Anthracyclinones. Part 2. The Use of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose as a Chiral Template Precursor in an Anthracyclinone Synthesis

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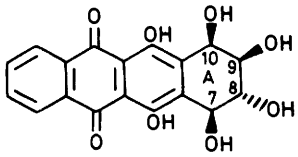
Reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose-(1,4) (**7a**) with *leuco*-quinizarin (**3**) in alkaline solution at 0 °C, followed by aerial oxidation, gave a good yield of (5*S*)-3-*O*-benzyl-1,2-*O*-isopropylidene-5-(quinizarin-2-yl)-α-D-xylofuranose (**8**) which with acid produced (5*S*)-3-*O*-benzyl-5-(quinizarin-2-yl)-α(β)-D-xylopyranose (**11**). Reaction of (**11**) with periodate, cold alkaline dithionite, aerial oxidation, and acid treatment gave the *O*-benzyl pentahydroxy anthracyclinone (**13**). Structures of the compounds were confirmed by u.v., mass, i.r., and ^{1}H n.m.r. spectroscopy.

In Part 1 of this series[1] we described the synthesis of the novel anthracyclinone (**1**) by a modified Marschalk reaction[2] of the aldehydoarabinose derivative (**2**) with *leuco*-quinizarin (**3**) in alkaline solution followed by ring closure of the first formed arabinityl quinizarin (**4**). We have been interested to extend this reaction to produce modifications in the stereochemistry in ring A of the novel tetrasubstituted anthracyclinone (**1**) and at the same time to explore the scope of other carbohydrates as chiral template precursors of this ring.

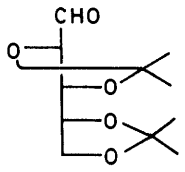
1,2:5,6-Di-*O*-isopropylidene-α-D-glucose (**5a**) is a very readily available and relatively inexpensive material which is easily converted into various potentially useful precursors of the required type including the 3-*O*-benzyl derivative (**5b**) which has been prepared by *O*-alkylation of (**5a**) with benzyl chloride and a base.[3] The *O*-benzyl derivative (**5b**) is readily converted into the diol (**6**) by treatment with 90% aqueous acetic acid during 7 h at 37 °C, and the diol with sodium metaperiodate smoothly furnishes the aldehyde (**7a**).[3]

Reaction of the foregoing aldehyde (**7a**) and *leuco*-quinizarin (**3**) with aqueous sodium hydroxide in methanolic tetrahydrofuran (THF) at 0 °C for 30 min under nitrogen followed by aerial oxidation gave a good (48%) yield of (5*S*)-3-*O*-benzyl-1,2-*O*-isopropylidene-5-(quinizarin-2-yl)-α-D-xylofuranose (**8**) which readily crystallised after a single chromatographic purification on silica gel. The structure assigned to compound (**8**) was confirmed by elemental analysis, by its i.r. [*e.g.* $\nu_{max.}$ 1 380 cm^{-1} (CMe_2)] and mass [*e.g.* *m/z* 518 (M^+) and ^{1}H n.m.r. [*e.g.* absence of signal for 2′-H, signals at δ 4.06 (d, 5-OH), 5.55 (d, 5-H), and 7.67 (3′-H) and full assignment of all other protons] spectra, and by its subsequent reactions. The spectroscopic data and homogeneity of the compound on t.l.c. in several solvent systems suggested that it was a single pure diastereoisomer as was the case with the analogous compound (**4**) described earlier.[1]

Reaction of the aldehyde (**7a**) with methylmagnesium iodide has been reported[4] to produce the L-*ido*-isomer (**9**) exclusively, in agreement with Cram's rule[5] and this, if relevant, would support an assignment of the 5*S* configuration to (**8**).† In this example reaction probably takes place through an intermediate having a planar five-membered ring that would direct addition to give the L-*ido* form. An alternative might include analogy with the reported reaction[6] of the *O*-methyl aldehyde (**7b**) with methanenitronate ion. In this case the L-*ido* form is also produced, accompanied however by the D-*gluco* form (**10**) which predominates (ratio L-*ido* to D-*gluco* *ca.* 1:2). In this reaction, which is characterised by the methanenitronate ion



(**1**)



