Carbohydrate Research, 203 (1990) 148–155
Elsevier Science Publishers B.V., Amsterdam

Note

Synthesis of the anomeric ethyl 2-(4,6-di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)acetates and their structural characterization*

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Received November 20th, 1989; accepted for publication in revised form February 11th, 1990)

Carbon–carbon bond-forming reactions at the anomeric position of carbohydrates have attracted considerable attention during the past few years in connection with the synthesis of chiral building blocks and natural products [2,6]. In a preceding paper, we described some of our results on the development of novel stereocontrolled routes of functionalized unsaturated *C*-glycopyranosyl derivatives using palladium(0)-catalyzed *C*-glycosylation of phenyl hex-2-enopyranosides with carbon nucleophiles[1]. This procedure controlled the stereochemistry of the product and the yields were excellent. It was thought that the unsaturated *C*-glycosyl derivatives **1***α* and **1***β*, obtained by this procedure with ethyl nitroacetate, should be particularly interesting as the nitro group should be covertible into other fuctionalities, or should permit *α*-alkylation. However, for such transformations to be synthetically useful, it is necessary that they proceed without anomerization. We now report the denitration of **1***α* and **1***β*, and the characterization of the resulting *C*-glycosyl derivatives **2***α* and **2***β* by n.m.r. and mass-spectral techniques.

RESULTS AND DISCUSSION

Denitration of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-*α*-D-*erythro*-hex-2-enopyranosyl)-2(*R,S*)-nitroacetate** (**1***α*) occurred readily in the presence of 4 equiv. of tributyltin hydride, with 2,2′-azoisobutyronitrile as initiator, in benzene at 80°. However, ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-D-*erythro*-hex-2-enopyranosyl)acetate (**2**) was ob-

* Part II of the series "Functionalized *C*-Glycosyl Compounds". For part I, see ref. 1.

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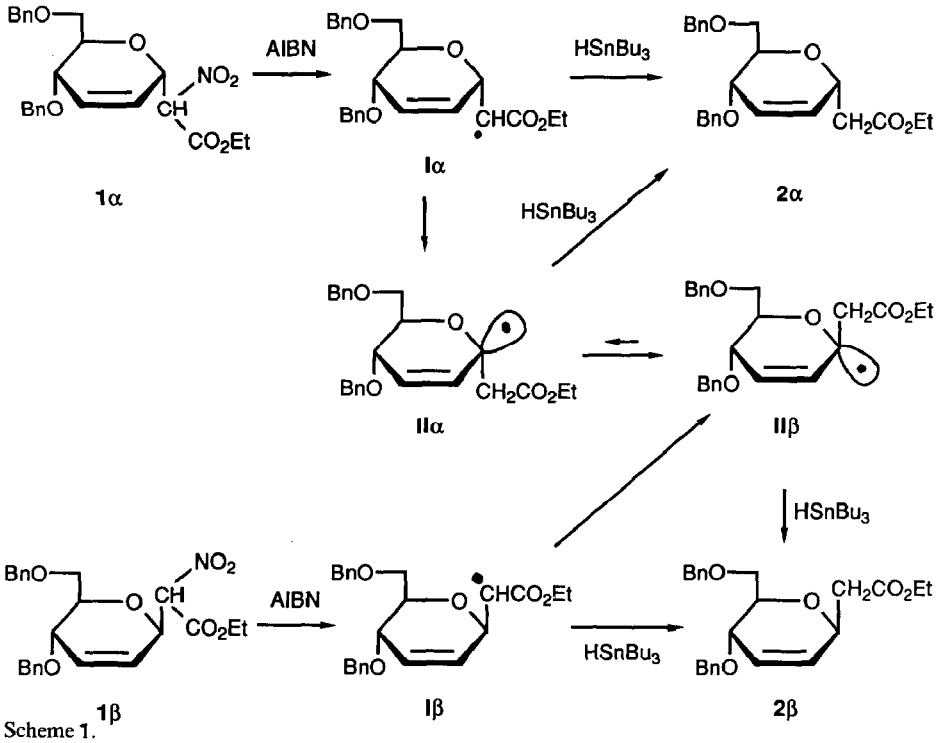
** Correctly termed ethyl 3,7-anhydro-6,8-di-*O*-benzyl-2,4,5-trideoxy-2-nitro-D-*allo*(D-*altro*)-oct-4-enonate, the name used here is for homomorphic convenience in comparing n.m.r. data for the glycopyranosyl group (Ed.).

