Carbohydrate Research, 164 (1987) 59–69
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CHIRAL BUILDING BLOCKS FROM METHYL α-D-MANNOPYRANOSIDE AND METHYL α-D-GLUCOPYRANOSIDE FOR ANTHRACYCLINONE SYNTHESIS*

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(Received September 24th, 1986; accepted for publication, November 24th, 1986)

ABSTRACT

The reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranoside-3-ulose with methyllithium and ethyl- and ethynylmagnesium bromide yielded predominantly the adducts methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside, methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-ethyl-α-D-*ribo*-hexopyranoside, and methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-ethynyl-α-D-*ribo*-hexopyranoside. Similarly, methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranoside-2-ulose gave exclusively methyl 4,6-*O*-benzylidene-3-deoxy-2-*C*-ethyl-α-D-*ribo*-hexopyranoside. Potential 1,4-dialdehyde building blocks for anthracyclinone synthesis were obtained in both enantiomeric forms from these precursors.

INTRODUCTION

Anthracyclinones are the aglycones of the anthracyclines, which are important antitumor antibiotics[1]. Total synthesis has provided derivatives possessing improved pharmacological properties (namely the 4-demethoxy compounds) that are not available from natural sources[1a,2]. It has thus become increasingly important to develop syntheses yielding enantiomerically pure anthracyclinones in order to avoid the loss of material and the tedious separation procedures that are encountered with racemic material.

Some time ago we developed a synthesis for racemic aglycones such as γ-rhodomycinone (**2**) by the intramolecular Marschalk reaction[3] of the hydroxyaldehyde[4] **1**. This approach involves the condensation of aldehydes with readily available 1,4-dihydroxyanthraquinones in their hydroquinone form.

In order to obtain enantiomerically pure anthracyclinones, aldehydes from the "chiral pool" of natural products can be reacted with anthrahydroquinones. Thus, starting from glucose, Shaw *et al.*[5] have prepared anthracyclinones hydroxyl-

*Dedicated to the memory of Karl Freudenberg on the centenary of his birth.

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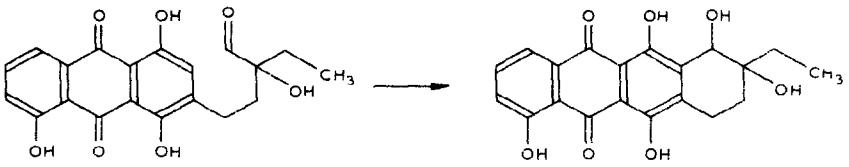

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ated at C-8 and having ethynyl side chains. The normally occurring 8-deoxy compounds, although limited to a hydroxymethyl side chain, have been synthesized from lactose by Monneret *et al.*[6]. Lactic acid was incorporated by our group to afford rhodomycinones having a methyl side chain[7].

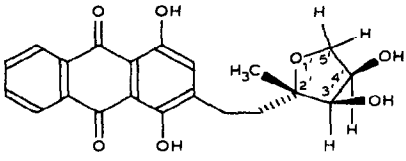
We now report the synthesis of branched sugar derivatives having potential aldehyde groups that can be liberated selectively to give four-carbon building blocks. These are available in both enantiomeric forms starting from methyl α-D-mannopyranoside (**3**) and methyl α-D-glucopyranoside, respectively.

RESULTS AND DISCUSSION

The first experiments were carried out with the glycos-3-ulose **4**, which was prepared in two steps from methyl α-D-mannopyranoside (**3**) by treatment of the di-*O*-benzylidene derivative with butyllithium using Horton and Weckerle's modification[8] of the procedure of Klemer and Rodemeyer[9]. Inspection of models suggested that attack of the organometallic reagent should occur preferentially from the less hindered side of **4** to afford mainly the adducts **5a–7a**. Actually, the tertiary alcohol **5a** was obtained from ketone **4** by treatment with methylmagnesium iodide in 1,2-dimethoxyethane[10] or in diethyl ether[11] (yield 60 and 86%, respectively), or better, by treating **4** with methyllithium in tetrahydrofuran (THF) (yield 95%). In addition, the reaction of ethyl- and ethynyl-magnesium bromide (0°, ether or THF) with **4** was also studied. Chromatography of the mother liquors from all these reactions afforded the polar epimers **8–10** as oils in addition to the major products **5a–7a**. The isomeric ratios ranged from 15.7–32.5. Fortunately, the major isomers could be separated by crystallization, and their structures determined unambiguously by nuclear Overhauser effects. For example, the ^{1}H-n.O.e. difference spectra of the epimeric ethyl compounds **6a** and **9** proved valid the relationship shown in the stereoformulas of **6a** and **9**, thus confirming earlier assignments[10-12].