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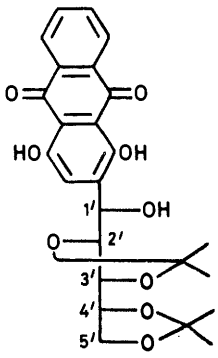
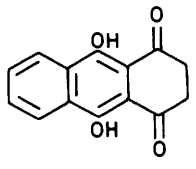
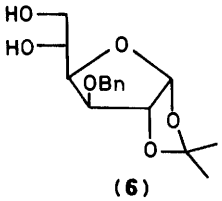


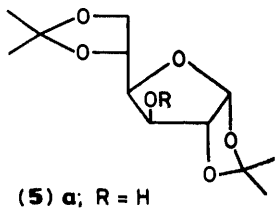
(**4**)



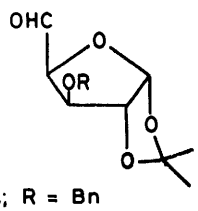
(**3**)



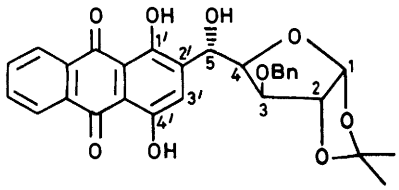
(**6**)



(**5**) **a**; R = H
b; R = Bn



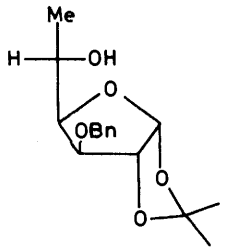
(**7**) **a**; R = Bn
b; R = Me



(**8**)

Bn = benzyl

† Recent *X*-ray crystal data (unpublished) indicate that the compound has indeed the 5*S* configuration.



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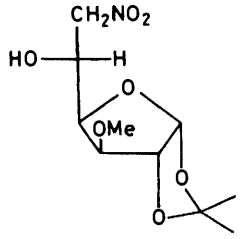
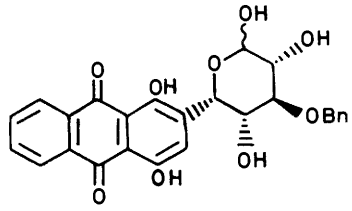


(10)

preferentially attacking the *re* face to produce the *R* configuration at C-5, the rotameric orientation of the aldehyde group is not contstrained by complexing as with the Grignard reaction. A preferred arrangement of the carbonyl double bond antiperiplanar to the C-4–O bond, plausible on grounds of dipole considerations, would be able to account for the result. These results applied to the quinizarinyl xylose (**8**) would therefore suggest the D-*gluco* (5*R*) form to be the more likely structure.

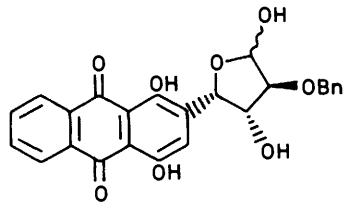
The isopropylidene group in compound (**8**) was readily removed by refluxing with 70% aqueous acetic acid to give an almost quantitative yield of a single product homogeneous on t.l.c. examination. The compound may be assigned the pyranose structure (**11**).



(11)

Although the mass spectrum might appear marginally to favour the furanose form [M^+, 478, *m/z* 460 ($M - H_2O$), 269 (80%), and 91 ($C_7H_7^+$, 100)] the ^{1}H n.m.r. spectrum leaves little doubt that the compound has the pyranose structure (**11**). In particular the ^{1}H n.m.r. spectrum possessed (in addition to the two phenolic hydroxy proton signals) three hydroxy proton signals (doublets) all of which exchanged with D_2O. One of the hydroxy proton signals appears as a distinct doublet at low field (centred at δ 6.87, *J* 8.1 Hz). This proton is coupled to a one-proton doublet (*J* 8.1 Hz) centred at δ 5.08 which collapses to a singlet in D_2O. The signal at δ 5.08 is assigned to the anomeric proton, at C-1 of the pyranose ring system, coupled to the 1-hydroxy proton. The benzylic hydrogen signal of 5-H in (**8**) is a doublet coupled to the 5-OH proton. However, in the hydrolysed product the corresponding 5-H proton signal is attributed to a one-proton singlet (δ 5.2), confirming the pyranose structure (**11**), the C-5–O bond being incorporated into the pyranose ring system. Spin decoupling experiments indicated that the two remaining hydroxy proton signals at δ 5.32 (d, *J* 6.3 Hz) and δ 4.8 (d, *J* 4.5 Hz) coupled to methine proton signals at δ 3.74 and δ 4.04 may respectively be assigned to the 2-OH and 4-OH protons. The configuration at the anomeric centre cannot be assigned with certainty but the data would indicate the presence of a single anomer and this would not be unreasonable since the quinizarinyl moiety at the pure chiral centre C-5 might well be expected to direct the course of cyclisation to the pyranose form so as to favour a specific single anomeric species.