0008-6215/90/$ 03.50

tained in 70% yield as a 54:46 mixture of *α* and *β* anomers. Performance of the reaction in toluene at 110° caused even more extensive anomerization, resulting in a 37:63 mixture (yield, 80%) of **2***α* and **2***β* when 5 equiv. of hydride were used; however, the trend was reversed to give the same yield of products in 7:3 ratio when a large excess (30 equiv.) of reductant in toluene solution was employed. In neat tributyltin hydride at 80°, decomposition took place and no **2** was formed. On the other hand, the *β* anomer **1***β* underwent denitration in toluene at 110°, in the presence of 30 equiv. of the hydride, with complete retention of configuration, to give **2***β* in 90% isolated yield.



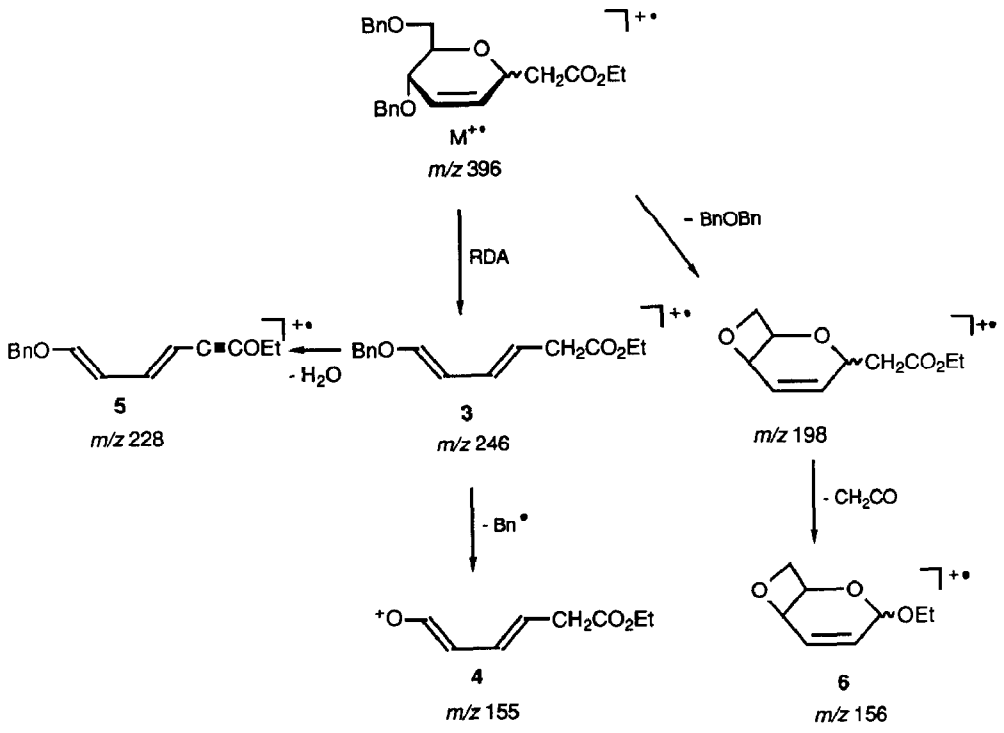
Scheme 1.

These results may be explained by the mechanism depicted in Scheme 1. The first step in the denitration of compound **1***α* is formation of the radical **I***α*, which can lead to the *C*-glycosyl compound **2***α* by reaction with tributyltin hydride. On the other hand, competitive isomerization may occur, giving the anomeric radical **II***α* in equilibrium with the more-stable[7] anomeric radical **II***β*. Hydrogen transfer to these radicals produces **2***α* and **2***β*. The isomerization of radical **I***α* to the allylic and anomeric radical **II***α* and then **II***β* is favoured by an increase in temperature, allowing the formation of a greater proportion of anomer **2***β*. On the other hand, increasing the amount of tributyltin hydride favours the immediate trapping of **I***α* and therefore increases the proportion of anomer **2***α*. In the case of **1***β*, the initial radical **I***β* isomerizes only to the more-stable anomeric radical **II***β*, and **2***β* is formed exclusively.

