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Note

Synthesis of furanose derivatives of 3-deoxy-D-*erythro*-2-hexulosonic acid and their 3-bromo and 3-deuterio analogs

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Abstract

Methanolysis of 2,4,6-tri-*O*-benzoyl-2,3-dibromo-3-deoxy-D-altrono-1,5-lactone gave methyl 3-bromo-3-deoxy-2,4,6-tri-*O*-benzoyl-α-D-*ribo*-hex-2-ulofuranosonate (**3**) and the anomeric mixture of the analogous 4,6-di-*O*-benzoyl derivative, having HO-2 free. Compound **3** was subjected to debromination with tributyltin hydride and tributyltin deuteride in the presence of 2,2′-azo-bisisobutyronitrile affording, respectively, the corresponding derivatives of 3-deoxy-D-*erythro*-2-hexulosonic acid and its 3-deuterio analog. The structure of the products and intermediates was established by spectroscopic methods and chemical transformations.

Keywords: 3-Deoxy-D-*erythro*-2-hexulosonic acid; 3-Deuterio derivatives; Furanose derivatives of 3-deoxy-2-hexulosonic acid; Aldonolactones; Methanolysis

1. Introduction

3-Deoxy-D-*erythro*-2-hexulosonic acid, commonly known as 3-deoxy-2-keto-D-gluconic acid is the first intermediate in the bacterial metabolism of D-gluconic and D-galactonic acids [1]. It is also a metabolite of the degradation of polygalacturonates by *Erwinia chrisantemi* [2]. The 3-deoxy-2-hexulosonic acid analog having the D-*threo* configuration was identified as a component of an extracellular polysaccharide of *Azotobacter vinelandii* [3]. For the chemical synthesis of 3-deoxy-2-hexulosonic acids a number of procedures have been developed; many of them starting from aldoses [4–8]. Just a few more recent approaches utilized 2-enonolactones as starting materials for the synthesis of 3-deoxy-D-*erythro*-2-hexulosonic acid and related compounds. Thus, Anker and co-workers [9] developed a six-step sequence from D-glucono-1,5-lactone. Limberg and Thiem [10] described the preparation of a derivative of D-galactono-1,4-lactone which underwent epimerization at C-4 during the elimination process, affording the precursors for the synthesis of 3-deoxy-2-hexulosonic acids. In connection with our studies on the use of unsaturated aldonolactones as convenient chiral templates [11], we report here a convenient access to furanose derivatives of 3-deoxy-D-*erythro*-2-hexulosonic acid, and their 3-bromo and 3-deuterio analogs.

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2. Results and discussion

The presence of benzoate and bromo substituents at C-2 in **2**, the product of bromination of **1** [12], suggested that this substance should react with such nucleophiles, as alcohols. Therefore, compound **2** was treated with methanol under reflux. Thin-layer chromatography (TLC) showed a gradual consumption of the starting material and the formation of two more-polar products. The ^{1}H NMR spectrum of the material isolated first by column chromatography showed a singlet (3 H) at δ 3.81, characteristic of a methyl ester, and the presence of 15 aromatic protons (3 benzoyl groups). The resonances for H-3 and H-4 appeared, respectively, as a doublet and a double doublet, strongly shifted upfield as compared with the spectrum of **2** [13]. The ^{13}C NMR spectrum showed the resonance of a quaternary ketal carbon at 102.3 ppm (C-2) that together with the downfield shifting for the C-5 signal (83.0 ppm) suggested that a furanose ring has been formed. Hence, the product was formulated as methyl 3-bromo-3-deoxy-2,4,6-tri-*O*-benzoyl-D-*ribo*-hex-2-ulofuranosonate (**3**). The anomeric configuration was assigned as α taking into account the probable mechanism for the formation of the furanose ring of **3**. The alcohol group at C-5, which results from the opening of the lactone by methanolysis, would approach to C-2 from the backside, with nucleophilic displacement of bromide and closure of the five-membered ring. The anomeric configuration was further confirmed as α by chemical transformations of **3**, which are described here.

