Notes

Differentially Protected Ribofuranoid Glycals

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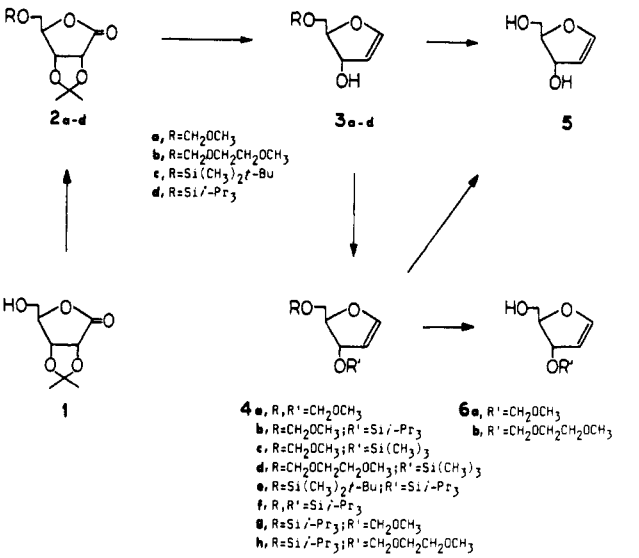
Ribofuranoid glycals are key intermediates in a palladium-mediated coupling reaction[1-6] leading to C-nucleosides[7] under study in our laboratory. Particularly important to us were ribofuranoid glycals in which the two hydroxyl groups (O-3 and O-5) bear different protecting groups which can be selectively removed. Similarly, we required ribofuranoid glycals in which one hydroxyl group was derivatized while the second remained free. Finally, the underivatized glycal 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol was needed. We report convenient procedures for the preparation of these versatile synthetic intermediates.

The general glycal synthesis procedure of Ireland[8,9] makes O-5 protected ribofuranoid glycals **3** readily available from the corresponding 2,3-isopropylidine protected ribonolactones **2** in a process involving reduction to the lactol (diisobutylaluminum hydride), formation of a ribofuranosyl chloride (carbon tetrachloride, tris(dimethylamino)phosphine), and a subsequent reductive fragmentation (lithium in ammonia).

The conditions used in the Ireland reductive fragmentation procedure[8,9] (lithium in ammonia) restrict the selection of protective groups for the 5-hydroxy function of **2**. Typically,[1,8,9] the methoxymethyl group has been used; in this study the similar (β-methoxyethoxy)methyl group[10] was also used and, in addition, the *tert*-butyldimethylsilyl and triisopropylsilyl[11] groups were employed in preparation of **2a-d** and their subsequent conversion to glycals **3a-d**.

In the synthesis of lasalocid A (X537A),[12] Ireland prepared, but did not isolate, labile 3-*O*-butyryl derivatives of 5-*O*-alkyl furanoid glycals by acylation. We[1] and others[13] have prepared 3,5-bis-O-substituted ribofuranoid glycals **4** by derivatization of **3**. 3-Alkoxy furanoid glycals have been prepared[14] by using another glycal synthesis procedure.[15] In the present study, derivatization of the free



3-hydroxyl of glycals **3a-d** produced an array of symmetrically (**4a,f**) and differentially protected (**4b-e,g,h**) 3,5-bis-O-substituted furanoid glycals.

The unprotected glycal, 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (**5**), was produced by efficient removal of silyl protective groups from **3c,d** or **4e,f** using fluoride ion.[16,17] In a similar way, silyl group removal from **4g,h** yielded the corresponding 3-O-derivatized 5-hydroxy glycals **6**.

Nuclear magnetic resonance (NMR) spectra (^1H and ^{13}C) for the glycals which were prepared are summarized in Table I.