The **2***α* and **2***β* anomers were chromatographically separated, and it was found that the *β* anomer was the more dextrorotatory product ($[\alpha]_D^{20}$ +55.6° and +99.6°

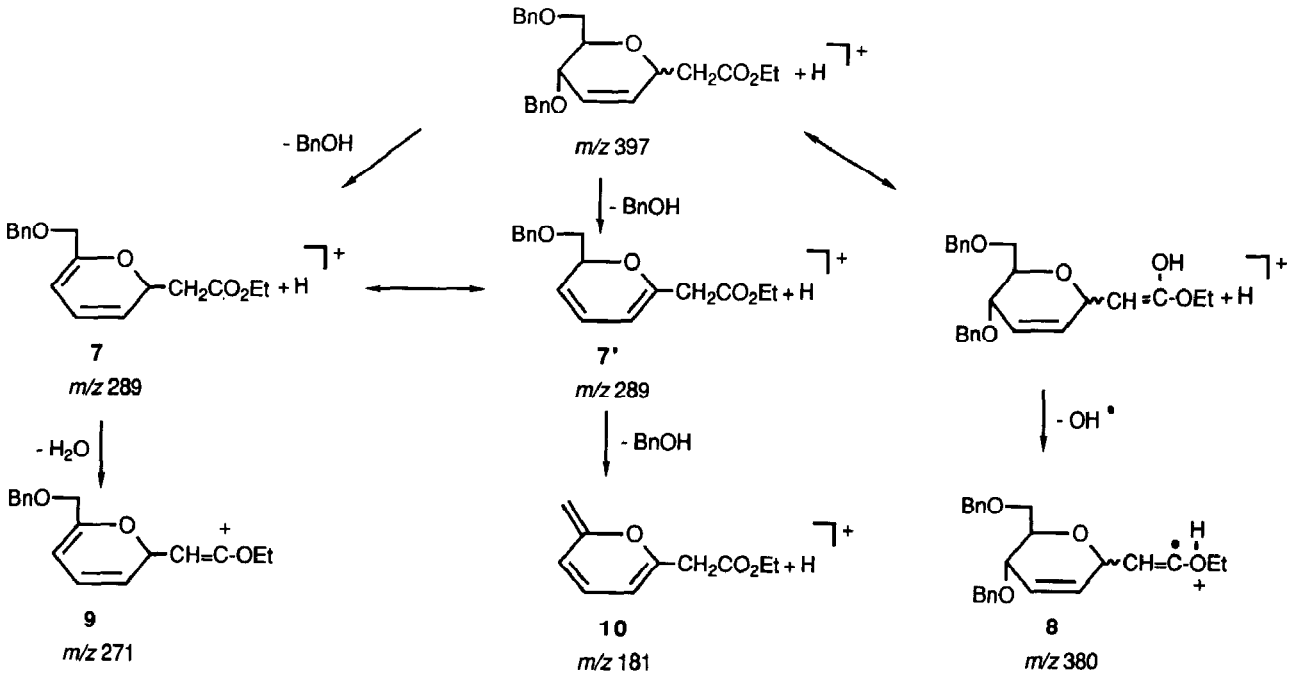
respectively for the α and β anomers). They thus did not follow the Hudson's rule[8] established for glycosides; however, recent results indicate clearly that this rule is generally violated for 2,3-unsaturated 1-*C*-glucopyranosyl derivatives[9].

The assignment of configuration at the anomeric centers was mainly established by ^{13}C-n.m.r. parameters, the two anomers showing the same $J_{4',5'}$ coupling constant ($J_{4',5'}$ 7.7 Hz). As expected from the γ-gauche effect of Stothers[10], the **2***α* anomer showed a C-5′ signal at higher field than the **2***β* anomer (δ C-5′ 71.64 p.p.m. for **2***α* and 77.60 p.p.m. for **2***β*); an upfield shift of the C-1′ signal in the α anomer was also found (δ C-1′ 69.84 p.p.m. for **2***α* and 71.56 for **2***β*). This assignment at C-1′ was confirmed by n.O.e. experiments. Irradiation at the C-2 methine protons (δ 2.51 and 2.72 p.p.m.) in compound **2***α* showed an enhancement of 8% in the C-5′ methine signal at δ 3,76 p.p.m.. Similar experiments, made on the anomer **2***β* by irradiation of the C-2 methine protons at 2.47 and 2.63 p.p.m., showed an enhancement only for the benzylic proton in position 6′. We also noted that the signal of H-1′ and the appendent CH_2 group resonate at higher frequencies in the β anomer, in accord with the results of Fraser-Reid[11].