The NMR spectra of the more polar product isolated from this reaction were more complex. Thus, signals for two methyl ester groups were observed and all the carbon signals appeared as two lines (in a $\sim$3:1 ratio), in particular those corresponding to the ketal carbons (100.8 and 104.7 ppm). Furthermore, the integral for the aromatic protons indicated that only two benzoyl groups remained in the molecule. These facts suggested that an anomeric mixture of methyl 3-bromo-3-deoxy-4,6-di-*O*-benzoyl-α,β-D-*ribo*-hex-2-ulofuranosonate (**4**) had been formed. This compound could result from the hydrolysis of the anomeric benzoate of **3** by the HBr released during the methanolysis. We speculated that this hydrolysis could be prevented by neutralizing the HBr generated during the reaction. Several conditions were attempted; the use of alkylamines led to partial debenzoylation, and pyridine had no effect on the product distribution. We were not able to prevent completely the formation of **4**, but when the alcoholysis was performed in the presence of basic alumina, the proportion of **4** in the reaction mixture decreased, and the overall yield of the transformation was 74%.

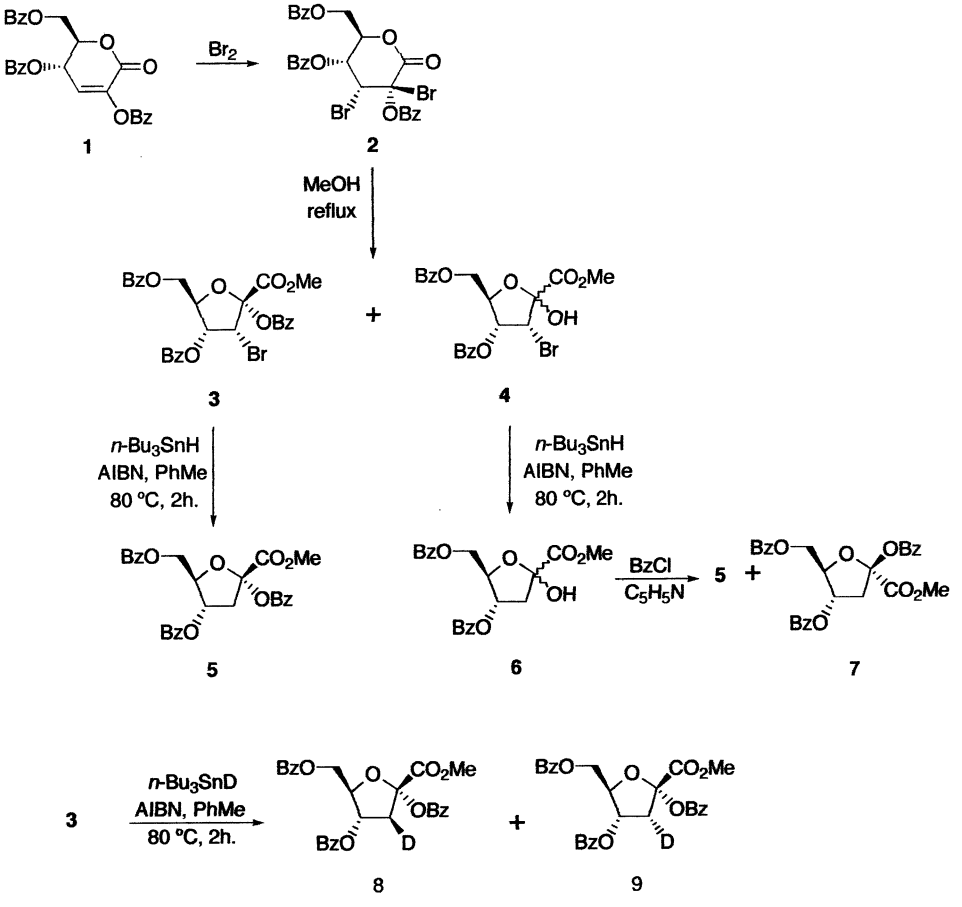
Reduction of the bromine in **3** would lead to a derivative of 3-deoxy-D-*erythro*-2-hexulosonic acid having a defined anomeric configuration. From the variety of reducing agents available, such as zinc–acetic acid, sodium cyanoborohydride–dimethyl sulfoxide and hydrogen–palladium, we found that tributyltin hydride and 2,2′-azo-bisisobutyronitrile (AIBN) was the most convenient. After the usual work-up the product of reduction (**5**) crystallized from the reaction mixture. The ^{1}H NMR spectrum of **5** confirmed the substitution of Br by H, as the resonances for H-3 and H-3′ appeared as double doublets at high fields (3.16 and 2.95 ppm, $J_{3,3'}$ 15.2, $J_{3,4}$ 6.7 and $J_{3',4}$ $\sim$1 Hz).