Since a glycol cleavage with periodate was needed to introduce the aldehyde group, the tertiary alcohol functions had to be protected. This was done with sodium hydride and benzyl bromide in THF using tetramethylammonium iodide as catalyst. Treatment of the benzyl ethers **5b** and **6b** with 75% aqueous acetic acid at 50° removed the benzylidene and then the methyl glycosidic functions to afford the crystalline 2-deoxy sugars **11a** and **12a**, which were further characterised as the β acetates (**11b** and **12b**). The open chain forms **13** and **14** are β-hydroxy aldehydes with the potential for coupling experiments to anthrahydroquinones (see below).

3
4
5a,b R = CH3
6a,b R = C2H5
7a,b R = HC≡C
a ser. R' = H
b ser. R' = Bn
8 R = CH3
9 R = C2H5
10 R = HC≡H
6a
9
11a,b R = CH3
12a,b R = C2H5
a ser. R' = H
b ser. R' = Ac
13 R = CH3
14 R = C2H5
15 R = CH3
16 R = C2H5
17 R = CH3
18 R = C2H5



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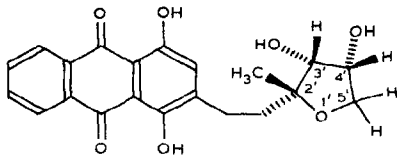

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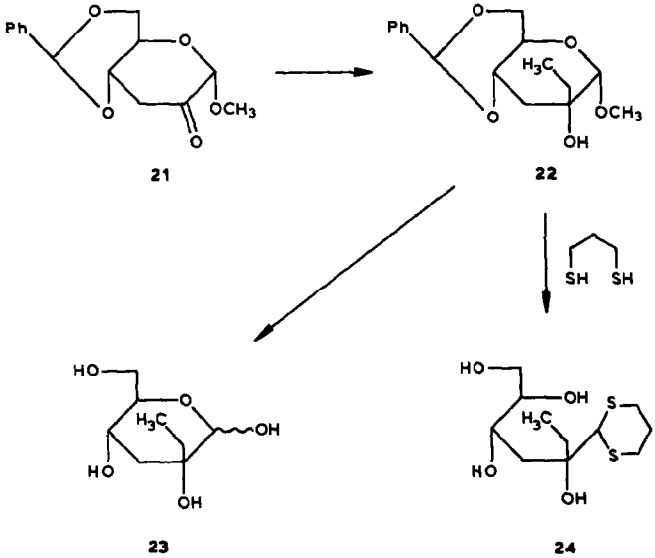
Preliminary work also showed that borohydride reduction of the triacetates **11b** and **12b** afforded the tetrols **15** and **16**. These can be cleaved by periodate to yield the aldehydes **17** and **18** as confirmed by ^{1}H-n.m.r. spectroscopy (data not included).

To demonstrate the ability of these building blocks to couple to anthraquinones, leucoquinizarine was treated with **11a** using the method of Lewis[13] (piperidine acetate in boiling 2-propanol) to yield the adducts **19** and **20**. Evidently, after the addition of the open chain form **13** to leucoquinizarine a displacement of the benzyloxy group took place, presumably *via* an intermediate carbocation, as the two isomers **19** and **20** were formed in almost equal amounts. The configurations of the *C*-glycosides **19** and **20** differed only at the quaternary branching point, but the assignment of the absolute configurations on the basis of coupling constants alone proved difficult. Again, nuclear Overhauser experiments enabled us to show the synclinal relationship of the C-2′ methyl group with the neighbouring proton at C-3′ in the less polar (2*R*) isomer **20**. Thus, the building blocks **5–7** are potential precursors for chiral anthracyclinones.

We have also investigated the possibilities for obtaining chiral starting materials for the synthesis of anthracyclinones having the natural absolute configuration. Two interesting suggestions with respect to the methyl series were provided by the literature. Howarth and Jones[14] proposed L-sugars as starting materials, and Funibashi *et al.*[15] investigated epoxidation followed by alanate reduction of 2,3-dideoxy-3-*C*-methylene hexopyranosides to afford **8** (ref. 16). However, 2-deoxy-L-*arabino*-hexose is not as readily available as is D-glucose, and the selectivity in the second procedure (**8**:**5a** = 61:18) was not satisfactory. Simple symmetry considerations reveal the possibility that the transposition of the carbonyl function to the 2-position might produce the desired configuration if the organometallic reagent still attacks from the same direction. The 3-deoxyhexopyranosidulose **21** needed for our investigation could be made in four steps from methyl α-D-glucopyranoside[16]. In their paper Hicks and Fraser-Reid also made the encouraging observation that addition of methylmagnesium iodide to **21** occurred preferentially from the side opposite the methoxy group. The reaction of ethylmagnesium bromide with **21** (−20°, diethyl ether) gave a 96% yield of the crude alcohol **22** in which no trace of any other isomer could be detected in the 300 MHz ^{1}H-n.m.r. spectrum. Careful analysis of the mother liquor revealed the presence of only 3% of the secondary alcohol formed by Grignard reduction.