Scheme 2. Proposed fragmentation pattern in e.i. mass-spectra of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-D-*erythro*-hex-2-enopyranosyl)acetate (**2**).

Although electron-impact mass spectrometry has been extensively used to analyze derivatized simple and complex *O*-glycosides[12,13], few studies have been directed towards the e.i. mass spectra of *C*-glycosyl compounds[14–18]. The e.i. mass spectra of



Scheme 3. Proposed fragmentation pattern of the protonated molecular ion $[M + H]^+$ in c.a.d.-m.i.k.e. and f.a.b.-c.a.d.-m.i.k.e. spectra of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-D-*erythro*-hex-2-enopyranosyl)acetate (**2**).

compounds **2***α* and **2***β* are quite similar and show (see experimental section) the molecular radical-ion $M^{+\cdot}$. The fragmentation pattern seems to be governed only by the breakdown of the molecular radical-ion $M^{+\cdot}$ by a retro-Diels–Alder reaction to afford the primary fragment-ion **3** at *m/z* 246 (Scheme 2). This ion loses a benzyl radical or a molecule of water, after enolization of the ester group, to afford the secondary fragment-ions **4** (*m/z* 155) and **5** (*m/z* 228) respectively. The molecular radical-ion M^+ could also lose a molecule of benzyl ether to give the unstable primary fragment-ion at *m/z* 198, which subsequently loses a molecule of ketene leading to the secondary fragment-ion **6** at *m/z* 156.

The positive fast-atom bombardement (f.a.b.) spectra of the functionalized *C*-glycopyranosyl derivatives **2***α* and **2***β* (see experimental section) show for the *α* anomer the protonated molecular-ion at *m/z* 397 and its $[(M + H)\text{-}H_2]^+$ fragment-ion at *m/z* 395; these two ions are also observed in the f.a.b. mass spectra of the *β* anomer in higher abundance. The f.a.b. mass spectra also show the very abundant $[(M + H) - BnOH]^+$