When the same dehalogenation was applied to compound **4** it led to the methyl 3-deoxy-2-hexulofuranosonate derivative **6** (an anomeric mixture). The configuration of both anomers was established on the basis of the chemical shifts and J values for the H-3,3′ signals (δ 2.42–3.07), applying the empirical rules described by Anker and co-workers [9]. These authors performed a careful ^{1}H NMR study on mixtures of furanoid and pyranoid methyl esters of 3-deoxy-D-*erythro*-2-hexulosonic acid. They named the hydrogens at C-3 as Ha, the one oriented towards the α face, and Hb to the opposite. In the case of furanose derivatives they found that $\delta_{Ha} > \delta_{Hb}$; that $J_{Ha,Hb}$ is larger for the α than for the β anomer, and that for the α anomer $J_{Ha,Hc} > J_{Hb,Hc}$ (Hc is H-4, this is the X component of the ABX system). Those couplings are more similar for the β anomer. Applying these rules, the signals for both anomers of **6** could be readily identified (δ H-3 and H-3′, 3.07 and 2.42, respec-

tively, for the α anomer; and 2.87 and 2.76, respectively, for the β anomer). From the integral of the signals the α:β ratio was determined to be 1.5:1. When the same analysis was applied to the ^{1}H NMR spectrum of **5** it allowed us to confirm its anomeric configuration as α, as well as that of compound **3** (the precursor of **5**).

In order to verify the results just discussed, compound **6** was benzoylated. The product obtained was homogeneous by TLC and indistinguishable from **5**. The ^{1}H NMR spectrum showed that both **5** and the corresponding β anomer **7** were present. The δ and J values obtained for the H-3 and H-3′ for each anomer showed good agreement with values predicted by Anker's rules, confirming the anomeric configuration assigned (Scheme 1).

Since 3-deoxy-2-hexulosonic acids participate in biosynthetic processes, their isotopic labeling would lead to compounds potentially useful in studies of metabolic pathways. The deuteration of **3** was attempted employing tributyltin deuteride as reducing agent. The reaction, performed under the conditions employed for the reduction with the analogous hydride, yielded a crystalline product. Its ^{1}H NMR spectrum showed, as expected, a remarkable change in the region of the H-3,3′ signals compared with those of **5**. The two signals, which appeared as a broad singlet at 2.95 ppm and a doublet at 3.16 ppm, were present in a ratio of 3:1. The broad singlet was the result of a small value for $J_{3,4}$, which indicates a *trans* relationship for H-3 and H-4 (as in **8**), whereas the $J_{3,4}$ value (6.6 Hz) was indicative of a *cis* relative orientation for H-3 and H-4 (as in **9**). The stereochemistry at C-3 showed that the replacement of bromine by deuterium took place with inversion of the configuration at C-3 to an extent of about 75%. This suggests that deuterium attacked the brominated carbon preferentially from the face opposite to that containing the anomeric substituent. Horton et al. [14] observed a sim-



Scheme 1.

ilar selectivity in the deuteration of anthracycline 2′-deoxy-2′-iodoglycoside derivatives.

The ^{13}C NMR and the mass spectra of the mixture of **8** and **9** also showed the presence of deuterium in these molecules. The ^{13}C NMR spectrum of **8** showed the C-3 signal as a triplet ($J_{C,D}$ 19 Hz) characteristic of a deuterated carbon. The pattern of fragmentation in the mass spectrum of **8** and **9** was identical to that of **5**, with most of the peaks shifted one mass unit to higher m/z values.

In summary, the sequence of β-elimination, bromination and methanolysis here reported provides a direct and high yielding access to 3-bromo derivatives of 3-deoxy-D-*erythro*-2-hexulosonic acid. They are useful intermediates for the synthesis of the corresponding 3-deuterio derivatives. An equivalent synthesis employing $^{3}HSnBu_3$ would furnish the analogous radiolabeled tritiated compounds, which are of potential value for metabolism studies.