Again, the proposed use of **22** and its congeners as chiral building blocks in



anthracyclinone synthesis made a procedure for the selective liberation of the masked 1,4-dialdehydes necessary. Cleavage of the acetal groups of **22** with 2.5% sulfuric acid afforded the free sugar **23**, which can react as an α-hydroxy aldehyde. A permanent fixation of the open-chain form was effected by conversion into the dithioacetal **24**, employing the method of Corey *et al.*[17]. Following known procedures[18], a β-hydroxyaldehyde may be obtained from the glycol cleavage of **24**. α-Hydroxyaldehydes protected as dithioacetals have also been shown to be excellent precursors in the synthesis of racemic anthracyclinones[19].

We believe that the chiral C_4 building blocks described here, having variable side chains and available in both enantiomeric forms, might prove useful in the synthesis of anthracyclinones and a variety of other natural products containing chiral tertiary alcoholic functions.

EXPERIMENTAL

General methods. — These were described in ref. 7 and the references cited therein.

*Methyl 4,6-O-benzylidene-2-deoxy-3-C-methyl-α-*D-ribo-*hexopyranoside* (**5a**) *and methyl 4,6-O-benzylidene-2-deoxy-3-C-methyl-α-*D-arabino-*hexopyranoside* (**8**). — A solution of methyllithium in *n*-octane (60 mL) was gradually added at −30° under nitrogen to **4** (3.76 g, 14.3 mmol) in dry tetrahydrofuran (120 mL). The solution was stirred for 2 h at −10° and then poured into cold 10% aqueous ammonium chloride. The mixture was extracted twice with dichloromethane (200 mL), and the organic phase was dried (Na_2SO_4) and evaporated to dryness at reduced pressure yielding a crystalline mass. Recrystallization from dichloro-

methane–ether–petroleum ether gave **5a** (2.82 g, 71%). Chromatography of the mother liquor on silica gel afforded the more polar isomer **8** (0.18 g, 4.5%). The physical and spectroscopic data for **5a** and **8** were in agreement with literature values[10–12,15].

*Methyl 4,6-O-benzylidene-2-deoxy-3-C-ethyl-α-*D-ribo-*hexopyranoside* (**6a**) *and methyl 4,6-O-benzylidene-2-deoxy-3-C-ethyl-α-*D-arabino-*hexopyranoside* (**9**). — Ketone **4** (6.00 g) was added in portions at 0° to a solution of ethylmagnesium bromide prepared from magnesium (1.47 g, 60 mmol) and ethyl bromide (4.5 mL, 60 mmol) in dry diethyl ether (100 mL). The mixture was vigorously stirred for 2 h with workup then proceeding as described for **5a**. Crystallization from a small amount of ether afforded **6a** (5.05 g). Chromatography of the mother liquor yielded more **6a** (0.30 g, 80% in all) and the polar **9** (0.26 g, 3.9%) as a colourless oil.

Compound **6a** had $[\alpha]_D^{20}$ +102° (*c* 0.50, chloroform); ^{1}H-n.m.r. (400 MHz): δ 0.94 (t, *J* 7.4 Hz, 3 H, CH_2CH_3), 1.49 (m, 1 H, CH_2CH_3), 1.80 (d, J_{gem} 14.5 Hz, 1 H, H-2), 1.81 (m, 1 H, CH_2CH_3), 2.03 (d, J_{gem} 14.5 Hz, 1 H, H-2), 3.28 (s, 1 H, OH), 3.41 (s, 3 H, OCH_3), 3.45 (d, $J_{4,5}$ 9.6 Hz, 1 H, H-4), 3.77 (t, $J_{5,6}$ 10.3 Hz, 1 H, H-6), 4.15 (m, 1 H, H-5), 4.33 (q, *J* 5.0 Hz, 1 H, H-6), 4.82 (d, *J* 3.8 Hz, 1 H, H-1), 5.59 (s, 1 H, PhCH), 7.35 (m, 3 H, Ph–H), and 7.50 (m, 2 H, Ph–H); m.s.: *m/z* 294 (7, M^+), 262 (48, $M^+ - CH_3OH$), 233 (8), 205 (15), 190 (27), 179 (87), 162 (68), 145 (44), 127 (45), 115 (44), and 105 (100).

Anal. Calc. for $C_{16}H_{22}O_5$: C, 65.3; H, 7.5. Found: C, 65.1; H, 7.4.

