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Multigram scale synthesis of formyl tetra-*O*-benzyl-β-D-*C*-glucopyranoside using benzothiazole as a formyl group equivalent

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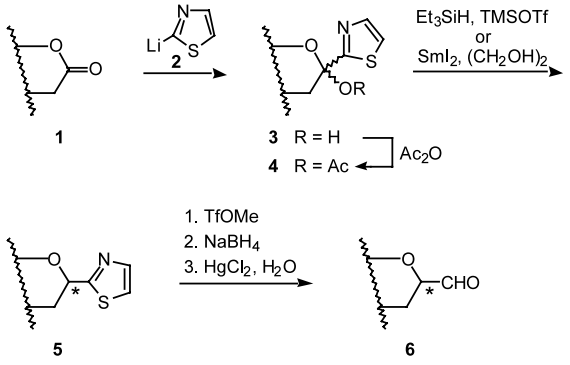
Abstract—The addition of 2-lithiobenzothiazole to D-gluconolactone followed by deoxygenation of the resulting ketose affords a mixture of benzothiazolyl α- and β-D-glucopyranoside; treatment of this mixture with sodium methoxide gives the β-anomer from which the title aldehyde is obtained in a pure form by transformation of the benzothiazole ring into the formyl group.

C-Glycosides are non-natural analogues of *O*- and *N*-glycosides in which the exocyclic heteroatom has been replaced by an all-carbon tether linking the aglycone moiety to the anomeric position.[1] These hydrolytically stable compounds can act as glycosidase inhibitors[2] or models for the study of carbohydrate recognition in biological systems.[3] Following this concept, during the last years we have prepared various *C*-di- and oligosaccharides,[4] *C*-glycosyl amino acids,[5] and *C*-glycosyl [60]fulleropyrrolidines.[6] In all cases the syntheses relied on the use of formyl *C*-glycosides **6** (Scheme 1) as versatile and configurationally stable building blocks. The strategy involved the coupling of the sugar aldehyde with another sugar moiety or an aglycone residue via a carbon–carbon bond forming reaction. Several *C*-glycosyl aldehydes were made available in our laboratory[4f,7] via the thiazole-based one-carbon homologation[8] of furanoses and pyranoses (Scheme 1). Since no epimerization occurs in the unmasking of the thiazole ring to the formyl group, the anomeric configuration of the final product was established in the deoxygenation step and thus the sugar aldehyde **6** has the same configuration as the thiazolyl *C*-glycoside **5**.



Scheme 1.

Although in most cases we obtained **5** as a single anomer via a highly stereoselective deoxygenation reaction, in the D-*gluco* series both thiazolyl *C*-glycosides **8** and **9** were formed (Scheme 2).[4f,7] However, the individual anomers were separated and readily transformed into the corresponding α- and β-linked formyl *C*-glycosides **10** and **11**.[9,10]

An approach toward the diastereoselective synthesis of the sugar aldehyde **11** has been recently proposed by Labéguère et al.[11] The method, based on the addition of the bis(methylthio)methane carbanion to lactone **7**, subsequent deoxygenation of the ketose, and unmasking of the formyl group, was actually a slight modification of a closely related synthesis of **11** reported some years ago by Genêt and co-workers.[12,13] Unfortunately, the yield of the key step, i.e. the conversion of the deoxygenated adduct into the aldehyde **11** was not reported.[11] Hence the efficiency of the method of Labéguère remains undetermined. Nevertheless, this paper prompted us to report on our efficient multigram scale

