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SYNTHESIS OF 4-DEOXY-β-RHODOMYCINONE VIA INCORPORATION OF A CHIRAL BUILDING BLOCK DERIVED FROM METHYL α-D-GLUCOPYRANOSIDE

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ABSTRACT

Methyl 4,6-*O*-benzylidene-3-deoxy-2-*C*-ethyl-α-D-*ribo*-hexopyranoside was converted in six steps into (*R*)-3-benzyloxy-3-(trityloxymethyl)pentanal. This chiral building block was coupled to leucoquinizarin to afford 4-deoxy-γ-rhodomycinone, using two successive Marschalk reactions. Hydroxylation at C-7 gave 4-deoxy-β-rhodomycinone.

INTRODUCTION

Several anthracycline antitumor antibiotics, obtained by total synthesis, are currently in clinical use or testing[1]. The 4-demethoxy compounds, such as 4-demethoxydoxorubicin or 2,3-dimethyl-4-demethoxydoxorubicin that cannot be obtained from natural sources, show promising pharmacological properties[1]. More recently, interest in the anthracyclines of the rhodomycinone family has been renewed due to reports on reduced cross-resistance to adriamycin[2] and the cell-differentiating ability[3] of some members of this class of anthracyclines.

The biological activity of anthracyclines is correlated strictly with the natural absolute configuration[1,4,5]. The use of enantiomerically pure, instead of racemic, aglycons in the glycosidation step of the synthesis of anthracyclines saves precious material and avoids tedious separation procedures. Therefore, it is not surprising that syntheses of optically pure anthracyclines have been described in many recent papers[6]. α-Hydroxy acids, such as lactic acid[7], α-hydroxybutyric acid[8], and malic acid[9], have been incorporated into rhodomycinones and daunomycinones. In addition, such sugar derivatives as isosaccharinic acid[10,11] or 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[12] have been used as chiral templates for the synthesis of anthracyclines. In most of these investigations, the Marschalk reaction[13] was used to couple the chiral building blocks with hydroxylated anthrahydroquinones. We have described the synthesis of chiral masked 1,4-dialdehydes from methyl α-D-mannopyranoside and methyl α-D-glucopyranoside in both enantiomeric forms as versatile building blocks for the synthesis of natural products[14]. However, only

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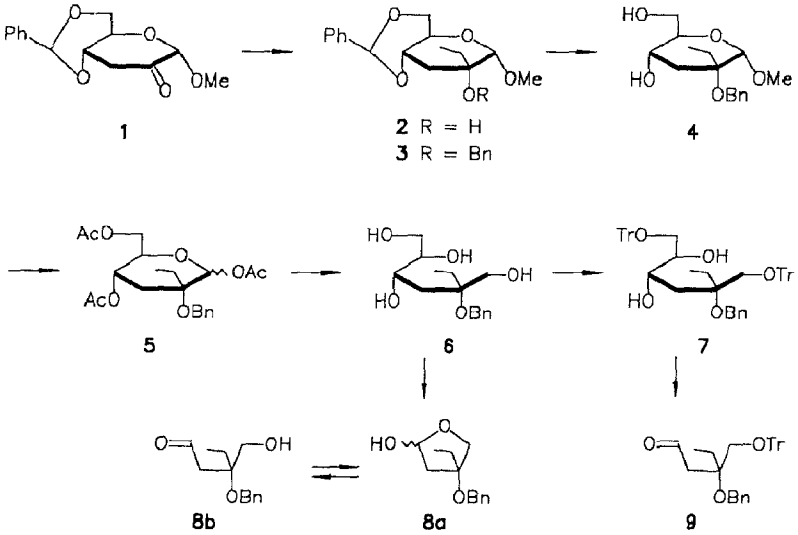
acyclic coupling products with quinizarin were isolated with one building block, and another chiral molecule was prepared only in its enantiomeric form. We now report on the synthesis of a tritylated building block **9** of correct absolute configuration from methyl α-D-glucopyranoside and the transformation into enantiomerically pure 4-deoxy-β-rhodomycinone (**16**).