Experimental Section

General Comments. Chemicals were used as received except for tetrahydrofuran which was distilled from lithium aluminum hydride under nitrogen. Thin-layer chromatography (TLC) was carried out on prescored silica gel GF plates (Analtech). For flash chromatography, silica gel 60 (230-400-mesh ASTM, E. Merck) was used. NMR spectra were obtained on a JEOL FX 90Q spectrometer and are referenced to internal tetramethylsilane. Mass spectra (EI) were obtained with a Finnegan 4023 GC/MS/DS system operating at 70 eV using a direct insertion probe. Infrared spectra were recorded with a Perkin-Elmer 283 infrared spectrophotometer. Melting points were measured with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out by Dr. G. Robertson, Florham Park, NJ. High-resolution mass spectra of glycals were performed by Dr. T. Wachs, Department of Chemistry, Cornell University. All new compounds were characterized by ^1H and ^{13}C NMR, mass and infrared spectrometry, and elemental analysis (and/or high-resolution mass spectrometry).

Synthetic Procedures. Each general procedure used in preparation of the differentially protected glycals is illustrated by using a specific example. Yields obtained in each of the procedures were good to excellent: **2** (93-99%); **3** (65-82%); **4** (63-98%); **5** (98%); **6** (88-97%).

2,3-*O*-(1-Methylethylidene)-5-*O*-(methoxyethoxymethyl)-D-ribonolactone (2b). The method of Corey[10] was used: to a precooled (ice bath) solution of **1**[18] (8.21 g, 43.6 mmol) and

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Table I. ^1H and ^{13}C Nuclear Magnetic Resonance Spectra of Glycals[a]

	^1H NMR chemical shifts (δ)						^{13}C NMR chemical shifts (δ)					
compd	H_1	H_2	H_3	H_4	H_5	other	C_1	C_2	C_3	C_4	C_5	other
3a[b]	6.52	5.14	4.72	4.43	3.39	OCH_2O, 4.63; OCH_3, 3.37	149.20	103.10	87.25	75.06	67.37	OCH_3, 54.93; OCH_2O, 96.27
3b	6.50	5.12	4.78–4.72	4.44	3.75–3.46	OCH_2O, 4.78–4.72; OCH_3, 3.35; OCH_2CH_2O, 3.75–3.46	149.65	103.00	87.51	75.43	66.92	OCH_3, 58.85; OCH_2CH_2O, 71.58, 67.90; OCH_2O, 95.91
3c	6.50	5.11	4.75	4.30	3.61	$Si(CH_3)_2$, 0.05, 0.04; $SiC(CH_3)_3$, 0.87	149.92	103.11	89.19	75.48	62.91	$Si(CH_3)_2C(CH_3)_3$, 25.81, 18.22, 5.40
3d	6.52	5.14	4.84	4.35	3.72	$SiCH(CH_3)_2$, 1.06	150.08	103.06	89.30	75.59	63.13	$SiCH(CH_3)_2$, 17.90, 11.89
4a[c]	6.56	5.14	4.86–4.82		3.60	OCH_2O's, 4.66, 4.69; OCH_3's, 3.37	150.17	101.04	85.54	81.70	67.45	OCH_2O's, 96.65, 95.35; OCH_3's, 55.42, 55.31
4b[c]	6.50	5.09	4.91	4.45	3.58	OCH_2O, 4.66; OCH_3, 3.37; $SiCH(CH_3)_2$, 1.05	148.84	103.60	87.83	76.11	67.44	OCH_3, 55.11; OCH_2O, 96.45; $SiCH(CH_3)_2$, 17.84, 12.10
4c	6.50	5.04	4.82	4.42	3.86	OCH_2O, 4.66; OCH_3, 3.56; $Si(CH_3)_3$, 0.14	149.16	103.27	87.29	75.92	67.30	OCH_3, 55.28; OCH_2O, 96.61; $Si(CH_3)_3$, 0.29
4d	6.48	5.02	4.79	4.40	3.60	OCH_2O, 4.73; OCH_2CH_2O, 3.76–3.54; OCH_3, 3.37; $Si(CH_3)_3$, 0.14	149.11	103.27	87.29	75.92	67.47	OCH_3, 58.91; OCH_2CH_2O, 71.64, 66.87; OCH_2O, 95.64; $Si(CH_3)_3$, 0.29
4e	6.48	5.06	4.93	4.33	3.62	$SiCH(CH_3)_2$, 1.07, 1.05; $Si(CH_3)_2$, 0.05; $SiC(CH_3)_3$, 0.89						
4f	6.48	5.00		4.43	3.72	$SiCH(CH_3)_2$, 1.05	149.00	103.60	89.46	75.75	63.29	$SiCH(CH_3)_2$'s, 18.00, 17.90, 12.67, 11.94
4g	6.54	5.12	4.82	4.44	3.84	OCH_2O, 4.69; OCH_3, 3.36; $SiCH(CH_3)_2$, 1.05, 1.06	150.24	100.78	86.92	81.23	62.86	OCH_2O, 94.99; OCH_3, 55.28; $SiCH(CH_3)_2$, 17.90, 11.99
4h	6.53	5.14	4.82	4.44	3.92–3.52	OCH_2O, 4.78; OCH_2CHO, 3.92–3.52; OCH_3, 3.38; $SiCH(CH_3)_2$, 1.06	150.14	100.84	86.86	81.33	62.91	OCH_3, 58.85; OCH_2CH_2O, 71.64, 66.82; OCH_2O, 93.96; $SiCH(CH_3)_2$, 17.79, 11.83
5[d]	6.53	4.93	4.54	4.08	3.34		148.44	104.02	89.23	73.79	61.49	
6a[e]	6.55	5.14	4.69	4.47	3.67	OCH_2O, 4.69; OCH_3, 3.37	150.61	101.91	88.09	81.92	62.63	OCH_3, 55.15; OCH_2O, 95.57
6b	6.53	5.13	4.73	4.49	3.79–3.48	OCH_2O, 4.77; OCH_2CH_2O, 3.79–3.48; OCH_3, 3.37	149.81	101.11	86.97	81.64	62.64	OCH_3, 58.85; OCH_2CH_2O, 71.64, 66.71; OCH_2O, 94.44