3. Experimental

General methods.—Melting points were determined with a Fisher–Johns apparatus and are uncorrected. TLC was performed on 0.2 mm Silica Gel 60 F_{254} (E. Merck) aluminum supported plates. Detection was effected by exposure to UV light or by dipping in 5% H_2SO_4 (v/v) in EtOH, followed by charring. Column chromatography was performed with Silica Gel 60 (230–400 Mesh, E. Merck). Optical rotations were measured with a Perkin–Elmer 343 polarimeter at 25 °C. NMR spectra were recorded on a Bruker AC 200 spectrometer (^1H at 200 MHz, ^{13}C at 50 MHz) in $CDCl_3$ with Me_4Si as an internal standard. EIMS was performed with a Trio-2 VG Masslab at 20 eV.

Methyl 3-bromo-3-deoxy-2,4,6-tri-O-*benzoyl*-α-D-ribo-*hex-2-ulofuranosonate* (**3**) *and methyl 3-bromo-3-deoxy-4,6-di*-O-*benzoyl*-α,β-D-ribo-*hex-2-ulofuranosonate* (**4**)

(a) By treatment of **2** *with MeOH.* A suspension of **2** [13] (1.10 g, 1.74 mmol) in dry MeOH (15 mL) was heated at the reflux temperature under a continuous steam of N_2. After 3 h, TLC showed no starting material (R_f 0.71, 9:1 PhMe–EtOAc) and formation of two polar products having R_f 0.63 and 0.32. The mixture was concd, and the resulting syrup was chromatographed using mixtures of increasing polarity of 10:1–5:1 cyclohexane–EtOAc. The material eluted first was the oily **3** (0.20 g, 20%); $[\alpha]_D + 23°$ (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.30–7.30 (m, 15 H, H-aromatic), 5.81 (dd, 1 H, $J_{3,4}$ 6.0, $J_{4,5}$ 3.2 Hz, H-4), 4.93 (d, 1 H, H-3), 4.85 (ddd, 1 H, $J_{5,6}$ 3.6, $J_{5,6'}$ 3.1 Hz, H-5), 4.79 (dd, 1 H, $J_{6,6'}$ 12.0 Hz, H-6), 4.68 (dd, 1 H, H-6′), 3.81 (s, 3 H, CO_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.8, 165.5, 165.2 ($PhCO_2$), 164.2 (C-1), 133.8–126.3 (C-aromatic), 102.3 (C-2), 83.0 (C-5), 72.6 (C-4), 63.0 (C-6), 53.4 (CO_2CH_3), 49.9 (C-3). Anal. Calcd for $C_{28}H_{23}BrO_9$: C, 57.65; H, 3.97. Found: C, 57.84; H, 4.08.

Eluted next was **4** (0.27 g, 32%); $[\alpha]_D$ −9° (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.35–7.40 (m, 10 H, H-aromatic), 5.69 (dd, H-4), 4.92 (d, H-3), 4.82–4.53 (m, H-5,6,6′), 3.90 (s, 3 H, $CO_2CH_3\beta$), 3.76 (s, 3 H, $CO_2CH_3\alpha$); ^{13}C NMR ($CDCl_3$): δ 168.0, 166.1, 165.8, 165.7, 165.2, 164.2 ($PhCO_2$, C-1α,β), 133.6–128.2 (C-aromatic), 100.8 (C-2α), 82.2 (C-5α), 72.9 (C-4α), 63.4 (C-6α), 53.7 ($CO_2CH_3\alpha$), 49.1 (C-3α,β); and for the β anomer 104.7 (C-2β), 80.0 (C-5β), 72.4 (C-4β), 63.9 (C-6β), 53.3 ($CO_2CH_3\beta$). Anal. Calcd for $C_{21}H_{19}BrO_8$: C, 52.63; H, 4.00. Found: C, 52.58; H, 4.36.

(b) By treatment of **2** *with MeOH in the presence of* Al_2O_3. To a solution of **2** (1.46 g, 2.25 mmol) in dry MeOH (25 mL) was added Al_2O_3 (100 mg) and heated under reflux in an atmosphere of N_2. After 3 h, TLC showed the formation of the same products as in (a) and no starting **2** remaining. The mixture was filtered, concd, and chromatographed to afford **3** (0.51 g, 38%) and **4** (0.40 g, 36%). Compounds **3** and **4** gave the same physical and spectroscopic properties as those of the products described in (a).