RESULTS AND DISCUSSION

The adduct **2**, obtained from methyl α-D-glucopyranoside via **1**[14], could be converted into the corresponding acyclic thioacetal derivative[14], but further transformation met with difficulties in the glycol cleavage steps. Instead, we changed the future aldehyde functionality at C-1 by borohydride reduction to an alcohol. In view of the planned glycol cleavage, the tertiary alcohol group of **2** was protected by benzylation to give **3** (89%). Treatment of **3** with aqueous 75% acetic acid then removed the benzylidene group to yield the diol **4** (92%). The benzyl ether at the tertiary position did not survive the harsh treatment with acid necessary to cleave the methyl glycoside. However, treatment of **4** with acetic anhydride and a catalytic amount of boron trifluoride etherate afforded the triacetate **5** as an α,β-mixture (80%). Transesterification during the borohydride reduction liberated simultaneously the acetylated hydroxy groups, giving the tetraol **6** (98%). The first building block **8**, for incorporation into anthracyclines, was obtained by glycol cleavage of **6** with 3 equiv. of sodium periodate. The ^{1}H-n.m.r. spectrum ($CDCl_3$) of the product, measured immediately after purification by t.l.c., revealed the acyclic compound **8b**. However, conversion into the furanoside hemiacetal **8a** in other solvents cannot be excluded (see below).

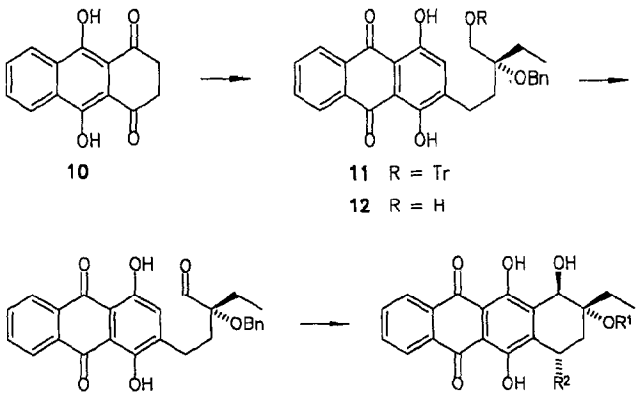
In order to prevent the formation of a cyclic acetal (a free aldehyde group is



important for the Marschalk reaction), the primary hydroxyl groups of **6** were tritylated[15], to afford the diol **7** (91%). The tritylated aldehyde **9** was isolated (72%) after glycol cleavage of **7** and subsequent chromatography.

Both building blocks **8** and **9** were each coupled in a Marschalk reaction with leucoquinizarin (**10**) in aqueous alcoholic alkali (Marschalk conditions[13], *cf.* ref. 16) or with piperidine acetate as catalyst in dry 2-propanol (Lewis conditions[17]). When building block **8** was coupled to **10** under modified Marschalk reaction conditions, using aqueous alkali in 2-propanol, only 17% of the adduct **11** was obtained. When primary alcohols were used as co-solvents, the tertiary benzyl ether at the labile β-position to the aldehyde function was replaced. Low yields were obtained also with a similar debenzylated building block by Florent *et al.*[10]. Mincher *et al.*[18] found that several hexopyranoses could not be coupled to **10** in Marschalk-type reactions. Evidently, the possibility for acyclic ω-hydroxyaldehydes to exist in cyclic hemiacetal structures, such as **8a**, prevents high yields in Marschalk reactions. As expected, the building block **9**, which contains a free aldehyde group, gave the adduct **11** in good yield (79%) under the conditions of Lewis[17]. Only poor yields were obtained using the more basic medium of the Marschalk reaction conditions, as the β-benzyloxy-aldehyde **8** presumably underwent β-elimination more rapidly than addition to **10**.

The subsequent steps to the tetracyclic γ-rhodomycinone (**14**) were straightforward and involved cleavage of the trityl ether **11**, using dilute trifluoroacetic acid[19] to give **12**, Pfitzner–Moffatt oxidation[20] of the primary alcohol **12** to yield the aldehyde **13** (82%), and an intramolecular version of the Marschalk reaction to give the tetracyclic anthracycline **14** (68%), using the phase-transfer procedure elaborated for racemic precursors[21,22]. In these earlier investigations, it was found that the stereochemical outcome of the cyclization reaction depended on the reaction conditions. Under conditions favouring chelation control (aprotic



solvents), the *cis*-diols preponderated, whereas, under non-chelating conditions (protic solvents or non-chelating counter ions such as quaternary ammonium salts), a large excess of the desired *trans*-diols[8,21,22] was obtained. In agreement with the "non-chelation" model, the cyclization of the benzyl ether **13** afforded the *trans*-compound **14** with only traces of a less polar *cis*-derivative (t.l.c.).