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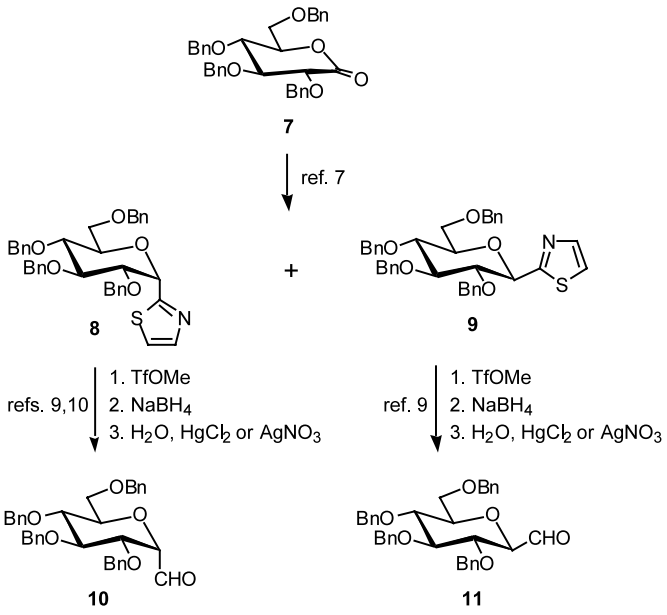
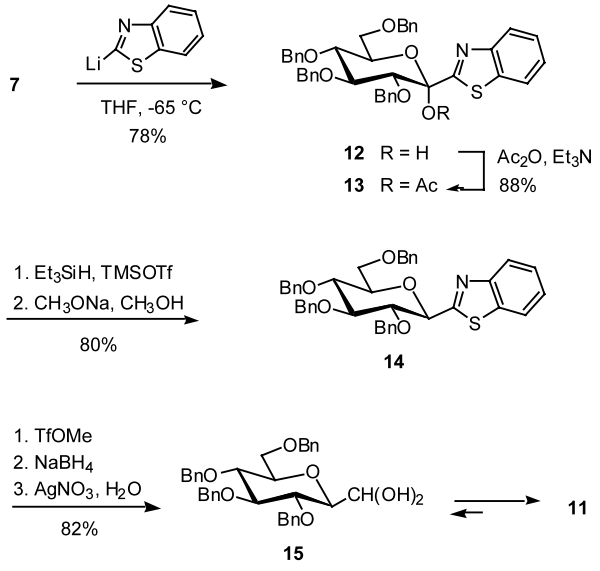


Scheme 2.

synthesis of formyl *C*-glucopyranoside **11** exploiting the benzothiazole ring as a formyl group equivalent.[14] The reaction at low temperature of D-gluconolactone[15] **7** (13.6 g) with 2-lithiobenzothiazole, prepared in situ from butyllithium and benzothiazole, afforded the ketose **12**[16] as a single anomer in 78% yield (58% by direct crystallization from the crude mixture) (Scheme 3). The activation of the anomeric position by *O*-acetylation gave crystalline **13**[17] that was submitted to the silane-based deoxygenation in the presence of trimethylsilyl triflate (TMSOTf) as a Lewis acid. This reaction quantitatively afforded a ca. 4:6 mixture of benzothiazolyl α- and β-D-*C*-glucosides from which the β-anomer **14** was recovered as white

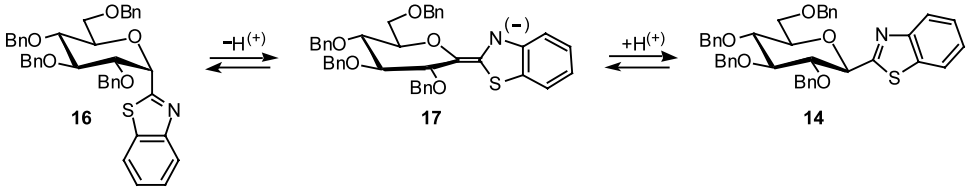


Scheme 3.

crystals by trituration with cyclohexane.[18] The mother liquor containing the α-anomer **16** was then treated at room temperature with sodium methoxide in methanol to give the almost complete transformation of that compound into the more stable equatorial isomer **14** (Scheme 4). Upon trituration of the crude reaction mixture with cyclohexane the β-*C*-glucoside **14** was recovered in a pure crystalline form and 80% combined yield from **13**.[18] The anomeric configuration of **14** was confirmed by ^{1}H NMR analysis since a coupling constant of 9.0 Hz was observed between the H-1 and H-2 protons. This large value indicates a transdiaxial arrangement of the above mentioned protons as expected for a β-D-glucopyranoside derivative adopting a $^4C_1$ conformation. Finally, the conversion of the benzothiazole ring of **14** into the formyl group was carried out on a multigram scale as well through a three-step reaction sequence involving *N*-methylation, hydride reduction, and metal-assisted hydrolysis to give the formyl *C*-glucopyranoside **11** together with its hydrated form, the *gem*-diol **15**, in a rewarding 82% yield without chromatographic purification.[19] The latter compound was isolated as an amorphous solid by trituration at room temperature with cyclohexane and characterized by high-field NMR spectroscopy. We observed that **15** slowly equilibrated in solution of $CDCl_3$ to give the sugar aldehyde **11**. However, heating at 160°C in DMSO-d_6 allowed the fast conversion of the mixture of **11** and **15** into almost pure **11**.