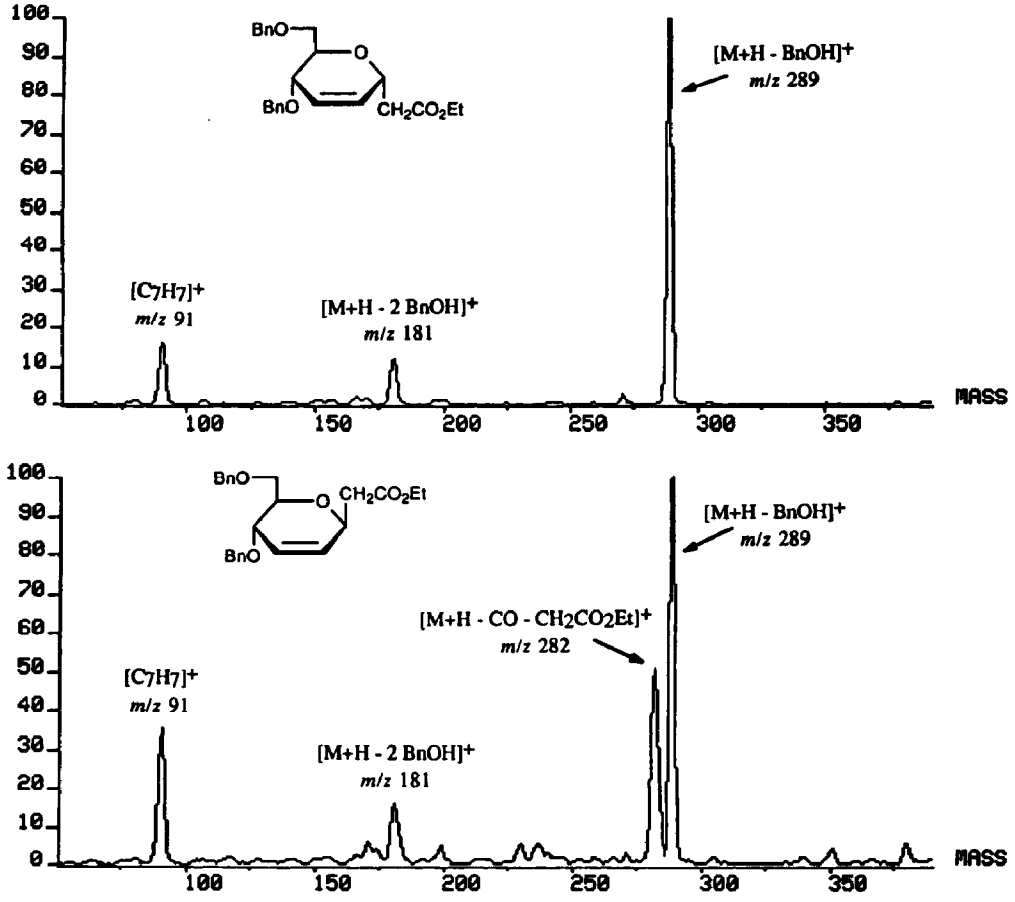


Fig. 1. F.a.b.-c.a.d.-m.i.k.e. spectra of the protonated molecular ion $[M + H]^+$ of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-D-*erytro*-hex-2-enopyranosyl)acetate (**2***α*) and (**2***β*).

fragment-ion at *m/z* 289. To obtain further structural information, the mass-analyzed ion kinetic energy (m.i.k.e.) and the collision-activated dissociation (c.a.d.)–m.i.k.e.spectra of the protonated molecular ions $[M + H]^+$ of the two anomers **2***a* and **2***β* were recorded. The f.a.b.-m.i.k.e. spectra (see Experimental section) showed a fragment-ion at *m/z* 289, assigned structure **7**, and produced by elimination of a molecule of benzyl alcohol from the $[M + H]^+$ ion (Scheme 3). Additionally for the *β* anomer, a minor fragment-ion at *m/z* 380 (structure **8**), probably produced by the loss of a hydroxyl radical, was observed.

The f.a.b.-c.a.d.-m.i.k.e. spectrum of **2***a* was more complex. The fragment-ion at *m/z* 289 is the base peak, as in the f.a.b.-m.i.k.e. spectrum. This fragment-ion **7** loses a molecule of water to afford the fragment-ion at *m/z* 271 (structure **9**). Isomerization of the conjugated double-bonds in **7** affords the isomeric fragment assigned structure **7'**, which loses an additional molecule of benzyl alcohol to afford the fragment-ion at *m/z* 181 (structure **10**). This fragment-ion could also be formed by isomerization of the double bond in the protonated molecular-ion, followed by the successive loss of two molecules of benzyl alcohol. A fragment at *m/z* 91 resulting from benzyl–oxygen cleavage was also present. The f.a.b.-c.a.d.-m.i.k.e. spectum for **2***β* shows fragment-ions at *m/z* 289, 181, and 91 identical with those found for the *α* anomer, but additionally an intense fragment-ion at *m/z* 282 was present. It can formally be derived from the protonated molecular-ion by loss of CO and CH_2CO_2Et, and because of its absence from the spectrum of **2***a*, it serves to distinguish the two anomers.

In conclusion, denitration of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-*β*-D-*erythro*-hex-2-enopyranosyl)-2(*R,S*)-nitroacetate (**1***β*) gives stereospecifically ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-*β*-D-*erythro*-hex-2-enopyranosyl)acetate (**2***β*); by the same procedure, the *α* anomer **1***a* gives mixtures of anomeric products **2***a* and **2***β*. These two anomers show identical e.i. and positive f.a.b. mass spectra. However the f.a.b.-m.i.k.e. and f.a.b.-c.a.d.-m.i.k.e. mass spectra of the protonated molecular-ions are different and are characteristic fingerprints of these molecules.

EXPERIMENTAL

General methods. — N.m.r. spectra (^1H, ^{13}C) were recorded with a Bruker MSL 300 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Mass spectra were obtained with a NERMAG R.10.10.S, VG 30 F, or VG ZAB 2-SEQ apparatus. The matrix used for the positive f.a.b., f.a.b.-m.i.k.e. and f.a.b.-c.a.d.-m.i.k.e. spectra was 3-nitrobenzyl alcohol. In this latter case, the apparatus was fitted with a cesium-ion gun delivering about 2*μ*A of cesium ion current with ~35 keV energy. C.a.d.-m.i.k.e. analyses were obtained using helium as the collision gas at such a pressure that the intensity of the mass-selected beam was decreased to 50% of its original value. All reactions were monitored by t.l.c. on Silica Gel 60 F_{254} (Merck) or h.p.l..c. on silica column (Nucleoside 100, 5 *μ*m) using 4:1 hexane–EtOAc as the eluent. Preparative column chromatography was performed on Silica Gel 60 Merck (230–400 mesh ASTM). Ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-D-*erythro*-hex-2-enopyranosyl)-2 (*R,S*)-nitroacetates (**1***α*) and (**1***β*) were obtained according to the procedure previously described[1].