The excellent control of the stereochemistry in the cyclization step again confirms the strategy (*cf.* ref. 7) of using β-hydroxy- or β-alkoxy-aldehydes instead of α-hydroxy- or α-alkoxy-aldehydes for the first coupling reaction to leuco-quinizarin (**10**). The *trans* configuration of **14** was confirmed by cleavage of the benzyl ether with boron tribromide to give 4-deoxy-γ-rhodomycinone **15**, which was identical with an authentic reference sample prepared in an independent synthesis[8]. Stereoselective *cis*-hydroxylation[8] at C-7 via bromination and solvolysis afforded enantiomerically pure 4-deoxy-β-rhodomycinone (**16**).

EXPERIMENTAL

General methods. — These have been described[22].

*Methyl 2-O-benzyl-4,6-O-benzylidene-3-deoxy-2-C-ethyl-α-*D-ribo-*hexopyranoside* (**3**). — A solution of **2**[14] (5.33 g, 18.1 mmol) in anhydrous *N,N*-dimethylformamide (70 mL) was stirred with sodium hydride (60%; 1.07 g, 27.15 mmol) for 30 min at 50°. Benzyl bromide (6.19 g, 36 mmol) was added and stirring was continued for 4 h. The mixture was poured into ice–water and extracted with ether (2 × 200 mL). The combined extracts were dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Recrystallization of the residue from ether gave **3** (6.90 g, 76%), m.p. 79°, $[\alpha]_D^{20}$ +56° (*c* 0.6, chloroform). ^{1}H-N.m.r. data (300 MHz): δ 1.00 (t, 3 H, *J* 7.4 Hz, CH_3CH_2), 1.84 (q, 2 H, *J* 7.4 Hz, CH_2CH_3), 2.16 (dd, 2 H, *J* 4.2, $J_{3,4}$ 9.5 Hz, H-3), 3.46 (s, 3 H, OMe), 3.62 (m, 1 H, H-5), 3.77 (dd, 1 H, $J_{4,5}$ 10.5, $J_{3,4}$ 9.5 Hz, H-4), 3.88 (dd, 1 H, $J_{5,6}$ 4.3, J_{gem} 9.5 Hz, H-6), 4.28 (dd, $J_{5,6}$ 4.3, J_{gem} 9.5 Hz, H-6), 4.47 (d, 1 H, *J* 10.9 Hz, CH_2Ph), 4.50 (s, 1 H, H-1), 4.59 (d, 1 H, *J* 10.9 Hz, CH_2Ph), 5.54 (s, 1 H, H-7), 7.37 (m, 5 H, Ph). Mass spectrum: *m/z* 384 (70%, M^+), 353 (75, M^+ − OMe), 293 (97, M^+ − Bn), 246 (24), 233 (32), 105 (36), and 91 (100).

Anal. Calc. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.86; H, 7.32.

*Methyl 2-O-benzyl-3-deoxy-2-C-ethyl-α-*D-ribo-*hexopyranoside* (**4**). — A solution of **3** (4.08 g, 10.6 mmol) in aqueous 75% acetic acid (30 mL) was stirred for 2 h at 55°, then concentrated under reduced pressure. The residue crystallized from ether–light petroleum to afford **4** (2.90 g, 92%), m.p. 93°, $[\alpha]_D^{24}$ +58° (*c* 0.4, chloroform); ν_{max} 2980 cm^{-1} (broad, OH). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 0.95 (t, 3 H, *J* 7.5 Hz, CH_3CH_2), 1.75 (m, 2 H, CH_2CH_3), 1.92 (m, 1 H, H-3*a*), 2.14 (dd, 1 H, $J_{3e,4}$ 4.9, J_{gem} 11.5 Hz, H-3*e*), 3.44 (s, 3 H, OMe), 3.55 (dt, 1 H, $J_{5,6}$ 4.3, $J_{4,5}$ 9.6 Hz, H-5), 3.72 (dq, 1 H, $J_{3e,4}$ 4.9, $J_{4,5}$ 9.6 Hz, H-4), 3.84 (m, 2 H, H-6), 4.42 (d, 1 H, *J* 10.5 Hz, CH_2Ph), 4.50 (s, 1 H, H-1), 4.53 (d, 1 H, *J* 10.5 Hz, CH_2Ph), 7.3 (m, 5 H, Ph). E.i.-mass spectrum (25°): *m/z* 173 (5%, M^+ − Bzl − MeOH), 158 (13, M^+ − BnO − MeOH), 127 (30), 91 (100).