The ^{1}H-n.m.r. spectrum (400 MHz) of **9** showed: δ 0.95 (t, *J* 7.5 Hz, 3 H, CH_2CH_3), 1.67 (m, 1 H, H-2), 1.77 (m, 1 H, CH_2CH_3), 2.02 (m, 1 H, CH_2CH_3), 2.19 (dd, 1 H, H-2), 3.30 (s, 3 H, OCH_3), 3.37 (s, 1 H, OH), 3.62 (d, $J_{4,5}$ 9.7 Hz, 1 H, H-4), 3.69 (t, *J* 10.1 Hz, 1 H, H-6), 3.79 (m, 1 H, H-5), 4.25 (m, 1 H, H-6), 4.71 (d, $J_{1,2}$ 4.1 Hz, 1 H, H-1), 5.53 (s, 1 H, PhCH), 7.35 (m, 3 H, Ph–H), and 7.47 (m, 2 H, Ph–H); mass spectrum as for **6a**.

Anal. Found: C, 64.39; H, 7.43.

*Methyl 4,6-O-benzylidene-2-deoxy-3-C-ethynyl-α-*D-ribo-*hexopyranoside* (**7a**) *and methyl 4,6-O-benzylidene-2-deoxy-3-C-ethynyl-α-*D-arabino-*hexopyranoside* (**10**). — A solution of ethylmagnesium bromide was prepared from magnesium (2.8 g, 115 mmol) and ethyl bromide (9.0 mL, 120 mmol) in dry tetrahydrofuran (100 mL). A stream of acetylene was bubbled through the solution for 10 min and then ketone **4** (4.00 g, 15 mmol) in tetrahydrofuran (30 mL) was added over a period of 30 min. Workup proceeded as described for **5a** to afford **7a** (2.50 g, 56%) and the polar isomer **10** (77 mg, 1.7%) as an oil.

The ^{1}H-n.m.r. spectrum (300 MHz) of **7a** showed: δ 2.20 (ddd, 1 H, $J_{1,2}$ 4.0, J_{gem} 15.0, $J_{2,OH}$ 0.7 Hz, H-2), 2.42 (dd, 1 H, $J_{1,2}$ 0.8, J_{gem} 15.0 Hz, H-2), 2.45 (s, 1 H, C≡CH), 3.40 (s, 3 H, OCH_3), 3.70 (d, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.77 (t, 1 H, *J* 10.3 Hz, H-6), 4.16 (m, 1 H, H-5), 4.32 (m, 1 H, H-6), 4.78 (dd, 1 H, $J_{1,2}$ 0.8, $J_{1,2}$ 4.0 Hz, H-1), 5.67 (s, 1 H, PhCH), 7.37 (m, 3 H, Ph–H), and 7.53 (m, 2 H, Ph–H); m.s.: *m/z* 290 (8, M^+), 259 (7, $M^+ - CH_3O$), 190 (12), 179 (100), 153 (23), 145 (71), 141 (28), 128 (46), 123 (47), 112 (73), 107 (82), and 105 (83).

Anal. Calc. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.2. Found: C, 66.4; H, 6.3.

The ^{1}H-n.m.r. spectrum (300 MHz) of **10** showed: δ 2.16 (dd, 1 H, H-2), 2.39 (dd, 1 H, H-2), 2.70 (s, 1 H, C≡C*H*), 3.39 (s, 3 H, OCH_3), 3.64 (d, 1 H, H-4), 3.75 (t, 1 H, H-6), 4.14 (m, 1 H, H-5), 4.29 (m, 1 H, H-6), 4.75 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.57 (s, 1 H, PhC*H*), 7.39 (m, 3 H, Ph–H), and 7.54 (m, 2 H, Ph–H); mass spectrum as for **7a**.

Anal. Found: C, 66.4; H, 6.1.

*Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-3-C-methyl-α-*D-ribo-*hexopyranoside* (**5b**). — A suspension of alcohol **5a** (560 mg, 2 mmol) and sodium hydride (112 mg, 5 mmol) in dry tetrahydrofuran (30 mL) was stirred 1 h at 40° under nitrogen. Benzyl bromide (680 mg, 4 mmol) and tetrabutylammonium iodide (0.5 g) were then added and stirring was continued for 1.5 h at 55°. The mixture was poured onto ice (100 g) and extracted twice with dichloromethane (100 mL). Evaporation at reduced pressure and filtration through a short column of silica gel (dichloromethane) afforded crystalline benzyl ether **5b** (537 mg, 74%), m.p. 108° (from ether); ^{1}H-n.m.r. (400 MHz): δ 1.39 (s, 3 H, CH_3), 1.75 (dd, 1 H, $J_{1,2}$ 4.6, J_{gem} 14.9 Hz, H-2), 2.34 (d, 1 H, J_{gem} 14.9 Hz, H-2), 3.36 (s, 3 H, OCH_3), 3.51 (d, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 3.69 (t, 1 H, *J* 10.4 Hz, H-6), 4.30 (dd, 1 H, $J_{5,6}$ 5.3, J_{gem} 10.4 Hz, H-6), 4.43 (m, 1 H, H-5), 4.69 (d, 1 H, J_{gem} 9.9 Hz, PhCH_2), 4.70 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 4.72 (d, 1 H, J_{gem} 9.9 Hz, PhCH_2), 5.51 (s, 1 H, PhC*H*), 7.33 (m, 6 H, Ph–H), and 7.47 (m, 4 H, Ph–H); m.s.: *m/z* 338 (8, $M^+ - CH_3OH$), 160 (13), 141 (10), 121 (13), 111 (15), 105 (53), and 91 (100).