Methyl 3-deoxy-2,4,6-tri-O-*benzoyl*-α-D-erythro-*hex-2-ulofuranosonate* (**5**).—Tributyltin hydride (0.117 mL, 0.435 mmol) and a small crystal of AIBN were added to a solution of **3** (0.17 g, 0.29 mmol) in dry toluene (0.8 mL). The solution was heated for 2 h at 80 °C, when TLC showed that the starting **3** (R_f 0.48, 3:1 cyclohexane–EtOAc, revealed as

a brown spot) was completely converted into a product of similar mobility (R_f 0.46, blue spot). The mixture was diluted with hexane (30 mL) and extracted with MeCN (2 × 30 mL). The MeCN extract was washed with hexane (30 mL), and then concd, affording crystalline **5** (90 mg, 61%). Chromatography of the material in the mother liquors led to an additional crop of **5** (34 mg, overall yield 84%). Compound **5** gave m.p. 117–118 °C (from ~10:1 hexane–EtOAc); $[\alpha]_D + 28°$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.20–7.30 (m, 15 H, H-aromatic), 5.70 (ddd, 1 H, $J_{4,5}$ 1.5 Hz, H-4), 4.91 (ddd, 1 H, H-5), 4.72, 4.60 (dd, 2 H, $J_{5,6} \sim J_{5,6'} \sim 4$, $J_{6,6'}$ 12.8 Hz, H-6,6′), 3.79 (s, 3 H, CO_2CH_3), 3.16 (dd, 1 H, $J_{3,3'}$ 15.2, $J_{3,4}$ 6.7 Hz, H-3), 2.95 (dd, 1 H, $J_{3',4}$ ~1 Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 166.6, 166.0, 165.9, 165.2 ($PhCO_2$, C-1), 133.6, 133.4, 133.2, 130.0, 129.7, 129.1, 128.4, 128.3 (C-aromatic), 106.3 (C-2), 86.2 (C-5), 74.6 (C-4), 63.8 (C-6), 53.2 (CO_2CH_3), 41.2 (C-3). MS *m*/*z*: 445 (3.9%), 383 (1.8%), 260 (3.5%), 228 (1.4%), 155 (1.8%), 139 (33.8%), 105 (100%). Anal. Calcd for $C_{28}H_{24}O_9$: C, 66.66; H, 4.79. Found: C, 66.31; H, 4.89.

Methyl 3-deoxy-4,6-di-O-*benzoyl*-α,β-D-erythro-*hex-2-ulofuranosonate* (**6**).—A solution of **4** (92 mg, 0.158 mmol) in PhMe (0.6 mL) was treated with tributyltin hydride (0.13 mL, 0.474 mmol) and AIBN, as described for **3**. Chromatography (15:1 PhMe–EtOAc) afforded **6** (50.5 mg, 80%), which was slower moving (R_f 0.30, 6:1 PhMe–EtOAc) than the starting **4** (R_f 0.35); ^1H NMR ($CDCl_3$): δ 8.20–7.35 (m, 10 H, H-aromatic), 5.69 (m, H-4β), 5.64 (ddd, H-4α), 4.77 (ddd, $J_{4,5}$ 3.7 Hz, H-5α), 4.70–4.55 (H-5β, 6α, 6β, 6′β), 4.53 (dd, $J_{5,6'}$ 4.0, $J_{6,6'}$ 12.0 Hz, H-6′α), 3.87 (s, CO_2CH_3β), 3.74 (s, CO_2CH_3α), 3.07 (dd, $J_{3,3'}$ 14.4, $J_{3,4}$ 7.5 Hz, H-3α), 2.87 (dd, $J_{3,3'}$ 13.9, $J_{3,4}$ 5.5 Hz, H-3β), 2.76 (dd, $J_{3',4}$ 7.0 Hz, H-3′β), 2.42 (dd, $J_{3',4}$ 2.6 Hz, H-3′α); ^{13}C NMR ($CDCl_3$): δ 170.0, 169.9, 166.2, 166.0 ($PhCO_2$, C-1), 133.3–128.3 (C-aromatic), 102.4 (C-2α), 83.1 (C-5α,β), 75.2 (C-4α,β), 63.9 (C-6α), 53.3 (CO_2CH_3α,β), 40.8 (C-3α), 102.7 (C-2β), 64.7 (C-6β), 41.0 (C-3β).