Anal. Calc. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.89; H, 8.18.

1,4,6-Tri-O-*acetyl-2*-O-*benzyl-3-deoxy-2*-C-*ethyl*-D-ribo-*hexopyranose* (**5**). — A solution of **4** (2.66 g, 8.96 mmol) in acetic anhydride (6 mL) at 0° was stirred with freshly distilled boron trifluoride etherate (0.7 mL) for 4 h at 0°, then poured into cold saturated aqueous $NaHCO_3$ (50 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to dryness. An α,β-mixture (2.947 g, 80%) of the triacetate **5**, obtained as an oil after chromatography (CH_2Cl_2) of the residue on silica gel, had ν_{max} 1750 (ester), 1230 cm^{-1} (ether). ^{1}H-N.m.r. data (400 MHz): δ 1.03 (t, 3 H, *J* 7.4 Hz, CH_3CH_2), 1.95 (m, 3 H, CH_2CH_3, H-3*a*), 2.06, 2.09, 2.11 (each s, each 3 H, 3 OAc), 2.38 (dd, 1 H, $J_{3,4}$ 5.0, J_{gem} 11.1 Hz, H-3*e*), 3.98 (ddd, 1 H, $J_{4,5}$ 4.3, $J_{5,6}$ 2.8 Hz, H-5), 4.17 (m, 2 H, H-6), 4.33 (d, 1 H, *J* 11 Hz, CH_2Ph), 4.46 (d, *J* 11 Hz, 1 H, CH_2Ph), 4.87 (m, 1 H, H-4), 6.11 (s, 1 H, H-1), 7.27 (m, 5 H, Ph). Mass spectrum: *m/z* 348 (100%, M^+ − AcOH), 330 (12, M^+ − AcOH − H_2O), 289 (96, M^+ − 2 AcOH), 229 (94), 272 (3).

Anal. Calc. for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.72; H, 6.90.

(2R,3S,5R)-5-O-Benzyl-5-(hydroxymethyl)-1,2,3,5-heptanetetraol (**6**). — A solution of **5** (731 mg, 1.74 mmol) in anhydrous ethanol (5 mL) at 0° was stirred with sodium borohydride (700 mg) overnight. The mixture was cooled to 0°, treated with acetic acid (5 mL), stirred for 1 h at 0°, and then concentrated to dryness under reduced pressure. A solution of the residue in dichloromethane was filtered and eluted from a short column of silica gel (CH_2Cl_2, then 10% MeOH in CH_2Cl_2) to afford **6** (453 mg, 89%), m.p. 69°. ^{1}H-N.m.r. data (400 MHz, CD_3OD): δ 0.98 (t, 3 H, *J* 7.5 Hz, H-7), 1.65 (dd, 1 H, $J_{3,4a}$ 9.7, J_{gem} 15 Hz, H-4a), 1.78 (m, 2 H, H-6), 2.17 (dd, 1 H, $J_{3,4b}$ 1.2, J_{gem} 15 Hz, H-4b), 3.48 (ddd, 1 H, $J_{1,2}$ 3.9, $J_{2,3}$ 6.4 Hz, H-2), 3.63, 3.79 (each 1 d, each 1 H, *J* 12 Hz, H-5′), 3.62 (m, 1 H, H-1b), 3.76 (dd, 1 H, $J_{1,2}$ 3.9, J_{gem} 11 Hz, H-1a), 3.95 (ddd, 1 H, $J_{2,3}$ 6.4, $J_{3,4b}$ 1.2, $J_{3,4a}$ 9.7 Hz, H-3), 4.5 (s, 2 H, CH_2Ph), 7.4 (m, 5 H, Ph). F.a.b.-mass spectrum (positive ion): *m/z* 307 (20, M^+ + Na), 289 (1), 265 (1), 201 (10), 199 (11), 91 (100).

Anal. Calc. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.37; H, 8.58.