Anal. Calc. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 70.7; H, 7.1.

*Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-3-C-ethyl-α-*D-ribo-*hexopyranoside* (**6b**). — A mixture of **6a** (3.55 g, 2 mmol), sodium hydride (0.75 g), benzyl bromide (3 mL, 25 mmol), and tetrabutylammonium iodide (0.5 g) in dry tetrahydrofuran (50 mL) was allowed to react as described for **5b** to afford the oily benzyl ether **6b** (4.26 g, 92%). Compound **6b** had $[\alpha]_D^{20}$ +126° (*c* 0.55, chloroform); ^{1}H-n.m.r. (400 MHz): δ 0.96 (t, 3 H, *J* 7.5 Hz, CH_2CH_3), 1.63, (m, 1 H, CH_2CH_3), 1.75 (dd, 1 H, $J_{1,2}$ 4.7, J_{gem} 14.7 Hz, H-2), 2.09 (m, 1 H, CH_2CH_3), 2.24 (d, 1 H, J_{gem} 14.7 Hz, H-2), 3.37 (s, 3 H, OCH_3), 3.60 (d, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 3.69 (t, 1 H, *J* 10.4 Hz, H-6), 4.30 (dd, 1 H, $J_{5,6}$ 5.4, J_{gem} 10.4 Hz, H-6), 4.42 (m, 1 H, H-5), 4.60 (d, 1 H, J_{gem} 11.8 Hz, PhCH_2), 4.75 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.89 (d, 1 H, J_{gem} 11.8 Hz, PhCH_2), 5.47 (s, 1 H, PhC*H*), 7.32 (m, 6 H, Ph–H), and 7.43 (m, 4 H, Ph–H); m.s.: *m/z* 352 (12, $M^+ - CH_3OH$), 174 (27), 155 (26), 149 (20), 125 (45), 121 (37), 105 (59), 97 (51), and 91 (100).

Anal. Calc. for $C_{23}H_{28}O_5$: C, 71.8; H, 7.3. Found: C, 72.1; H, 7.4.

*Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-3-C-ethynyl-α-*D-ribo-*hexopyranoside* (**7b**). — An amount of **6a** (200 mg) was benzylated as described for **5a** to afford **7b** (156 mg, 59%) as an oil; ^{1}H-n.m.r. (300 MHz): δ 1.49 (dd, 1 H, J_{gem} 14.9, $J_{1,2}$ 4.5 Hz, H-2), 2.55 (s, 1 H, C≡C*H*), 2.58 (dd, 1 H, J_{gem} 14.9, $J_{1,2}$ 0.6 Hz, H-2), 3.36 (s, 3 H, OCH_3), 3.72 (t, 1 H, $J_{5,6}$ 10.3 Hz, H-6), 3.81 (d, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 4.30 (m, 1 H, H-5), 4.39 (m, 1 H, H-6), 4.73 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1),

4.83 (d, 1 H, J_{gem} 11.8 Hz, PhCH_2), 4.91 (d, 1 H, J_{gem} 11.8 Hz, PhCH_2), 5.58 (s, 1 H, PhC*H*), 7.28 (m, 6 H, Ph–H), and 7.44 (4 H, Ph–H).

*3-O-Benzyl-2-deoxy-3-C-methyl-*D*-ribo-hexopyranose* (**11a**). — A solution of the glycoside **5b** (2.0 g) was stirred in aqueous acetic acid (75 mL) for 2 h at 55°. The solvent was then evaporated under reduced pressure, and the residue was crystallized from ether to afford **11a** (1.21 g, 79%), m.p. 132°, $[\alpha]_D^{20}$ +18° (*c* 0.50, chloroform); ^{1}H-n.m.r. (400 MHz): δ 1.40 (s, 3 H, CH_3), 1.46 (m, 1 H, H-2), 2.39 (dd, 1 H, J_{gem} 15.0, $J_{1,2}$ 1.8 Hz, H-2), 3.27 (d, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.73 (m, 2 H, CH_2OH), 3.85 (m, 1 H, H-4), 4.47 (d, 1 H, J_{gem} 10.9 Hz, PhCH_2), 4.52 (d, 1 H, J_{gem} 10.9 Hz, PhCH_2), 5.02 (m, 1 H, H-1), and 7.32 (m, 5 H, Ph–H); m.s.: *m/z* 219 (2, $M^+ - CH_3OH - OH$), 160 (7), 134 (10), 113 (48), 108 (52), 101 (36), and 91 (100).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5. Found: C, 63.1; H, 7.8.