Hence, the efficient base-promoted transformation of the benzothiazolyl α-*C*-glucoside **16** into the β-anomer **14** allows to overcome the serious drawback in this method due to the unselective deoxygenation of the ketose acetate **13**. Very likely the equilibration of **16** into **14** takes place through the sugar carbanion **17** enjoying a considerable stabilization by delocalization of the charge in the benzothiazole ring (Scheme 4). The formation of small amounts of 1-*C*-benzothiazolyl-3,4,6-tri-*O*-benzyl-D-glucal originated by elimination of the benzyloxy group at C-2 of **17** also supports the proposed pathway. Quite surprisingly a similar equilibration was not observed by treating the thiazolyl α-*C*-glucoside **8** with sodium methoxide since only unchanged **8** was recovered after 24 h at room temperature. On the other hand, harsher reaction conditions (reflux, 24 h) afforded a mixture of **8** and **9**, and 1-*C*-thiazolyl-glucal derivative in a ca. 1:2:1 ratio.

In summary we have demonstrated that the replacement of thiazole with benzothiazole as a masked formyl group constitutes a substantial improvement in the preparation of tetrabenzylated formyl β-D-*C*-glucopyranoside. The use of benzothiazole allowed to elegantly overcome the unselectivity of the ketose deoxygenation and led to highly crystalline intermediates which were handled in a multigram scale to give the target sugar aldehyde avoiding column chromatography purification.



Scheme 4.

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9. In earlier work (Ref. 7b) the use of $HgCl_2$ in the unmasking step of the thiazole ring to the formyl group afforded the pure β-linked aldehyde **11** in 76% yield from **9** whereas a 9:1 mixture of **10** and **11** was obtained from **8**. However, we have now observed that employing $AgNO_3$ in the unmasking protocol gives the α-linked aldehyde **10** in pure form and 85% yield (see the experimental procedure in Ref. 10). In a similar way the β-linked aldehyde **11** is obtained in 86% yield.
10. A mixture of **8** (182 mg, 0.30 mmol), activated 4-Å powdered molecular sieves (0.3 g), and anhydrous CH_3CN (3 mL) was stirred at rt for 10 min, then methyl triflate (44 μL, 0.39 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0°C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (3 mL) was added $NaBH_4$ (23 mg, 0.60 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in CH_2Cl_2 (50 mL) was washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated to afford a pale yellow syrup. To a vigorously stirred solution of the thiazolidines in CH_3CN (3 mL) was added dropwise H_2O (0.3 mL) and then $AgNO_3$ in one portion (51 mg, 0.30 mmol). The mixture was stirred at rt for 10 min, then diluted with 1 M phosphate buffer at pH 7 (10 mL) and partially concentrated to remove CH_3CN (bath temperature not exceeding 40°C). The suspension was extracted with CH_2Cl_2 (40+10 mL), the combined organic phases were dried (Na_2SO_4), and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 30 mL) was filtered through a pad of Celite (0.5×3 cm, *h*×*d*), and concentrated to afford **10** (141 mg, 85%) as a colorless syrup more than 95% pure by ^1H NMR analysis; $[\alpha]_D = +87$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 25°C, 400 MHz): δ 9.98 (s, 1 H, H-1), 7.38–7.24 and 7.18–7.12 (2 m, 20 H, 4 Ph), 4.86 and 4.72 (2 d, 2 H, $J = 11.8$ Hz, PhCH_2), 4.85 and 4.77 (2 d, 2 H, $J = 11.3$ Hz, PhCH_2), 4.76 and 4.47 (2 d, 2 H, $J = 11.0$ Hz, PhCH_2), 4.62 and 4.48 (2 d, 2 H, $J = 12.2$ Hz, PhCH_2), 4.38 (d, 1 H, $J_{2,3} = 6.7$ Hz, H-2), 3.98 (dd, 1 H, $J_{3,4} = 8.8$ Hz, H-3), 3.99–3.95 (m, 1 H, H-6), 3.72 (dd, 1 H, $J_{6,7a} = 2.5$, $J_{7a,7b} = 10.8$ Hz, H-7a), 3.68 (dd, 1 H, $J_{6,7b} = 3.6$ Hz, H-7b), 3.68–3.61 (m, 2 H, H-4, H-5). The aldehyde **10** was stable in solution of $CDCl_3$ for 3 days at rt. Afterwards, a partial conversion into **11** was observed.
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15. Known lactone **7** (Kuzuhara, H.; Fletcher, H. *J. Org. Chem.* **1967**, *32*, 2531) was prepared on a 5–15 g scale in quantitative yield by oxidation of the corresponding hemiacetal with pyridinium chlorochromate (Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647).
16. To a cooled (−65°C), stirred solution of *n*-BuLi (22.1 mL, 35.35 mmol, of a 1.6 M solution in hexane) in anhydrous Et_2O (80 mL) was added dropwise a solution of freshly distilled 2-benzothiazole (4.78 g, 35.35 mmol) in anhydrous Et_2O (40 mL) over a 30 min period. The yellow solution was stirred at −65°C for 30 min, then a solution of lactone **7** (13.60 g, 25.25 mmol) in anhydrous Et_2O (80 mL) was added slowly (30 min). After an additional hour at −65°C the mixture was allowed to warm to −50°C in 30 min, then diluted with Et_2O (200 mL) and poured into 200 mL of a 1 M phosphate buffer at pH 7. The layers were separated and the organic phase was filtered to