A solution of the pyranosyl quinizarin (**11**) in acetone–THF was treated with aqueous sodium metaperiodate (1.1 equiv.) at 0 °C for 3 h to produce a quantitative yield of a transformed product which was readily isolated in solid form and homogeneous on t.l.c. in several solvent systems. The structure assigned to this compound (**12**) was confirmed by elemental

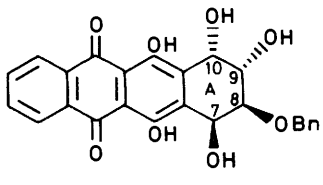


(12)

analysis, i.r. (absence of aldehyde absorption), and mass [M^+, 448, *m/z* 430 ($M - H_2O$), 412 ($M - 2H_2O$, 70%), 240 (quinizarin), and 91 ($C_7H_7^+$, 100)] spectral data.

In preliminary experiments the reaction of (**12**) with sodium dithionite in aqueous alkali at 0 °C for 30 min resulted in the complete disappearance of starting material with production of a single major product. Aerial oxidation of the *leuco*-derivative, produced under these conditions, to the corresponding quinizarin derivative however is relatively slow since first the excess of dithionite has to be oxidised, and after acidification of the oxidised solution and work-up the proportion of initial major product had decreased (t.l.c.) and several by-products had appeared, the chromatographic behaviour of which suggested that loss of the benzylic hydroxy group may have occurred due to over-exposure of the first formed compound to sodium dithionite. However, if the crude *leuco*-derivative is first isolated by acidification of the alkaline dithionite reaction mixture under nitrogen, and then redissolved in dilute aqueous dithionite-free alkali and the solution aerated, a more rapid oxidation occurs and a major product is produced and readily obtained in crystalline form after column chromatography on silica gel.

The anthracyclinone structure (**13**) assigned to the compound was confirmed by elemental analysis and spectroscopic data. The u.v. absorption spectrum of the compound in methanol was typical of a 2,3-disubstituted quinizarin and further confirmation that cyclisation to the anthracyclinone system had taken place was provided by the ^{1}H n.m.r. spectrum which showed complete absence of the 3′-H singlet of the quinizarin chromophore. In addition to the molecular ion (M^+, 448) the mass spectrum of the compound showed *m/z* 430 ($M - H_2O$), 412 ($M - H_2O$), and 91 (100%) and the presence of an intense fragment peak at *m/z* 298 could be attributed to the characteristic retro-Diels–Alder fragment diagnostic for the tetracyclic system possessing hydroxy functions at C-7 and C-10.



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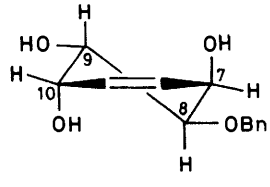

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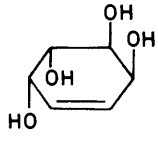

(15)

The 400 MHz n.m.r. spectrum of (**13**) in $CDCl_3$ possessed the following features. In addition to the AA'BB' signal of the four aromatic protons there was a five-proton multiplet centred at δ 7.4 corresponding to the protons of the phenyl group. The spectrum also showed three hydroxy proton singlets (in addition to 2 phenolic OH signals) at δ 2.84—3.14, all of which exchanged with D_2O. The methylene protons of the 8-*O*-benzyl group were geminally coupled (*J* 10 Hz) and appeared at δ 4.77 and 4.88. Two other signals [both double doublets (*J* 3.75, 10 Hz)] were present at δ 4.03 and 4.29, each integrating to one proton, the former being assigned 8-H and the latter to 9-H, since 8-H would be expected to occur at slightly higher field owing to the shielding effect of the *O*-benzyl group. It was deduced from the spectrum that $J_{8,9} = 10$ Hz and that $J_{7,8} = J_{9,10} = 3.75$ Hz. These values strongly suggest structure (**13**) for the anthracyclinone. The conformation of ring A is probably that shown in (**14**) which is the same as the known conformation of the model compound conduritol E (**15**),[7] where the coupling constants $J_{1,2} = J_{3,4} = 4.3$ Hz, and $J_{2,3} = 9.3$ Hz, correlate well with the corresponding couplings $J_{7,8}$, $J_{9,10}$, and $J_{8,9}$ of (**13**), respectively.