*3-O-Benzyl-2-deoxy-3-C-ethyl-*D*-ribo-hexopyranose* (**12a**). — A solution of the benzyl ether **6b** (2.00 g) in 75% aqueous acetic acid was treated as described for **5b**→**11a** to afford **12a** (1.20 g, 81%), m.p. 146° (ether), $[\alpha]_D^{20}$ +15° (*c* 0.47, chloroform); ^{1}H-n.m.r. (400 MHz): δ 0.97 (t, 3 H, *J* 7.5 Hz, CH_2CH_3), 1.55 (dd, 1 H, J_{gem} 14.0, $J_{1,2}$ 9.0 Hz, H-2), 1.80 (m, 2 H, CH_2CH$_3$), 2.25 (dd, 1 H, J_{gem} 14.0, $J_{1,2}$ 1.5 Hz, H-2), 3.49 (d, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.75 (m, 2 H, CH_2OH), 3.87 (m, 1 H, H-5), 4.50 (m, 2 H, PhCH_2), 5.08 (m, 1 H, H-1), and 7.30 (m, 5 H, Ph–H); m.s. (f.a.b.): *m/z* 305 ($M + Na^+$), 265 ($M^+ - OH$), 247, 205, 157, and 91 (100).

Anal. Calc. for $C_{15}H_{22}O_5$: C, 63.8; H, 7.8. Found: C, 63.8; H, 7.6.

*1,4,6-Tri-*O*-acetyl-3-*O*-benzyl-2-deoxy-3-*C*-methyl-β-*D*-ribo-hexopyranose* (**11b**). — A solution of **11a** (300 mg, 1 mmol) in acetic anhydride (1 mL) and pyridine (2 mL) was kept for 12 h at room temperature. Evaporation of the solvent, dissolution of the residue in dichloromethane, and washing the solution with water and then dilute sodium hydrogencarbonate afforded, after evaporation of the solvent, **11b** (416 mg, 90%) as an oil. Crystallization from ether–petroleum ether gave 305 mg of crystalline β-anomer, m.p. 67°, $[\alpha]_D^{20}$ +39.2° (*c* 0.5, chloroform); i.r.: 1740 cm^{-1} (ester); ^{1}H-n.m.r. (300 MHz): δ 1.30 (s, 3 H, CH_3), 1.73 (dd, 1 H, J_{gem} 13.8, *J* 10.0 Hz, H-2), 2.07, 2.11, 2.12 (3 s, each 3 H, COCH_3), 2.34 (dd, 1 H, J_{gem} 10.7, *J* 2.2 Hz, H-2), 4.01 (dm, 1 H, H-5), 4.30–4.39 (m, 2 H, H-6), 4.56 (AB, 2 H, OCH_2), 4.98 (d, 1 H, *J* 9.8 Hz, H-4), 6.06 (dd, 1 H, *J* 10.1, *J* 2.2 Hz, H-1), and 7.35 (m, 5 H, Ph–H); m.s.: *m/z* 393 ($M^+ - 1, 3$), 349 (8), 335 (38), 334 (18), 307 (18), 291 (12), 287 (14), 280 (20), 279 (100), 274 (39), and 261 (15).

Anal. Calc. for $C_{20}H_{26}O_8$: C, 60.9; H, 6.6. Found: C, 61.0; H, 6.7.

*1,4,6-Tri-*O*-acetyl-3-*O*-benzyl-2-deoxy-3-*C*-ethyl-β-*D*-ribo-hexopyranose* (**12b**). — A solution of **12a** (325 mg) was treated as described for **11a** to afford **12b** (449 mg, 94%). Crystallization from ether–petroleum ether gave the β-anomer (267 mg), m.p. 103°; i.r.: 1740 cm^{-1}; ^{1}H-n.m.r. (300 MHz): δ 0.94 (t, 3 H, *J* 7.5 Hz, CH_2CH_3), 1.54 (sext, 1 H, CH_2CH$_3$), 1.73 (dd, 1 H, J_{gem} 13.5, $J_{1,2}$ 10.0 Hz, H-2), 1.92 (sext, 1 H, CH_2CH$_3$), 2.09, 2.10, 2.13 (3 s, each 3 H, COCH_3), 2.22 (dd, 1 H,

J_{gem} 13.5, $J_{1,2}$ 2.3 Hz, H-2), 4.02 (dd, 1 H, *J* 11.5, *J* 1.3 Hz, H-5), 4.34 (m, 2 H, H-6), 4.61 (dd, 2 H, J_{gem} 11.3 Hz, PhCH_2), 5.08 (d, 1 H, *J* 9.5 Hz, H-4), 6.12 (dd, 1 H, $J_{1,2}$ 10.0, $J_{1,2}$ 2.3 Hz, H-1), and 7.35 (m, 5 H, Ph–H).

Anal. Calc. for $C_{21}H_{28}O_8$: C, 61.8; H, 6.9. Found: C, 61.9; H, 7.0.