(3R)-3-Benzyloxy-3-(hydroxymethyl)pentanal (**8**). — A solution of **6** (1.52 g, 5.36 mmol) in water (30 mL) and 1,4-dioxane (30 mL) was treated with $NaHCO_3$ (1.2 g) and, during 45 min, with $NaIO_4$ (1.2 g, 3.3 equiv.; 3 portions), then stirred for 18 h, filtered, and extracted thrice with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford **8** (0.81 g, 68%) as an oil; ν_{max} 3400 (OH), 1720 (CO), 730 cm^{-1} (Ar). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 0.96 (t, 3 H, *J* 7.4 Hz, H-5), 1.78 (m, 2 H, *J* 7.4 Hz, H-4), 2.69 (m, 2 H, $J_{1,2}$ 2.5 Hz, H-2), 4.33 (m, 2 H, H-3′), 4.48 (s, 2 H, CH_2Ph), 7.32 (m, 5 H, Ph), 9.87 (t, 1 H, *J* 2.5 Hz, H-1). Mass spectrum (70°): *m/z* 222 (2%, M^+), 191 (100, M^+ − CH_2OH), 186 (36), 174 (26).

(2R,3S,5R)-5-Benzyloxy-1,5-bis(triphenylmethyloxy)-2,3-heptanediol (**7**). — A solution of **6** (6.56 g, 23.10 mmol) in anhydrous pyridine (100 mL) was treated portionwise with trityl chloride (16.09 g, 57.7 mmol; 2.5 equiv.), and then stirred

for 18 h at room temperature[15]. The mixture was poured onto ice and extracted with CH_2Cl_2 (3 × 50 mL), the combined extracts were concentrated to dryness under reduced pressure, and the residue was purified by column chromatography (CH_2Cl_2) on silica gel, to yield **7** (16.164 g, 91%) as an oil. ^{1}H-N.m.r. data: δ 0.70 (t, 3 H, J 7.5 Hz, H-7), 1.72 (m, 3 H, H-4a, H-6), 2.01 (m, 1 H, H-4b), 3.27 (ddd, 2 H, $J_{1a,2}$ 4.7, $J_{1b,2}$ 6.3, J_{gem} 9.5 Hz, H-1), 3.68 (m, 1 H, H-3), 3.96 (s, 2 H, H-1), 4.40 (dd, 2 H, J 10.7 Hz, CH_2Ph), 7.30 (m, 35 H, 7 Ph).

Anal. Calc. for $C_{53}H_{52}O_5$: C, 82.78; H, 6.82. Found: C, 83.00; H, 6.79.

(3R)-3-Benzyloxy-3-(triphenylmethyloxymethyl)pentanal (**9**). — A solution of **7** (1.35 g, 1.75 mmol) in 1,4-dioxane (12 mL) and water (3 mL) was treated with sodium periodate (1.35 g, 3.6 equiv.) as described for **8**. The major part of the glyoxal trityl ether was crystallized from ether–pentane. Chromatography on silica gel (CH_2Cl_2/10% pentane) of the material in the mother liquor gave **9** (602 mg, 74%), isolated as an oil, $[\alpha]_D^{21}$ −14° (*c* 0.2, chloroform); ν_{max} 1720 cm^{-1}. ^{1}H-N.m.r. data (400 MHz): δ (t, 3 H, J 7.4 Hz, H-5), 1.77 (m, 2 H, J 7.4 Hz, H-4), 2.71 (d, 2 H, J 2.7 Hz, H-2), 3.24, 3.36 (2 d, 2 H, J 10 Hz, H-3'), 4.36 (dd, 2 H, J 2.7, J 11 Hz, CH_2Ph), 7.5 (m, 20 H, 4 Ph), 9.77 (t, 1 H, J 2.7 Hz, H-1).

Anal. Calc. for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.04; H, 7.06.