collect the ketose **12** which crystallized during the extraction. The white solid was washed with H_2O and Et_2O (10 mL) and dried to give pure **12** (9.87 g, 58%). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 4:1 to 3:1) to give **12** (3.40 g, 20%) as a white solid; mp 115–117°C (Et_2O); $[\alpha]_D=-20$ (*c* 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08–8.05, 7.88–7.85, 7.53–7.49, and 7.44–7.40 (4 m, 4 H, BTh), 7.36–7.20 and 7.09–6.92 (2 m, 20 H, 4 Ph), 4.92 (s, 2 H, PhCH_2), 4.87 and 4.66 (2 d, 2 H, $J=10.8$ Hz, PhCH_2), 4.70 (s, 1 H, OH), 4.65 and 4.54 (2 d, 2 H, $J=12.1$ Hz, PhCH_2), 4.60 and 4.31 (2 d, 2 H, $J=11.0$ Hz, PhCH_2), 4.22 (ddd, 1 H, $J_{4,5}=10.2$, $J_{5,6a}=4.0$, $J_{5,6b}=1.8$ Hz, H-5), 4.13 (dd, 1 H, $J_{2,3}=J_{3,4}=9.2$ Hz, H-3), 4.05 (d, 1 H, H-2), 3.90 (dd, 1 H, H-4), 3.85 (dd, 1 H, $J_{6a,6b}=11.4$ Hz, H-6a), 3.72 (dd, 1 H, H-6b).

17. To a solution of **12** (5.60 g, 8.31 mmol) in anhydrous CH_2Cl_2 (50 mL) were added at rt distilled triethylamine (15 mL) and acetic anhydride (15 mL). The solution was kept at rt for 24 h and then concentrated. The residue was triturated with Et_2O (2×20 mL) to give pure **13** (5.23 g, 88%); mp 136–137°C (cyclohexane); $[\alpha]_D=+27$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06–8.03 and 7.87–7.84 (2 m, 2 H, BTh), 7.49–7.01 (m, 22 H, 4 Ph, BTh), 4.98 and 4.91 (2 d, 2 H, $J=11.0$ Hz, PhCH_2), 4.88 and 4.67 (2 d, 2 H, $J=10.5$ Hz, PhCH_2), 4.77 and 4.64 (2 d, 2 H, $J=12.0$ Hz, PhCH_2), 4.50 and 4.26 (2 d, 2 H, $J=10.8$ Hz, PhCH_2), 4.22 (dd, 1 H, $J_{2,3}=9.4$, $J_{3,4}=9.1$ Hz, H-3), 3.99 (dd, 1 H, $J_{4,5}=10.2$ Hz, H-4), 3.92 (dd, 1 H, $J_{5,6a}=3.2$, $J_{6a,6b}=11.6$ Hz, H-6a), 3.84–3.80 (m, 2 H, H-5, H-6b), 3.67 (d, 1 H, H-2), 2.24 (s, 3 H, Ac).