Borohydride reduction of **11b** *and* **12b**. — A suspension of **11b** (100 mg, 0.37 mmol) and sodium borohydride (30 mg, 0.75 mmol) in ethanol (20 mL) was stirred for 12 h at room temperature. The mixture was neutralized with dilute hydrochloric acid, the solvent was evaporated under reduced pressure, and the oily residue was extracted with dichloromethane. Evaporation of the extract gave (2*R*, 3*R*, 4*S*)-4-benzyloxy-4-methyl-1,2,3,6-hexanetetrol (**15**; 52 mg, 81%), i.r.: 3450 cm^{-1} (broad, OH); ^{1}H-n.m.r. (60 MHz): δ 1.3 (s, 3 H, CH_3), 1.6 (m, 2 H, CH_2), 4.0 (m, 6 H, 2 CH_2OH, 2 C*H*OH), 4.6 (m, 2 H, PhCH_2), and 7.4 (m, 5 H, Ph–H).

Similarly an ethanolic solution of **12b** (410 mg) was reduced with sodium borohydride (73 mg), to afford (2*R*, 3*R*, 4*S*)-4-benzyloxy-4-ethyl-1,2,3,6-hexanetetrol (**16**; 226 mg, 87%) as an oil, i.r.: 3440 cm^{-1} (broad, OH); ^{1}H-n.m.r. (300 MHz); δ 1.07 (t, 3 H, CH_2CH_3), 1.87–2.08 (m, 4 H, 2 CH_2), 2.9 (broad, 1 H, O*H*), 3.2 (broad, 1 H, O*H*), 3.7–3.9 (m, 6 H), 4.1 (broad, 1 H, O*H*), 4.37 (d, 1 H, J_{gem} 10.5 Hz, OCH_2), 4.50 (d, 1 H, OCH_2), and 7.3 (m, Ph–H); m.s.: *m/z* 284 (18, M^+), 283 (100, $M^+ - 1$), 255 (9), 175 (56), 171 (11), 145 (7).

*(2'*S*, 3'*R*, 4'*R*)-2-[2-(3,4-Dihydroxy-2-methyltetrahydrofuran-2-yl)ethyl]-1,4-dihydroxy-9,10-anthraquinone* (**19**) *and (2'*R*, 3'*R*, 4'*R*)-2-[2-(3,4-dihydroxy-2-methyltetrahydrofuran-2-yl)ethyl]-1,4-dihydroxy-9,10-anthraquinone* (**20**). — A solution of leucoquinizarine (242 mg, 1 mmol), **11a** (100 mg, 0.36 mmol), and piperidine acetate[14] (300 mg) in 2-propanol (20 mL) was stirred under nitrogen for 10 h at 50°. The hydroquinones were then reoxidized by bubbling air through the solution. The solution was acidified with 50 mL of cold M hydrochloric acid and the products were separated by column chromatography on silica gel. From the polar fraction **19** (35 mg), m.p. 150–155° (dec.) and a less polar adduct **20** (29 mg), m.p. 160–165° were isolated.

The i.r. spectrum for **19** showed: 3400 (OH), 1622 (quinone), and 1587 cm^{-1} (aromatic); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.34 (s, 3 H, CH_3), 1.85 (t, 2 H, CH_2), 2.4 (m, 1 H, O*H*), 2.6 (m, 1 H, O*H*), 2.82–2.89 (m, 2 H, CH_2), 3.79 (dd, 1 H, *J* 4.0, J_{gem} 10.2 Hz, H-5'), 3.97 (bd, 1 H, H-3'), 4.06 (dd, 1 H, *J* 5.5, J_{gem} 10.2 Hz, H-5'), 4.40 (m, 1 H, H-4'), 7.19 (s, 1 H, H-3), 7.83 (m, 2 H, H-6,7), 8.35 (m, 2 H, H-5,8), 12.97 (s, 1 H, O*H*), and 13.42 (s, 1 H, O*H*); m.s.: *m/z* 384 (M^+), 383 (34), 310 (20), 294 (34), 293 (100), 279 (18), 268 (35), 254 (34), and 225 (17); high resolution m.s.: calc. for $C_{21}H_{20}O_7$, M^+ 384.1209; found, 384.1207.

For compound **20** the i.r. spectrum showed: 3350 (broad, OH), 1620 (quinone), and 1586 cm^{-1} (aromatic); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.31 (s, 3 H, CH_3), 1.94–1.99 (m, 2 H, CH_2), 2.4 (m, 1 H, O*H*), 2.80–2.86 (m, 2 H, CH_2), 2.9 (m, 1 H, O*H*), 3.74 (dd, 1 H, *J* 5.2, J_{gem} 10.0 Hz, H-5'), 3.93 (d, 1 H, $J_{3',4'}$ 5.5 Hz, H-3'), 4.12 (dd, 1 H, *J* 6.5, J_{gem} 10.0 Hz, H-5'), 4.48 (q, 1 H, H-4'), 7.22 (s, 1 H,

H-3), 7.83 (m, 2 H, H-6,7), 8.36 (m, 2 H, H-5,8), 12.97 (s, 1 H, O*H*), and 13.59 (s, 1 H, O*H*); m.s.: *m/z* 384 (M^+, 10), 383 (46), 310 (13), 294 (42), 293 (100), 279 (13), 268 (45), 254 (38), 225 (19); high resolution m.s.: found, 384.1207.