(3'R)-2-[3-Benzyloxy-3-(triphenylmethyloxymethyl)pentyl]-1,4-dihydroxy-9,10-anthraquinone (**11**). — A solution of anhydrous piperidine (5.45 mL, 55 mmol) in 2-propanol (12 mL) was treated at 0° with acetic acid (1.63 mL, 28.50 mmol). A solution of **9** (802 mg, 1.72 mmol) and leucoquinizarin (**10**, 1.34 g, 5.53 mmol) in 2-propanol (12 mL) was added under nitrogen and stirred for 8 h at 18°. Air was bubbled through the solution to re-oxidize the anthrahydroquinone, and the mixture was poured into cold M HCl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to dryness. Column chromatography of the residue on silica gel (CH_2Cl_2) gave **11** (0.936 g, 79%), m.p. 92°, $[\alpha]_D^{26}$ +8° (*c* 0.1, chloroform); ν_{max} 3440 (OH), 1630 (quinone), 1590 cm^{-1} (Ar); λ_{max} (lg ε) 208 (4.54), 250 (4.8), 255 (4.74), 287 (4.18), 319 (3.68), 470 (4.16), 484 nm (4.19). ^{1}H-N.m.r. data (400 MHz): δ 0.82 (t, 3 H, J 7.4 Hz, CH_3CH$_2$), 1.84 (m, 2 H, J 7.4 Hz, CH_2CH$_3$), 2.00 (m, 2 H, $J_{1',2'}$ 5.2 Hz, H-2'), 2.45 (m, 1 H, H-1'), 2.65 (m, 1 H, H-1'), 3.21 (dd, 2 H, J 9.5, J 25 Hz, CH_2OTr), 7.0 (s, 1 H, H-3), 7.83 (m, 2 H, H-6,7), 8.3 (m, 2 H, H-5,8), 12.93 (s, 1 H, OH), 13.35 (s, 1 H, OH). E.i.-mass spectrum: *m/z* 688 (0.05%, M$^+$), 580 (0.03, M$^+$ − OBn), 397 (15, M$^+$ − CH$_2$OTr − H$_2$O), 307 (12, M$^+$ + 1 − CH$_2$OTr − H$_2$O − Bn), 243 (100), 91 (58).

Anal. Calc. for $C_{46}H_{40}O_6$: C, 80.21; H, 5.85. Found: C, 80.12; H, 5.94.

(3'R)-2-[3-Benzyloxy-3-(hydroxymethyl)pentyl]-1,4-dihydroxy-9,10-anthraquinone (**12**). — (*a*) A solution of **8** (100 mg, 0.45 mmol) in tetrahydrofuran (20 mL) and 2-propanol (10 mL) was treated under nitrogen with **10** (436 mg, 1.8 mmol) and M NaOH (2.7 mL), and then stirred for 5 h at room temperature. Air was then bubbled through the solution to re-oxidize the anthrahydroquinone. The mixture was acidified with M HCl and extracted with dichlormethane, and the extract was dried (Na_2SO_4) and concentrated to dryness. T.l.c. (CH_2Cl_2–2%

MeOH) of the residue afforded **12** (35 mg, 17%), m.p. 77° (from ether), $[\alpha]_D^{25}$ +32° (*c* 0.1, chloroform); ν_{max} 3450 (OH), 1620 (quinone), 1590 cm^{-1} (Ar); λ_{max} (lg ε) 208 (4.39), 233 (4.32), 250 (4.62), 286 (4.01), 483 (4.02), 515 (3.83), 562 nm (2.76). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 0.99 (t, 3 H, *J* 7.5 Hz, CH_3CH_2), 1.75 (m, 2 H, *J* 7.5 Hz, CH_2CH_3), 1.92 (m, 2 H, H-2'), 2.80 (t, 2 H, *J* 8 Hz, CH_2Ph), 3.69 (s, 2 H, CH_2OH), 4.52 (s, 2 H, CH_2Ph), 7.15 (s, 1 H, H-3), 7.38 (m, 5 H, Ph), 7.81 (m, 2 H, H-6,7), 8.32 (m, 2 H, H-5,8), 12.94 (s, 1 H, OH), 13.45 (s, 1 H, OH). Mass spectrum (140°): *m/z* 446 (2, M^+), 398 (4), 397 (2), 340 (14), 307 (16), 267 (10), 91 (100).

Anal. Calc. for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.66; H, 6.19.

(*b*) A suspension of **11** (100 mg, 0.15 mmol) in 1-butanol (4 mL) was treated[19] with trifluoroacetic acid (2 mL). After 10 min, the mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. Concentration of the extract afforded **12** quantitatively.