18. To a stirred mixture of **13** (5.73 g, 8.00 mmol), activated 4-Å powdered molecular sieves (8.0 g), and triethylsilane (12.8 mL, 80.0 mmol) in anhydrous CH_2Cl_2 (65 mL) was added TMSOTf (2.17 mL, 12.00 mmol). The mixture was stirred at rt for 1.5 h, then diluted with triethylamine (3 mL) and CH_2Cl_2 (100 mL), and filtered through Celite. The solution was washed with H_2O (30 mL), dried (Na_2SO_4), and concentrated to afford a ca. 1.5:1 mixture of **14** and **16**. The residue was triturated with cyclohexane (2×20 mL) to give pure **14** (3.16 g, 60%) as a white solid. The mother liquor was concentrated, and the residue was treated with a 0.2 M solution of CH_3ONa in CH_3OH (50 mL). After 24 h at rt the reaction mixture was neutralized with acetic acid, concentrated, diluted with CH_2Cl_2 (100 mL), washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated. The residue was triturated with cyclohexane (2×10 mL) to give **14** (1.05 g, 20%) as a white solid; mp 137–139°C; $[\alpha]_D=-11$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06–8.03 and 7.98–7.95 (2 m, 2 H, BTh), 7.58–7.00 (m, 22 H, 4 Ph, BTh), 4.96 and 4.91 (2 d, 2 H, $J=11.0$ Hz, PhCH_2), 4.87 and 4.64 (2 d, 2 H, $J=10.8$ Hz, PhCH_2), 4.78 (d, 1 H, $J_{1,2}=9.0$ Hz, H-1), 4.65 and 4.57 (2 d, 2 H, $J=12.2$ Hz, PhCH_2), 4.55 and 4.25 (2 d, 2 H, $J=10.6$ Hz, PhCH_2), 3.88 (dd, 1 H, $J_{2,3}=8.6$, $J_{3,4}=8.7$ Hz, H-3), 3.82 (dd, 1 H, H-2), 3.79 (dd, 1 H, $J_{4,5}=9.5$ Hz, H-4), 3.78 (d, 2 H, $J_{5,6}=3.2$ Hz, 2 H-6), 3.70 (ddd, 1 H, H-5).