Methyl 3-deoxy-2,4,6-tri-O-*benzoyl*-β-D-erythro-*hex-2-ulofuranosonate* (**7**) *and its* α *anomer* (**5**).—Compound **6** (44 mg, 0.11 mmol) was dissolved in dry pyridine (0.5 mL) and benzoyl chloride (0.5 mL) was added. The mixture was stirred at rt for 3 h, when TLC showed the conversion of starting **6** (R_f 0.30, 6:1 PhMe–EtOAc) into a less polar product (R_f 0.65). The mixture was diluted with CH_2Cl_2 (50 mL), washed with 0.1 M aq HCl (50 mL), satd aq $NaHCO_3$ (50 mL), and with satd aq NaCl (50 mL). The organic layer was dried ($MgSO_4$), concd, and the residue was chromatographed (15:1 hexane–EtOAc) affording the mixture of anomers **5** and **7** (51 mg, 92%). From the NMR spectra of this mixture it was possible to identify the signals corresponding to **7**. ^1H NMR ($CDCl_3$): δ 8.20–7.35 (m, 15 H, H-aromatic), 5.75 (m, 1 H, H-4), 4.90 (m, 1 H, H-5), 4.69 (dd, 1 H, $J_{5,6}$ 4.8, $J_{6,6'}$ 12.0 Hz, H-6), 4.59 (dd, 1 H, $J_{5,6'}$ 4.7 Hz, H-6′), 3.85 (s, 3 H, CO_2CH_3), 3.19 (dd, 1 H, $J_{3,3'}$ 14.9, $J_{3,4}$ 6.8 Hz, H-3), 3.02 (dd, 1 H, $J_{3',4}$ 4.7 Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 167.6, 166.0, 165.9, 165.0 ($PhCO_2$, C-1), 133.6-128.3 (C-aromatic), 105.5 (C-2), 84.8 (C-5), 73.9 (C-4), 63.8 (C-6), 53.2 (CO_2CH_3), 42.2 (C-3).

Methyl 3-deoxy-3-deutero-2,4,6-tri-O-*benzoyl*-α-D-arabino- (**8**) *and* α-D-ribo-*hex-2-ulofuranosonate* (**9**).—Compound **3** (0.22 g, 0.377 mmol) was dissolved in toluene (1.5 mL) and to the solution were added tributyltin deuteride (0.153 mL, 0.566 mmol) and a small amount of AIBN. The reaction and work-up was conducted as described for the preparation of **5**. Crystallization from 10:1 hexane–EtOAc afforded the crystalline mixture of **8** and **9** (105 mg, 55%). From the mother liquors an additional amount was obtained (75 mg, overall yield 95%); m.p. 116–117 °C; $[\alpha]_D + 27.4°$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.20–7.30 (m, 15 H, H-aromatic), 5.70 (m, H-4), 4.92 (m, H-5), 4.68 (m, H-6,6′), 3.79 (s, CO_2CH_3), 3.16 (d, 0.25 H, $J_{3,4}$ 6.6 Hz, H-3), 2.95 (bs, 0.75 H, H-3, the integral for H-3 indicated a 3:1 ratio for **8**: **9**); ^{13}C NMR ($CDCl_3$): δ 166.6, 166.1, 165.9, 165.3 ($PhCO_2$, C-1), 133.6-128.3 (C-aromatic), 106.3 (C-2), 86.2 (C-5), 74.6 (C-4), 63.9 (C-6), 53.2 (CO_2CH_3), 40.9 (C-3, $J_{C,D}$ 19 Hz). MS *m*/*z*: 446 (3.8%), 384 (2.0%), 261 (2.6%), 229 (1.0%), 156 (1.0%), 140 (25.5%), 105 (100%). Anal. Calcd for $C_{28}H_{23}DO_9$: C, 66.53; H, 4.99. Found: C, 66.26; H, 4.91.

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