[a] Chemical shifts in ppm downfield from tetramethylsilane; spectra were recorded in $CDCl_3$ unless otherwise noted. Coupling constants for ring hydrogens of the glycals are: $J_{1,2}$ = 2.4–2.7 Hz; $J_{1,3}$ = 0.9–1.2 Hz; $J_{2,3}$ = 2.4–2.7 Hz; $J_{3,4}$ = 2.4–3.2 Hz; $J_{4,5(5')}$ = 4.5–7.3 Hz; $J_{5,5'}$ = 10.3–10.8 Hz (when R = alkylsilyl). [b] See ref 8, 9. [c] See ref 1. [d] Dimethyl sulfoxide-d_6. [e] Acetone-d_6 was used for ^{13}C spectrum.

diisopropylethylamine (11.4 mL, 65.4 mmol) in 80 mL of methylene chloride was added dropwise methoxyethoxymethyl chloride (7.47 ml, 65.4 mmol) under nitrogen. The resulting solution was allowed to warm to room temperature and stirred for 6 h. The completion of the reaction was indicated by TLC (ether, R_f(**2b**) 0.66; R_f(1) 0.65; clearly distinguished by sulfuric acid staining). After evaporation of the volatiles in vacuo, the residue was dissolved in ether, washed with saturated ammonium chloride (aq) and brine, and dried over magnesium sulfate. The dried solution was stirred with 2.5 g of silica gel for 2 min, the silica gel was removed by filtration, and concentration of the filtrate in vacuo afforded 11.25 g (93%) of **2b** as a colorless oil: IR (film) 1770 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found: C, 51.93; H, 7.42.