19. A mixture of **14** (3.29 g, 5.00 mmol), activated 4-Å powdered molecular sieves (2.5 g), anhydrous CH_2Cl_2 (25 mL), and anhydrous CH_3CN (25 mL) was stirred at rt for 10 min, then methyl triflate (0.85 mL, 7.50 mmol) was added. The suspension was stirred at rt for 30 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0°C), stirred suspension of the crude *N*-methylbenzothiazolium salt in CH_3OH (50 mL) was added $NaBH_4$ (190 mg, 5.00 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in CH_2Cl_2 (200 mL) was washed with H_2O (40 mL), dried (Na_2SO_4), and concentrated to afford a pale yellow syrup (2.95 g). To a vigorously stirred solution of the diastereomeric benzothiazolines in CH_3CN (50 mL) was added dropwise H_2O (5 mL) and then $AgNO_3$ in one portion (1.70 g, 10.00 mmol). The mixture was stirred at rt for 15 min, then diluted with 1 M phosphate buffer at pH 7 (5 mL). Stirring was continued for an additional 15 min, then the reaction mixture was diluted with 1 M phosphate buffer at pH 7 (50 mL) and partially concentrated to remove CH_3CN (bath temperature not exceeding 40°C). The suspension was extracted with CH_2Cl_2 (200+50 mL), the combined organic phases were dried (Na_2SO_4), filtered through a pad of Celite (1×6 cm, *h*×*d*), and concentrated to give a yellow syrup (2.47 g). A solution of the residue in Et_2O (ca. 100 mL) was filtered through another pad of Celite (1×4 cm, *h*×*d*), and concentrated to afford **11** together with the *gem*-diol **15** (2.26 g, 82%) as a colorless syrup. High temperature ^1H NMR experiments showed that this mixture was transformed into at least 95% pure aldehyde **11**. Compound **11**. ^1H NMR ($CDCl_3$, 25°C, 400 MHz): δ 9.65 (d, 1 H, $J_{1,2}=1.6$ Hz, H-1), 7.39–7.24 and 7.18–7.12 (2 m, 20 H, 4 Ph), 4.89 (s, 2 H, PhCH_2), 4.80 and 4.54 (2 d, 2 H, $J=10.7$ Hz, PhCH_2), 4.78 and 4.64 (2 d, 2 H, $J=10.5$ Hz, PhCH_2), 4.61 and 4.55 (2 d, 2 H, $J=12.3$ Hz, PhCH_2), 3.82 (dd, 1 H, $J_{2,3}=9.8$ Hz, H-2), 3.76 (dd, 1 H, $J_{3,4}=J_{4,5}=8.7$ Hz, H-4), 3.75 (dd, 1 H, $J_{6,7a}=2.1$, $J_{7a,7b}=11.0$ Hz, H-7a), 3.70 (dd, 1 H, $J_{6,7b}=$ 4.3 Hz, H-7b), 3.67 (dd, 1 H, H-3), 3.63 (dd, 1 H, $J_{5,6}=9.6$ Hz, H-5), 3.52 (ddd, 1 H, H-6). ^1H NMR (DMSO-d_6, 160°C, 300 MHz): δ 9.63 (d, 1 H, $J_{1,2}=1.6$ Hz, H-1), 7.40–7.19 (m, 20 H, 4 Ph), 4.80 (s, 2 H, PhCH_2), 4.75 and 4.62 (2 d, 2 H, $J=11.5$ Hz, PhCH_2), 4.73 and 4.64 (2 d, 2 H, $J=11.5$ Hz, PhCH_2), 4.58 and 4.54 (2 d, 2 H, $J=11.5$ Hz, PhCH_2), 3.98 (dd, 1 H, $J_{2,3}=8.6$ Hz, H-2), 3.87 (dd, 1 H, $J_{3,4}=J_{4,5}=7.7$ Hz, H-4), 3.78 (dd, 1 H, H-3), 3.76–3.68 (m, 3 H, H-6, 2 H-7), 3.59 (dd, 1 H, $J_{5,6}=8.3$ Hz, H-5). Compound **15**. ^1H NMR ($CDCl_3$, 25°C, 400 MHz): δ 7.38–7.23 and 7.18–7.13 (2 m, 20 H, 4 Ph), 5.16 (ddd, 1 H, $J_{1,2}=1.6$, $J_{1,OH}=9.8$, $J_{1,OH}=8.4$ Hz, H-1), 4.92 (s, 2 H, PhCH_2), 4.90 and 4.71 (2 d, 2 H, $J=10.8$ Hz, PhCH_2), 4.82 and 4.56 (2 d, 2 H, $J=10.8$ Hz, PhCH_2), 4.56 and 4.51 (2 d, 2 H, $J=12.0$ Hz, PhCH_2), 3.74 (dd, 1 H, $J_{3,4}=9.2$, $J_{4,5}=8.8$ Hz, H-4), 3.73 (dd, 1 H, $J_{6,7a}=2.3$, $J_{7a,7b}=10.8$ Hz, H-7a), 3.70 (dd, 1 H, $J_{2,3}=9.4$ Hz, H-3), 3.69 (dd, 1 H, $J_{6,7b}=4.3$ Hz, H-7b), 3.62 (dd, 1 H, $J_{5,6}=9.7$ Hz, H-5), 3.51 (ddd, 1 H, H-6), 3.39 (dd, 1 H, H-2), 3.28 (d, 1 H, OH), 3.26 (d, 1 H, OH).