Experimental

Evaporations were carried out with a Buchi rotary evaporator, under water-pump vacuum with a flask temperature below 40 °C, unless otherwise stated. U.v. spectra were measured with a Unicam SP 800 spectrophotometer, i.r. spectra with a Perkin-Elmer 681 spectrophotometer, ^1H n.m.r. (100 MHz) spectra with a JEOL JNM-MH-100 spectrometer (tetramethylsilane as internal standard), unless otherwise stated, and mass spectra with an A.E.I. MS 903 spectrometer. We thank P.C.M.U. and I.C.I. Ltd. for high-resolution ^1H n.m.r., and field desorption mass spectra. Silica gel (0.05—0.2 mm, 70—270 mesh; Machery-Nagel and Co.) was used for column chromatography. Thin-layer chromatograms were run on Silica Gel 60 F_{254} (0.2 mm thick) pre-coated aluminium plates (Merck) and Cellulose F_{254} (0.1 mm thick) pre-coated aluminium plates (Merck) in the systems (A) toluene–ethyl acetate (4:1); (B) toluene–ethyl acetate (1:1), (C) chloroform–ethyl acetate (4:1).

3-O-*Benzyl*-1,2-O-*isopropylidene*-α-D-xylo-*pentodialdofuranose*-(1,4) (**7a**).—3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**)[3] (8.8 g) was dissolved in methanol (84 cm³) and the solution was cooled to 0 °C and vigorously stirred while a solution of sodium periodate (6.72 g) in water (84 cm³) was added dropwise during 90 min. The mixture was stirred for a further 90 min at 0 °C and ethane-1,2-diol (1 cm³) was added. The solution was filtered and concentrated (< 30 °C) to remove methanol. The remaining aqueous solution was saturated with sodium chloride and extracted with chloroform (6 × 50 cm³). The organic layer was dried ($MgSO_4$), filtered, and evaporated to leave a pale yellow syrup of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose-(1,4) (**7a**) (7.6 g, 96.1%), $\nu_{max.}$(KBr) 3 460 (OH), 1 740 (CHO), and 1 380 cm⁻¹ (CMe_2). The compound was used immediately in the following preparation.

(5S)-3-O-*Benzyl*-1,2-O-*isopropylidene*-5-(*quinizarin*-2-*yl*)-α-D-*xylofuranose* (**8**).—To a solution of *leuco*-quinizarin (6.6 g) in methanol (200 cm³) and THF (250 cm³) cooled to 0 °C was added 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose-(1,4) (7.6 g) and the mixture was then treated with a solution of sodium hydroxide (5 g) in water (30 cm³) for 30 min under nitrogen. T.l.c. [System (A)] showed one major product (R_F 0.64), in addition to traces of other compounds (R_F 0.61 and R_F 0.0) and quinizarin (R_F 0.86). A steady stream of air was passed through the reaction mixture for 2 h and the resultant purple solution was added dropwise to a rapidly stirred mixture of hydrochloric acid (35 cm³; 36%), water (70 cm³), and crushed ice (70 g). The resultant red precipitate (10.8 g) was collected by filtration, washed with water, and air-dried.