(2R)-2-Benzyloxy-4-(1,4-dihydroxy-9,10-anthraquinon-2-yl)-2-ethylbutanal (**13**). — A solution of **12** (0.46 g, 0.91 mmol) in anhydrous dimethyl sulfoxide (11.62 mL) and toluene (21.06 mL) was treated under nitrogen with pyridine (0.56 mL), trifluoroacetic acid (0.12 mL, 1.64 mmol), and dicyclohexylcarbodi-imide[20] (2.61 g, 12.66 mmol). The solution was stirred for 21 h at room temperature, then diluted with ether (50 mL), and treated for 30 min with a solution of oxalic acid (1.14 g) in methanol (15 mL). The mixture was filtered, extracted twice with aqueous $NaHCO_3$ and then with water, dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Crystallization of the residue from ether–pentane afforded **13** (331 mg, 82%), m.p. 92°, $[\alpha]_D^{20}$ +11.6° (*c* 0.1, chloroform); ν_{max} 1620 (quinone), 1590 cm^{-1} (Ar); λ_{max} (lg ε) 209 (447), 250 (4.44), 287 (3.79), 318 (3.34), 469 (3.79), 484 (3.83), 517 (3.64), 564 nm (2.84). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 0.96 (t, 3 H, *J* 7.4 Hz, CH_3CH_2), 1.89 (dq, 2 H, *J* 7.4 Hz, CH_2CH_3), 2.12 (m, 2 H, H-3), 2.64 (m, 1 H, H-4), 2.85 (m, 1 H, H-4), 4.56 (dd, 2 H, J_{gem} 11 Hz, CH_2Ph), 7.11 (s, 1 H, H-3'), 7.37 (m, 5 H, Ph), 7.81 (m, 2 H, H-6',7'), 8.32 (m, 2 H, H-5',8'), 9.75 (s, 1 H, CHO), 12.90 (s, 1 H, OH), 13.38 (s, 1 H, OH). E.i.-mass spectrum (100°): *m/z* 444 (60%, M^+), 415 (100, $M^+ - CHO$), 397 (16, $M^+ - CHO - H_2O$), 307 (24), 267 (12).

Anal. Calc. for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 73.06; H, 5.56.

(7R,8R)-8-Benzyloxy-8-ethyl-7,8,9,10-tetrahydro-6,7,11-trihydroxy-5,12-naphthacenequinone (**14**). — A solution of **13** (380 mg, 0.86 mmol) in CH_2Cl_2 (8 mL) was treated at 0° under nitrogen with tetrabutylammonium hydrogensulfate (20 mg), a solution of $Na_2S_2O_4$ (900 mg, 5.16 mmol) in water (20 mL) and M NaOH (9 mL), and 4 drops of Triton B. The mixture was re-oxidized with air after stirring for 4 h at room temperature, acidified with M HCl, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated to dryness, and the residue was crystallized from CH_2Cl_2–ether to afford **14** (273 mg, 67%), m.p. 186°, $[\alpha]_D^{21}$ −105° (*c* 0.11, chloroform); ν_{max} 3500 cm^{-1} (broad OH); λ_{max} (lg ε) 208 (4.32), 252 (4.57), 287 (3.89), 458 (3.87), 517 (3.76), 562 nm (2.69). ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 1.10 (t, 3 H, *J* 7.4 Hz, CH_3CH_2), 1.91 (m, 2 H, CH_2CH_3),

2.01 (m, 1 H, H-9), 2.08 (m, 1 H, H-9), 2.68 (dt, 1 H, *J* 6.1, J_{gem} 19.2 Hz, H-10), 2.97 (ddd, *J* 2, *J* 4.2, J_{gem} 19.2 Hz, H-10), 4.45 (dd, 2 H, *J* 11.2, *J* 23.6 Hz, CH_2Ph), 4.96 (s, 1 H, H-7), 7.21 (m, 5 H, Ph), 7.80 (m, 2 H, H-2,3), 8.31 (m, 2 H, H-1,4), 13.33 (s, 1 H, OH), 13.62 (s, 1 H, OH).

Anal. Calc. for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 73.19; H, 5.40.

