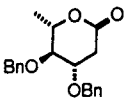
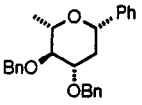
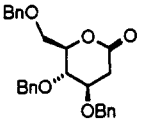
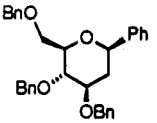
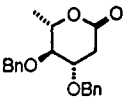
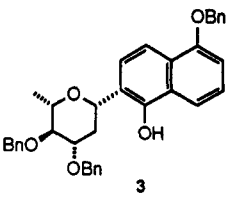
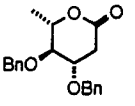
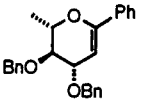
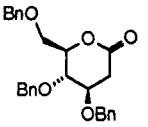
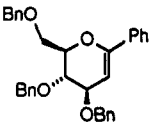
0022-3263/93/1958-3191$04.00/0 

**Table I**

| entry | starting lactone | product | yield |
|---|---|---|---|
| a |  |  1 | 91% |
| b |  |  2 | 75% |
| c |  |  3 | 70% |
| d |  |  4 | 86% |
| e |  |  5 | 87% |

## Experimental Section

**Materials and Methods.** All reactions were carried out under a nitrogen atmosphere using dry, freshly distilled solvents and oven-dried glassware, unless otherwise noted. Tetrahydrofuran was distilled from sodium/benzophenone; dichloromethane was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. $^1$H and $^{13}$C NMR data are reported as $\delta$ values relative to tetramethylsilane. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center by David Jacobs on a VG 70S spectrometer.

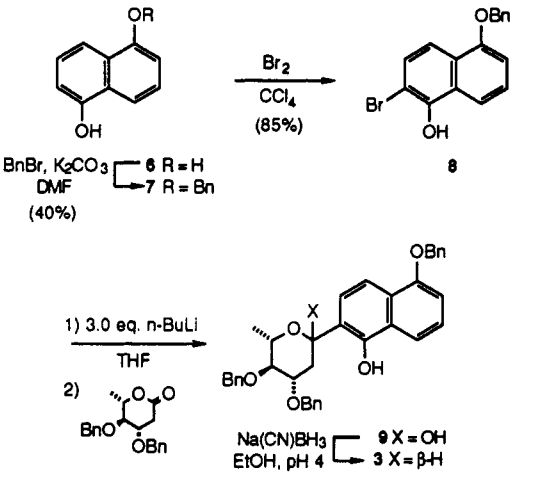
**General Procedure for the Preparation of 2-Deoxy-β-*C*-phenylglycosides.** Under nitrogen, a 2 M solution of phenylmagnesium chloride in tetrahydrofuran (0.40 mL, 0.80 mmol) was added dropwise to a solution of 3,4-di-*O*-benzyl-2,6-dideoxy-D-gluconolactone (50 mg, 0.15 mmol) in tetrahydrofuran (1 mL) at −78 °C. After 30 min, a saturated solution of ammonium chloride (3 mL) was added. The mixture was extracted three times with diethyl ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Without purification, the product was dissolved in absolute ethanol (1 mL) followed by the addition of sodium cyanoborohydride (58 mg, 0.92 mmol) and Bromocresol Green indicator (~5 mg). The pH of the solution was adjusted to 4.5 by the addition of methanolic HCl as indicated by the persistence of a yellow color (pH <4.5). The mixture was heated to 50 °C and the pH maintained below 4.5 by the intermittent addition of methanolic HCl. After 1 h, the reaction was allowed to cool to room temperature and saturated sodium bicarbonate solution added. The mixture was extracted three times with diethyl ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography with hexane–ethyl acetate (10:1) to afford 55 mg (91%) of phenylglycoside 1 as a white solid: mp 174–177 °C; $[\alpha]^D_{20}$ −3.92° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) 2927, 2864, 1600, 1444, 1358, 1294, 1074 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.40–7.20 (m, 15H), 5.05–4.60 (m, 4H), 4.39 (dd, $J$ = 11.2, 1.8 Hz, 1H), 3.80 (m, 1H), 3.52 (qd, $J$ = 8.4, 5.0 Hz, 1H), 3.20 (app t, $J$ = 8.9 Hz, 1H), 2.40 (ddd, $J$ = 12.8, 5.0, 1.9 Hz, 1H), 1.74 (ddd, $J$ = 12.9, 11.4, 11.0 Hz, 1H), 1.38 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 141.73, 138.79, 138.73, 128.56, 128.46, 128.22, 128.15, 127.96, 127.81, 127.75, 126.13, 84.15, 81.04, 77.29, 75.72, 75.34, 71.33, 39.11, 18.45; high-resolution mass spectrum (EI) $m/z$ 388.2018 [(M)$^+$, calcd for $C_{26}H_{28}O_3$ 388.2038].