A solution of the solid (10 g) in toluene–ethyl acetate (4:1) was filtered and applied to a silica gel column (7 × 25 cm) and eluted by the same solvent mixture. The major product fraction [R_F 0.64, System (A)] was separated from quinizarin and the minor products of the reaction, and was obtained in crystalline form upon evaporation of the solvent mixture. (5S)-3-O-*Benzyl*-1,2-O-*isopropylidene*-5-(*quinizarin*-2-*yl*)-α-D-*xylofuranose* (**8**) (6.78 g, 48%) crystallised from ethanol as fine red needles, m.p. 182 °C (Found: C, 67.15; H, 5.0%; M^+, 518. $C_{29}H_{26}O_9$ requires C, 67.2; H, 5.0%; *M*, 518); *m/z* 518, 503 (*M* − CH_3), 269, 240, and 91 (C_7H_7, 100%); $\nu_{max.}$ 3 475 (OH), 1 625 (quinone), and 1 380 cm⁻¹ (CMe_2); δ ($CDCl_3$; 220 MHz) 1.34 and 1.45 (2 × 3 H, CMe_2), 4.06 (1 H, d, $J_{5.5\text{-OH}}$ 2.7 Hz, 5-OH, exch. with D_2O), 4.32 1 H, d, ($J_{1,2}$ 4.2 Hz, 2-H), 4.65 and 4.87 (2 × 1 H, d, *J* 11.8 Hz, OCH_2Ph), 4.75 (2 H, m, 3- and 4-H), 5.55 (1 H, d, $J_{5.5\text{-OH}}$ 2.7 Hz, 5-H), 6.11 (1-H, d, $J_{1,2}$ 4.2 Hz, 1-H), 7.42 (m, 5 H, Ph), 7.67 (s, 1 H, 3'-H), AA'BB' signal [δ_A 7.79—7.86 (6'- and 7'-H), δ_B 8.26—8.35 (5'- and 8'-H)], 12.88 (1 H, s, 4'-OH, exch. D_2O), and 13.48 (1 H, s, 1'-OH, exch. D_2O); $\lambda_{max.}$(EtOH) (log $\varepsilon_{max.}$) 208 (4.43), 230 (4.28), 251 (4.55), 280 (3.99), and 480 nm (3.90).

(5S)-3-O-*Benzyl*-5-(*quinizarin*-2-*yl*)-α-(β)-D-*xylopyranose* (**11**).—3-*O*-Benzyl-1,2-*O*-isopropylidene-5-(quinizarin-2-yl)-α-D-xylofuranose (**8**) (3 g) was dissolved in aqueous acetic acid (70%; 250 cm³) and the solution was heated under reflux for 1 h. T.l.c. [System (B)] revealed the complete disappearance of the starting material (R_F 0.85), and the presence of a single new product, R_F 0.48. The solution was evaporated to dryness and added toluene was repeatedly evaporated to give a solid residue, (5R-3-O-*benzyl*-5-(*quinizarin*-2-*yl*)-α-(β)-D-*xylopyranose* (**11**) (2.7 g, 97.5%), which crystallised from ethanol as orange-red platelets, m.p. 192 °C (Found: C, 65.3; H, 4.55%; M^+, 478. $C_{26}H_{22}O_9$ requires C, 65.25; H, 4.6%; *M*, 478); *m/z* (*M* − H_2O), 269, 240, and 91 ($C_7H_7^+$, 100%); δ[$(CD_3)_2SO$] 3.74 (1 H, dd, $J_{2.2\text{-OH}}$ 6.3 Hz, 2-H), 3.88 (1 H, t, 3-H), 4.04 (1 H, dd, $J_{4,4\text{-OH}}$ 4.5 Hz, 4-H), 4.8 (1 H, d, *J* 4.5 Hz, 4-OH, exch. D_2O), 5.08 (1 H, d, $J_{1.1\text{-OH}}$ 8.1 Hz, 1-H), 5.2 (1 H, s, 5-H), 5.32 (1 H, d, *J* 6.3 Hz, 2-OH, exch. with D_2O), 6.87 (1 H, d, *J* 8.1 Hz, 1-OH, exch. with D_2O), 7.43 (6 H, m, 3'-H and Ph), AA'BB' signal [δ_A 7.88—8.0 (6'- and 7'-H), δ_B 8.1—8.25 (5'- and 8'-H)], and 10.2 and 10.74 (2 × 1 H, 1'- and 4'-OH, both exch. with D_2O).