Methyl 4,6-O-benzylidene-3-deoxy-2-C-ethyl-α-D-ribo-hexopyranoside (**22**). — A solution of ethylmagnesium bromide in dry diethyl ether (100 mL) was prepared from magnesium (1.47 g, 60 mmol) and ethyl bromide (6.57 g, 60 mmol). The solution was cooled to −40° and 6.00 g of **21** (ref. 13) was added portionwise. After being stirred for 1.5 h at −20° the mixture was poured into cold water, and a saturated solution of ammonium chloride was added until the precipitate redissolved. The solution was extracted with 300 mL of ether, which was dried ($NaSO_4$), filtered, and evaporated to dryness. Crystallization from a small amount of ether afforded **22** (6.28 g, 94%), m.p. 116°, $[\alpha]_D^{20}$ +94.2° (*c* 0.58 chloroform); ^{1}H-n.m.r. (300 MHz): δ 1.00 (t, 3 H, *J* 7.5 Hz, CH_2CH_3), 1.71 (m, 2 H, *J* 7.3 Hz, CH_2CH_3), 1.83 (t, 1 H, J_{gem} 11.9 Hz, H-3), 2.18 (dd, 1 H, J_{gem} 11.9, *J* 4.3 Hz, H-3), 3.45 (s, 3 H, OCH_3), 3.74 (m, 2 H, H-6), 4.26 (m, 1 H, H-5), 4.31 (s, 1 H, H-1), 5.51 (s, 1 H, H-7), 7.32 (m, 3 H, Ph–H), and 7.48 (m, 2 H, Ph–H); m.s.: *m/z* 294 (0.2, M^+), 263 (24, $M^+ - CH_3OH$), 233 (4), 216 (7), 162 (47), 156 (26), 145 (48), 128 (51), and 105 (100).

Anal. Calc. for $C_{16}H_{22}O_5$: C, 65.3; H, 7.5. Found: C, 65.3; H, 7.6.

3-Deoxy-2-C-ethyl-D-ribo-hexose (**23**). — A solution of **22** (100 mg, 0.34 mmol) was stirred under reflux in 2.5% sulfuric acid (10 mL). The cooled solution was diluted with water (10 mL), neutralized with barium carbonate, filtered, and evaporated under reduced pressure. The residue was filtered through a short column of silica gel (9:1 dichloromethane–methanol) to afford **23** (55 mg, 85%) as an oil.

Anal. Calc. for $C_8H_{16}O_5$: C, 50.0; H, 8.4. Found: C, 50.0; H, 8.1.

3-Deoxy-2-C-ethyl-D-ribo-hexose trimethylene dithioacetal (**24**). — Essentially the procedure given by Corey *et al.*[17] was followed. A mixture of **22** (4.32 g, 14.7 mmol) and propane-1,3-dithiol (7.95 g, 73.5 mmol) was stirred for 12 h at 0° and 12 h at 20° in a mixture of chloroform (6 mL) and 6M hydrochloric acid (36 mL). The mixture was diluted with water (40 mL) and neutralized by the addition of lead carbonate. The suspension was filtered, and the filtrate was evaporated to dryness under reduced pressure and purified by passage over a short column of silica gel (9:1 dichloromethane–methanol) to afford **24** (oil, 3.39 g, 82%), $[\alpha]_D^{20}$ −9.7° (*c* 0.57, methanol); i.r.: 3450 (broad, OH), 2962, 2930, 2872, and 910 cm^{-1}; ^{1}H-n.m.r. (300 MHz): δ 0.98 (t, 3 H, *J* 7.3 Hz, CH_3CH_2), 1.82 (m, 3 H), 2.12 (m, 1 H, *J* 3.4, *J* 14.2 Hz), 2.88 (m, 4 H, 2 × SCH_2), 3.71 (dd, 1 H, $J_{5,6}$ 2.8, J_{gem} 11.9 Hz, H-6), 3.78 (dt, 1 H, $J_{5,6}$ 2.8, $J_{4,5}$ 7.5 Hz, H-5), 3.88 (dd, 1 H, *J* 3, J_{gem} 11 Hz, H-6), 4.31 (s, 1 H, H-1), 4.49 (dt, 1 H, $J_{3,4}$ 7.3, $J_{4,5}$ 7.5 Hz, H-4).

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