*General procedure for the denitration of ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-*D*-erythro-hex-2-enopyranosyl)-2(*R,S*)-nitroacetate* (**1**). — To compound **1** (0.25 g, 0.56 mmol) dissolved in 5 mL of toluene (or benzene) under argon was added Bu_3SnH with a syringe (4.9 g, 18 mmol). 2,2′-Azoisobutyronitrile (0.082 g, 0.5 mmol) in 2 mL of toluene was added and the mixture was warmed for 3 h at 110°. After cooling, the solution was evaporated to a syrup.

*Ethyl 2-(2,3-dideoxy-4,6-di-*O*-benzyl-*D*-erythro-hex-2-enopyranosyl)acetate* (**2***a*). — Denitration of **1***a* (0.250 g, 0.56 mmol), followed by column chromatography (4:1 hexane–EtOAc), gave **2***a* (0.138 g, 56%), which was eluted first, as an oil, $[\alpha]_D^{20}$ +55.6° (*c* 1.1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$, 300 MHz): δ 1.23 (t, 3 H, CH_3), 2.51 (dd, 1 H, $J_{2a,1'}$ 6.0, $J_{2a,2b}$ 15.0 Hz, H-2a), 2.72 (dd, 1 H, $J_{2b,1'}$ 8.6, $J_{2b,2a}$ 15.0 Hz, H-2b), 3.64 (dd, 1 H, $J_{6',6''}$ 10.3, $J_{6',5'}$ 3.0 Hz, H-6′), 3.70 (dd, 1 H, $J_{6'',6'}$ 10.3, $J_{6'',5'}$ 4.3 Hz, H-6″), 3.76 (ddd, 1 H, $J_{5',4'}$ 7.7, $J_{5',6'}$ 3.0, $J_{5',6''}$ 4.3 Hz, H-5′), 4.04 (dddd, 1 H, $J_{4',5'}$ 7.7, $J_{4',3'}$ 2.2, $J_{4',2'}$ 1.7, $J_{4',1'}$ 2.1 Hz, H-4′), 4.13 (q, 2 H, O*CH*$_2$CH$_3$), 4.47 and 4.59 (2 × d, 2 × 1 H, *J* 11.4 Hz, O-C*H*$_2$Ph), 4.50 and 4.60 (2 × d, 2 × 1 H, *J* 12.4 Hz, OC*H*$_2$Ph), 4.71 (m, 1 H, $J_{1',2a}$ 6.0, $J_{1',2b}$ 8.6, $J_{1',2'}$ 2.5, $J_{1',3'}$ 2.2, $J_{1',4'}$ 2.1 Hz, H-1′), 5.84 (ddd, 1H, $J_{2',1'}$ 2.5, $J_{2',3'}$ 10.3, $J_{2',4'}$ 1.7 Hz, H-2′), 5.96 (ddd, 1 H, $J_{3',1'}$ 2.2, $J_{3',2'}$ 10.3, $J_{3',4'}$ 2.2 Hz, H-3′), and 7.2–7.4 (m, 10 H, Ph); ^{13}C-n.m.r. ($CDCl_3$, 75.45 MHz): δ 14.10 (CH_3), 39.65 (C-2), 60.49 (O*CH*$_2$-CH$_3$), 69.19 (C-6′), 69.32 (C-4′), 69.84 (C-1′), 71.02 (OCH$_2$Ph), 71.64 (C-5′), 73.33 (O*CH*$_2$Ph), 126.59 (C-2′), 130.10 (C-3′), 127.47, 127.64, 127.70, 127.80, 128.23, 128.30, 138.15 and 138.25 (C_6H_5), and 170.56 (CO); e.i. (70 eV): *m/z* (%) 246 (5.8), 228 (1.2), 181 (1.2), 156 (0.3), 155 (1.5), 130 (3.0), 107 (13), 91 (100), 77 (1.7); positive f.a.b.-m.s.: *m/z* (%) 398 (9.1), 397 (29.3), 396 (4.3), 395 (12.5), 290 (18.4), 289 (66.1), 182 (11.6), 181 (57.5), and 149 (100); positive f.a.b.-m.i.k.e. m.s.: *m/z* 289 ([M + H]$^+$ - BnOH, 100 %).