(7R,8R)-8-Ethyl-7,8,9,10-tetrahydro-6,7,8,11-ttetrahydroxy-5,12-naphthacenequinone (**15**) *(4-deoxy-γ-rhodomycinone).* — A solution of **14** (102 mg, 0.23 mmol) in dry CH_2Cl_2 (10 mL) was treated at −78° under nitrogen with a M solution of boron tribromide in CH_2Cl_2 (0.5 mL). The mixture was stirred for 5 h at room temperature, then treated with saturated aqueous $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2, and the extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from ether afforded **15** (51 mg, 63%), m.p. 204°. ^{1}H-N.m.r. data (400 MHz, $CDCl_3$): δ 1.11 (t, 3 H, *J* 7.4 Hz, Me), 1.69 (m, 2 H, *J* 7.4 Hz, CH_2CH_3), 1.93 (m, 2 H, H-9), 2.84 (ddd, 1 H, J_{gem} 19.5, *J* 6.6, *J* 10.6 Hz, H-10), 2.97 (ddd, 1 H, J_{gem} 19.5, *J* 6.0, *J* 2.4 Hz, H-10), 4.79 (s, 1 H, H-7), 7.82 (m, 2 H, H-2,3), 8.33 (m, 2 H, H-1,4), 13.35 (s, 1 H, OH), 13.69 (s, 1 H, OH). E.i.-mass spectrum (130°): *m/z* 354 (38%, M^+), 336 (24, $M^+ - H_2O$), 307 (14, $M^+ - H_2O$ − Et), 279 (38), 254 (100), 239 (20).

4-Deoxy-α-rhodomycinone (**16**). — Hydroxylation at C-7, via bromination and solvolysis was performed on **15** (100 mg), to afford **16** (82 mg, 77%) as described[22]. All the physical properties were identical with those of a sample prepared independently[8].

REFERENCES

1 F. ARCAMONE, *Doxorubicin,* Academic Press, New York, 1980.
2 C. A. SCOTT, D. WESTMACOTT, M. J. BROADHURST, F. L. THOMAS, AND M. J. HALL, *Br. J. Cancer,* 53 (1986) 595–600.
3 T. TSUJI, H. MOROKA, M. TAKEZAWA, T. ANDO, A. MURAI, AND H. SHIBAI, *Agric. Biol. Chem.*, 50 (1986) 1697–1701.
4 S. T. CROOKE AND S. D. REICH (Eds.), *Anthracyclines, Current Status and New Developmens,* Academic Press, New York, 1980.
5 F. ARCAMONE, in J. M. CASSADY AND J. D. DOWES (Eds.), *Anticancer Agents based on Natural Product Models,* Vol. 16, Academic Press, New York, 1980, pp. 1–41.
6 K. KROHN AND V. S. EKKUNDI, in H. E. J. ATTA-UR-RAHMAN (Ed.), *Studies in Natural Product Chemistry,* Elsevier, Amsterdam, 1989, in print.
7 K. KROHN AND U. MÜLLER, *Tetrahedron,* 42 (1986) 6635–6644.
8 K. KROHN AND I. HAMANN, *Liebigs Ann. Chem.*, (1988) 949–953.
9 K. KROHN, H. RIEGER, E. BROSER, P. SCHIESS, S. CHEN, AND T. STRUBIN, *Liebigs Ann. Chem.*, (1988) 943–948.
10 J. C. FLORENT, J. UGHETTO-MONFRIN, AND C. MONNERET, *J. Org. Chem.*, 52 (1987) 1051–1056.
11 J.-C. FLORENT, A. GENOT, AND C. MONNERET, *Tetrahedron Lett.*, 26 (1985) 5295–5298.
12 D. J. MINCHER AND H. SHAW, *J. Chem. Soc., Perkin Trans. 1,* (1984) 1279–1282.
13 C. MARSCHALK, F. KOENIG, AND N. OUROUSOFF, *Bull. Soc. Chim. Fr.*, 3 (1936) 1545–1575.
14 K. KROHN, E. BROSER, AND H. HEINS, *Carbohydr. Res.*, 164 (1987) 59–69.
15 S. K. CHAUDHARY AND O. HERNANDEZ, *Tetrahedron Lett.*, (1979) 95–98.
16 K. KROHN AND C. HEMME, *Liebigs Ann. Chem.*, (1979) 19–34.
17 C. E. LEWIS, *J. Org. Chem.*, 35 (1970) 2938–2942.
18 D. J. MINCHER, G. SHAW, AND E. DE CLERCQ, *J. Chem. Soc., Perkin Trans. 1,* (1983) 613–618.
19 M. MACCOSS AND D. J. CAMERON, *Carbohydr. Res.*, 60 (1978) 206–209.
20 K. E. PFITZNER AND J. G. MOFFAT, *J. Am. Chem. Soc.*, 87 (1965) 5670–5678.
21 K. KROHN AND B. BEHNKE, *Liebigs Ann. Chem.*, (1983) 1818–1838.
22 K. KROHN AND W. PRIYONO, *Tetrahedron,* 40 (1984) 4609–4616.