2,3-*O*-(1-Methylethylidene)-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]ribonolactone (2c). A mixture of 1[18] (5.20 g, 27.6 mmol), imidazole (4.70 g, 69.1 mmol), and *tert*-butyldimethylsilyl chloride (5.00 g, 33.2 mmol) in 10 mL of dimethylformamide was stirred at room temperature under nitrogen for 22 h. The product was purified with three repetitive flash chromatographic separations using ether–petroleum ether 1:1 (R_f 0.78), 1:2 (R_f 0.67), 1:6 (R_f 0.25) sequentially to give 7.79 g (93%) of **2c** as white crystalls, mp 69–70 °C. IR (film): 1770 cm^{-1} (C=O). Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.67. Found: C, 55.83, H, 8.94.

1,4-Anhydro-2-deoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-*erythro*-pent-1-enitol (3c). Using the method of Ireland et al.,[8,9] a 1 M solution of diisobutylaluminum hydride in ether (30.1 mL, 30.1 mmol) was added dropwise over 15 min to a stirred solution of **2c** (7.00 g, 23.2 mmol) in 150 mL of ether at −78 °C under nitrogen. The reaction was quenched by addition of 6 mL of methanol after 2 h, and the mixture was allowed to warm to 0 °C. The mixture was then diluted with 75 mL of ether and extracted with disodium tartrate solution (0.5 M, aq). The resulting ether extract was dried over magnesium sulfate and evaporated in vacuo to yield 6.61 g (94%) of a colorless oil which was used in the next step without further purification.

To a solution of the above oil (6.54 g, 21.5 mmol) and carbon tetrachloride (2.49 mL, 25.8 mmol) in 60 mL of dry tetrahydrofuran, under nitrogen at −78 °C, was added 4.82 mL of 85% tris(dimethylamino)phosphine (22.5 mmol). After 30 min, the temperature of the reaction mixture was allowed to rise to 0 °C; the reaction mixture was then carefully added to a preprepared solution of lithium (1.79 g, 257 mmol) in 200 mL of ammonia kept at −78 °C. After ammonia refluxing (dry ice condenser) for 2 h, ammonium chloride (13.8 g, 258 mmol) was added. Ether (500 mL) was added to the resulting suspension, the ammonia was evaporated, and magnesium sulfate (5 g) was added. Filtration to remove salts and evaporation in vacuo afforded 10.8 of crude product which was purified by repetitive flash chromatography first with ether, then with 1:2 ether–petroleum ether to give 3.20 g (65%) of **3c** as a colorless oil. Anal. Calcd for $C_{11}H_{22}SiO_3$: C, 57.35; H, 9.62. Found: C, 57.40; H, 9.82.

1,4-Andro-2-deoxy-5-*O*-(methoxyethoxymethyl)-3-*O*-(trimethylsilyl)-D-*erythro*-pent-1-enitol (4d). To a precooled (ice bath) solution of **3b** (3.92 g, 19.2 mmol) in 150 mL of tetrahydrofuran under nitrogen were added triethylamine (8.1 mL, 57.6 mmol) in one portion and trimethylsilyl chloride (3.7 mL, 28.8 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h. After evaporation of the volatiles in vacuo, the residue was dissolved in ether, washed with saturated ammonium chloride (aq) and brine, and then dried over magnesium sulfate. The crude mixture was chromatographed on silica gel with ether–petroleum ether 1:3 (R_f 0.38) to afford 4.59 g (86%) of **4d** as a colorless oil: mass spectrum, m/z (relative intensity) 276 (0.1, $M^{+\cdot}$) 187 (62, M − $CH_2OCH_2CH_2OCH_3$), 157 (22). Anal. Calcd for $C_{12}H_{24}O_5Si$: C, 52.15; H, 8.75. Found: C, 52.88; H, 8.63.