Anal. Calc. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.45; H, 7.10.

*Ethyl-2-(2,3-dideoxy-4,6-di-*O*-benzyl-*D*-erythro-hex-2-enopyranosyl)acetate* (**2***β*). — Denitration of **1***β* (0.250 g, 0.56 mmol), followed by column chromatography (4:1 hexane–EtOAc), gave **2***β* (0.221 g, 90%) as an oil, $[\alpha]_D^{20}$ +99.5° (*c* 1.1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$, 300 MHz): δ 1.24 (t, 3 H, CH_3), 2.46 (dd, 1 H, $J_{2a,1'}$ 6.8, $J_{2a,2b}$ 15.0 Hz, H-2a), 2.63 (dd, 1 H, $J_{2b,1'}$ 7.3, $J_{2b,2a}$ 15.0 Hz, H-2b), 3.63 (dd, 1 H, $J_{6',6''}$ 11.2, $J_{6',5'}$ 4.2 Hz, H-6′), 3.65 (dd, 1 H, $J_{6'',6'}$ 11.2, $J_{6'',5'}$ 4.9 Hz, H-6″), 3.73 (m, 1 H, $J_{5',6'}$ 4.2, $J_{5',6''}$ 4.9, $J_{5',4'}$ 7.7 Hz, H-5′), 4.04 (dddd, 1 H, $J_{4',5'}$ 7.7, $J_{4',3'}$ 1.7, $J_{4',2'}$ 1.8, $J_{4',1'}$ 3.0 Hz, H-4′), 4.15 (q, 2 H, O*CH*$_2$CH$_3$), 4.45 and 4.60 (2 × d, 2 × 1 H, *J* 11.3 Hz, OC*H*$_2$Ph), 4.55 and 4.62 (2 × d, 2 × 1 H, *J* 12.5 Hz, OC*H*$_2$Ph), 4.58 (m, 1 H, $J_{1',2a}$ 6.8, $J_{1',2b}$ 7.3, $J_{1',2'}$ 2.1, $J_{1',3'}$ 1.2, $J_{1',4'}$ 3.0 Hz, H-1′), 5.81 (ddd, 1 H, $J_{2',1'}$ 2.1, $J_{2',3'}$ 10.3, $J_{2',4'}$ 1.8 Hz, H-2′), 5.94 (ddd, 1 H, $J_{3',1'}$ 1.2, $J_{3',2'}$ 10.3, $J_{3',4'}$ 1.7 Hz, H-3′) and 7.22–7.34 (m, 10 H, Ph); ^{13}C-n.m.r. ($CDCl_3$, 75.45 MHz): δ 14.10 (CH_3), 40.44 (C-2), 60.37 (O*CH*$_2$CH$_3$), 69.58 (C-6′), 70.38 (C-4′), 71.08 (OCH$_2$Ph), 71.58 (C-1′), 73.29 (O*CH*$_2$Ph), 77.64 (C-5′), 126.99 (C-2′), 130.30 (C-3′), 127.38, 127.61, 127.65, 127.76, 128.18, 128.26, 138.08 and 138.40 (C_6H_5), and 170.42 (C=O); e.i. (70 eV): *m/z* (%) 246 (4.6), 228 (1.2), 181 (1.2), 156 (6.3), 155 (2.0), 130 (2.9), 107 (3.8), 91 (100), and 77 (10); positive f.a.b.-m.s.: *m/z* (%) 398 (7.0), 397 (39.2), 396 (9.5), 395 (17.4), 290 (14.1), 289 (52.9), 182 (13.9), 181 (64.8), and 154 (100); positive f.a.b.-m.i.k.e. m.s.: *m/z* 380 ([M + H]$^+$ − OH, 15%), 289 ([M + H]$^+$ − BnOH, 100%).

Anal. Calc. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.60; H, 7.06.

ACKNOWLEDGMENTS

This work was supported by the Region Rhône-Alpes. The authors thank an anonymous referee for his suggestions and his improvement of the manuscript.

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