**2**: mp 69–71 °C; $[\alpha]^D_{20}$ + 23.7° (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 2993, 2870, 1952, 1877, 1812, 1601, 1444, 1357, 1299, 1066 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.41–7.24 (m, 20H), 4.96 (d, $J$ = 10.8 Hz, 1H), 4.80–4.56 (m, 5H), 4.42 (dd, $J$ = 11.1, 2.7 Hz, 1H), 3.90–3.50 (m, 5H), 2.38 (m, 1H), 1.75 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 141.61, 138.64, 128.43, 128.11, 127.81, 127.70, 127.56, 126.01, 81.15, 79.41, 78.30, 77.44, 75.01, 73.35, 71.27, 69.51, 39.02; high-resolution mass spectrum (EI) $m/z$ 494.2482 [(M)$^+$, calcd for $C_{33}H_{34}O_4$ 494.2457].

**3**: mp 120–121 °C; $[\alpha]^D_{20}$ −7.0° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 3359, 3056, 2982, 2928, 2874, 1951, 1733, 1597, 1355, 1177, 1099 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.73 (s, 1H), 7.84 (dd, $J$ = 15.3, 8.6 Hz, 2H), 7.50 (d, $J$ = 3.6 Hz, 1H), 7.45–7.20 (m, 15H), 6.95 (d, $J$ = 8.6 Hz, 1H), 6.86 (d, $J$ = 7.6 Hz, 1H), 5.19 (s, 2H), 5.00 (d, $J$ = 10.8 Hz, 1H), 4.75 (dd, $J$ = 11.6, 1.4 Hz, 1H), 4.70 (d, $J$ = 11.0 Hz, 2H), 4.60 (d, $J$ = 11.6 Hz, 1H), 3.77 (m, 1H), 3.59 (m, 1H), 3.27 (app t, $J$ = 8.9 Hz, 1H), 2.43 (m, 1H), 1.97 (app q, $J$ = 12.6 Hz, 1H), 1.43 (d, $J$ = 6.1 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 154.16, 150.67, 138.29, 137.16, 128.54, 128.43, 128.13, 127.86, 127.82, 127.63, 127.34, 126.62, 126.26, 125.23, 123.54, 118.12, 114.66, 113.67, 105.83, 83.44, 80.35, 79.34, 75.47, 71.36, 70.06, 37.71, 18.65; high-resolution mass spectrum (EI) $m/z$ 560.2583 [(M)$^+$, calcd for $C_{37}H_{36}O_5$ 560.2563.

**General Procedure for the Preparation of 2-Deoxy-*C*-phenylglycals.** Under nitrogen, a 2 M solution of phenylmagnesium chloride in tetrahydrofuran (0.40 mL, 0.80 mmol) was added dropwise to a solution of 3,4-di-*O*-benzyl-2,6-dideoxy-D-gluconolactone (50 mg, 0.15 mmol) in tetrahydrofuran (1 mL) at −78 °C. After 30 min, a saturated solution of ammonium chloride (3 mL) was added. The mixture was extracted three times with diethyl ether, and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Without purification, the product was dissolved in methylene chloride (0.75 mL) and cooled to 0 °C under a nitrogen atmosphere. A solution of Martin sulfurane (515 mg, 0.77 mmol) in methylene chloride (0.75 mL) was added and the mixture allowed to warm to room temperature. The reaction mixture was concentrated in vacuo when judged complete by TLC. The product was purified by flash chromatography with hexane–ethyl acetate (25:1) to afford 49 mg (86%) of phenylglycal 4: mp 71.5–73.5 °C; $[\alpha]^D_{20}$ +5.16° (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 2932, 1951, 1717, 1648, 1608, 1444, 1358, 1180, 1054, 739 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.62–7.25 (m, 15H), 5.41

**Scheme I**



(d, $J$ = 2.9 Hz, 1H), 5.00–4.50 (m, 4H), 4.40 (dd, $J$ = 6.6, 2.8 Hz, 1H), 4.13 (dq, $J$ = 9.1, 6.3 Hz, 1H), 3.59 (m, 1H), 1.50 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) 152.94, 138.55, 138.30, 134.57, 128.63, 128.43, 128.13, 128.00, 127.77, 127.64, 125.17, 96.26, 79.58, 77.54, 74.39, 73.94, 70.54, 17.59; high-resolution mass spectrum (EI) $m/z$ 386.1898 [$(M)^+$, calcd for $C_{26}H_{26}O_3$ 386.1882].

5: $[\alpha]^D_{20}$ −7.03 ($c$ 0.37, $CHCl_3$); IR ($CHCl_3$) 2994, 2920, 2866, 1648, 1599, 1446, 1358, 1031 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.61 (m, 2H), 7.50–7.25 (m, 18H), 5.43 (d, $J$ = 3.1 Hz, 1H), 4.87 (d, $J$ = 11.4 Hz, 1H), 4.80–4.50 (m, 5H), 4.39 (dd, $J$ = 6.0, 2.8 Hz, 1H), 4.26 (m, 1H), 3.98 (dd, $J$ = 6.0, 6.0 Hz, 1H), 3.90 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 152.96, 138.71, 138.48, 134.72, 128.81, 128.51, 128.48, 128.25, 128.06, 127.86, 127.79, 127.69, 125.42, 96.09, 77.36, 76.62, 74.43, 73.48, 70.45, 68.63; high-resolution mass spectrum (EI) $m/z$ 492.2319 [$(M)^+$, calcd for $C_{33}H_{32}O_4$ 492.2301].

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**Supplementary Material Available:** NMR spectra of 1–5 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.