(4R)-2-O-*Benzyl*-4-(*quinizarin*-2-*yl*)-α-(β)-D-*threose* (**12**).—The foregoing xylopyranose derivative (1 g) was dissolved in THF (200 cm³) and acetone (500 cm³) and the solution was cooled to 0 °C. A solution of sodium periodate (0.44 g) in water (30 cm³) was added to the mixture, and the temperature was kept at 0 °C for 3 h. T.l.c. [System (B)] indicated complete disappearance of starting material (R_F 0.48), and the presence of a single product (R_F 0.79). The solution was evaporated to dryness and the residue was extracted with chloroform (3 × 15 cm³). Evaporation of the extract gave a homogeneous (t.l.c.) red solid (probably a formate ester) which when dissolved in aqueous sodium hydroxide (1.5%), followed by acidification, afforded a solid precipitate (0.92 g), less mobile on t.l.c. (R_F 0.7) in the same solvent system. The O-*benzyl*-D-*threose* derivative (**12**) (0.92 g) was obtained as an orange-red solid, m.p. 184 °C, homogeneous on t.l.c. in several solvent systems (Found: C, 67.15; H, 4.4%; M^+, 448. $C_{25}H_{20}O_8$ requires C, 67.0, H, 4.45%; *M*, 448); *m/z* 430 (*M* − H_2O), 412 (*M* − $2H_2O$), 240, and 91 ($C_7H_7^+$, 100%); i.r. (KBr) no aldehyde absorption.

(7S, 8S, 9S, 10S)-8-*Benzyloxy*-7,8,9,10,-*tetrahydro*-6,7,9,10,11-*pentahydroxynaphthacene*-5,12-*dione* (**13**).—A solution of the foregoing threose derivative (**12**) (0.7 g) in methanol (20 cm^3) was cooled to 0 °C and treated with a solution of 4% aqueous sodium hydroxide (25 cm^3) containing sodium dithionite (0.4 g) for 30 min under nitrogen. T.l.c. [System (B)] showed the absence of starting material (R_F 0.7), the presence of one major product (R_F 0.41) and a second component (R_F 0.65), in addition to some other material (R_F = 0.0). The solution was poured into iced 5M-hydrochloric acid (100 cm^3) which afforded a brownish yellow precipitate (of the *leuco*-forms of the reaction products) which was collected by filtration and washed with water (10 × 100 cm^3). The solid was then dissolved in aqueous sodium hydroxide (2%; 50 cm^3) and the solution was aerated for 20 min, then acidified at 0 °C with 2M-hydrochloric acid to afford a red precipitate (0.67 g) which was washed with water and air-dried. A solution of the solid in toluene–ethyl acetate (1:1) was applied to a silica gel column (2 × 25 cm) and eluted by the same solvent mixture. An homogeneous fraction of the major product (R_F 0.41) was eluted from the column and evaporated to leave a red solid. Thus, the *benzyloxynaphthacenedione dihydrate* (0.44 g, 62%) crystallised from aqueous acetic acid as red needles, m.p. 196 °C (Found: C, 61.8; H, 4.9%; M^+, 44.8. $C_{25}H_{20}O_8 \cdot 2H_2O$ requires C, 61.95; H, 4.95%; *M*, 448); *m/z* 430 ($M - H_2O$), 412 ($M - 2H_2O$), 298 [retro-Diels–Alder fragment], 280 (298 − H_2O), 270 (298 − CO), and 91 ($C_7H_7^+$, 100%); $\lambda_{max.}$(EtOH) 252, 275, 281, and 390—550 nm (characteristic of a 2,3-disubstituted quinizarin); δ ($CDCl_3$; 400 MHz) 2.84, 3.0, and 3.14 (2 × 1 H, 7-, 9-, and 10-OH, all exch. with D_2O), 4.03 (1 H, dd, $J_{7.8}$ 3.75, $J_{8.9}$ 10 Hz, 8-H), 4.29 (1 H, dd, $J_{9.10}$ 3.75, $J_{8.9}$ 10 Hz, 9-H), 4.77 and 4.88 (2 × 1 H, d, *J* 10 Hz, CH_2Ph), 5.34 and 5.39 (2 × 1 H, d, $J_{7.8} = J_{9.10}$ = 3.75 Hz, 7- and 10-H), 7.4 (5 H, m, Ph), AA′BB′ signal [δ_A 7.8—7.88 (2- and 3-H), δ_B 8.27—8.38 (1- and 4-H)], and 13.41 and 13.47 (2 × 1 H, s, 6- and 11-OH, exch. with D_2O).

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