1,4-Anhydro-2-deoxy-3-*O*-(methoxymethyl)-5-*O*-[tris(1-methylethyl)silyl]-D-*erythro*-pent-1-enitol (4g). To a precooled solution of **2d** (963 mg, 3.53 mmol) and diisopropylethylamine (98%, 2.51 mL, 14.1 mmol) in 7 mL of methylene chloride was added dropwise 1.07 mL of chloromethyl methyl ether (1.07 mL, 14.1 mmol). The resulting mixture was stirred for 42 h. After evaporation of the volatiles, purification was accomplished by flash chromatography (silica gel, 1:3 ether–petroleum ether, R_f 0.80) to afford 852 mg (76%) of **4g** as a colorless oil. Mass spectrum, m/z (relative intensity) 317 (0.01, M + 1^+), 273 (0.1, M − Me_2CH). Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: 60.77; H, 10.39.

1,4-Anhydro-2-deoxy-3,5-bis-*O*-[tris(1-methylethyl)silyl]-D-*erythro*-pent-1-enitol (4f). Compound **4f** was prepared from **3d** (1.00 g, 3.7 mmol) and triisopropylsilyl chloride (0.85 g, 4.4 mmol) by using a procedure similar to that described for the preparation of **2c**. The reaction mixture was allowed to stir overnight and then subjected to flash chromatography using 1:1 ether–petroleum ether for elution to afford 1.92 g of **4f** and triisopropylsilanol. Rechromatography of this material using 1:9 ether–petroleum ether (R_f 0.92) as eluant gave 1.45 g (92%) of **4f** as an oil. Anal. Calcd for $C_{23}H_{48}O_3Si$: C, 64.4; H, 11.3. Found: C, 64.2; H, 11.4.

1,4-Anhydro-2-deoxy-D-*erythro*-pent-1-enitol (5). To a stirred, ice-cooled solution of **3d** (1.00 g, 3.67 mmol) in 60 mL of tetrahydrofuran was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3.86 mL, 3.86 mmol). The reaction was completed in 1 min based on TLC. After concentration in vacuo, the residue was chromatographed on silica gel with 2:1 ether–acetone (R_f 0.5) to afford 415 mg (98%) of **5** as an oil: mass spectrum, m/z (relative intensity) 116 (23, $M^{+\cdot}$); calcd for $C_5H_8O_3$ 116.0473, found 116.0479.

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Registry No. 1, 30725-00-9; **2a**, 72050-19-2; **2b**, 96760-89-3; **2c**, 75467-36-6; **2d**, 96760-90-6; **3a**, 72050-15-8; **3b**, 96760-91-7; **3c**, 96760-92-8; **3d**, 96760-93-9; **4a**, 86436-80-8; **4b**, 86436-81-9; **4c**, 96760-94-0; **4d**, 96760-95-1; **4e**, 96760-96-2; **4f**, 96760-97-3; **4g**, 96760-98-4; **4h**, 96760-99-5; **5**, 96761-00-1; **6a**, 96761-01-2; **6b**, 96761-02-3; methoxyethoxymethyl chloride, 3970-21-6; *tert*-butyldimethylsilyl chloride, 18162-48-6; trimethylsilyl chloride, 75-77-4; chloromethyl methyl ether, 107-30-2; triisopropylsilyl chloride, 13154-24-0.

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An Efficient Total Synthesis of Agrobactin and Its Gallium(III) Chelate

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A number of naturally occurring catecholamide iron chelators, siderophores, predicated on triamine backbones have recently been isolated and subsequently synthesized. These ligands include parabactin, isolated from *Paracoccus denitrificans*[1] and now accessible from two synthetic routes,[2,3] vibriobactin, isolated from *Vibreo cholera*[4] and recently synthesized,[5] and agrobactin, isolated from *Agrobacterium tumifaciens*[6] and as yet unavailable by synthetic methods. We now report the first synthesis of agrobactin utilizing the key intermediate ethyl 2,3-di-

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