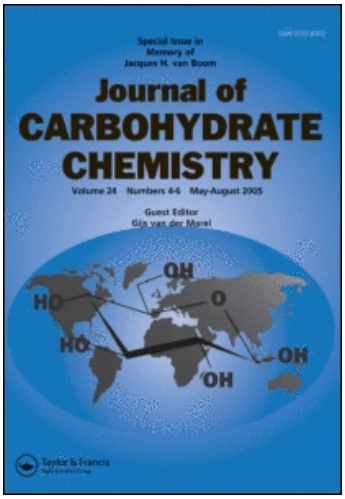

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On the Sulfonylation of Diethyl Galactarate: Some Structural Corrections - Synthesis and Characterisation of Derivatives of Diethyl 2,5-Dihydroxyhexa-2,4-dienoate

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ON THE SULFONYLATION OF DIETHYL GALACTARATE: SOME STRUCTURAL CORRECTIONS – SYNTHESIS AND CHARACTERISATION OF DERIVATIVES OF DIETHYL 2,5-DIHYDROXYHEXA-2,4-DIENOATE

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ABSTRACT

The structure of one of the major products resulting from the treatment of diethyl galactarate (**2**) with an excess of *p*-toluenesulfonyl chloride in pyridine has been shown to be diethyl 2,5-ditosyloxyhexa-2,4-diendioate (**5**) rather than hex-3-enoate **1** proposed earlier. The corresponding dimesyloxy derivative **6** was also prepared in a similar manner. Some additional aspects of the reactions, including some mechanistic proposals, are presented.

INTRODUCTION

Diethyl 2,5-tosyloxyhex-3-enoate (**1**) was required as a potential intermediate for the synthesis of some 2,5-disubstituted pyrrolidines with C_2-symmetry. Compound **1** was

suggested[1] more than forty years ago as one of the major products resulting from the treatment of diethyl galactarate (**2**) with an excess (4.4 equiv) of *p*-toluenesulfonyl chloride in pyridine during attempts to form the tetratosylate **3**. The other product from the reaction was claimed to be the diester **4**. A mechanism involving the action of pyridinium hydrochloride, produced *in situ*, on the unisolated compound **3** was proposed tentatively to account for the formation of **1**.

The designated structure of **1** was based on its elemental analysis, UV spectrum and micro-scale catalytic hydrogenation, which indicated the presence of one double bond. In addition, its lack of reaction with sodium iodide suggested the absence of contiguous tosyloxy groups. We now present evidence that the original structures **1** and **4** are incorrect and revised ones are proposed. Some other aspects of the reactions are also described.

RESULTS AND DISCUSSION

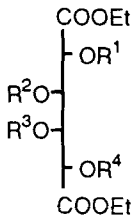
p-Toluenesulfonylation of compound **2** in the manner described[1] yielded the proposed **1** (50.5%), which was isolated and purified by column chromatography. The ^{1}H NMR spectrum of this product was simple and exhibited, *inter alia*, a two proton singlet at 6.98 ppm characteristic of two vinylic type hydrogen atoms. This observation suggested that the material probably possessed structure **5** rather than the earlier proposed **1**. This was also supported by the ^{13}C NMR spectrum in which the two resonances occurring at 121.91 and 132.28 ppm respectively were assigned to the individual carbon atoms of the two vinylic systems (C̲H=C-OTs and CH=C̲-OTs). The remainder of the spectrum was consistent with the proposed new structure **5**.

The chemical-ionisation mass spectrum of the material exhibited a principal proton-capture ion $[M+H]^+$ at *m/z* 539 establishing the molecular weight as 538 amu. A capture ion at *m/z* 541 would have been expected for the structure **1**. The remaining fragmentation ions of the spectrum were also in accordance with structure **5**. An accurate peak matching experiment ($[M+H]^+$ = 539.1045 amu) positively established the molecular weight of the compound as 538.1045 amu (calcd. for $C_{24}H_{26}O_{10}S_2$: 538.1046 amu).

Treatment of compound **2** with an excess of methanesulfonyl chloride in a similar manner yielded the corresponding crystalline dimesylate **6** (60 %), without recourse to column chromatography. The combined spectral characteristics of this product were again consistent with the assigned structure. Compound **6** has been prepared earlier[2] by an independent route involving direct methanesulfonylation of diethyl 2,5-dihydroxyhexa-

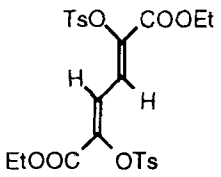
2,4-diendioate (**7**). The low field shift of the value 7.47 ppm for the vinylic protons at C-3 and C-4 in the ^{1}H NMR spectrum of **6**, compared with those of compound **5** at 6.98 ppm can be ascribed to differences in the stereochemistry about the two double bonds in these derivatives. These differences probably result from the variations of bulk of the two types of sulfonyl groups. On the basis of previous studies[3,4] on hexa-2,4-diendioate derivatives, compounds **5** and **6** are tentatively assigned the 2*Z*,4*Z* and 2*E*,4*E* configurations **5a** and **6a** respectively.

1

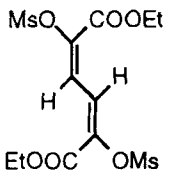


2 $R^1 = R^2 = R^3 = R^4 = H$
3 $R^1 = R^2 = R^3 = R^4 = Ts$
4 $R^1 = R^4 = H$; $R^2 = R^3 = Ts$
8 $R^1 = R^2 = R^3 = R^4 = Ms$
9 $R^1 = R^2 = R^3 = R^4 = Bz$
10 $R^1 = R^4 = Ts$; $R^2 = R^3 = H$
14 $R^1 = R^4 = Ts$; $R^2 = R^3 = Bz$
15 $R^1 = R^4 = Bz$; $R^2 = R^3 = H$

5 R = Ts
6 R = Ms
7 R = H
16 R = Bz

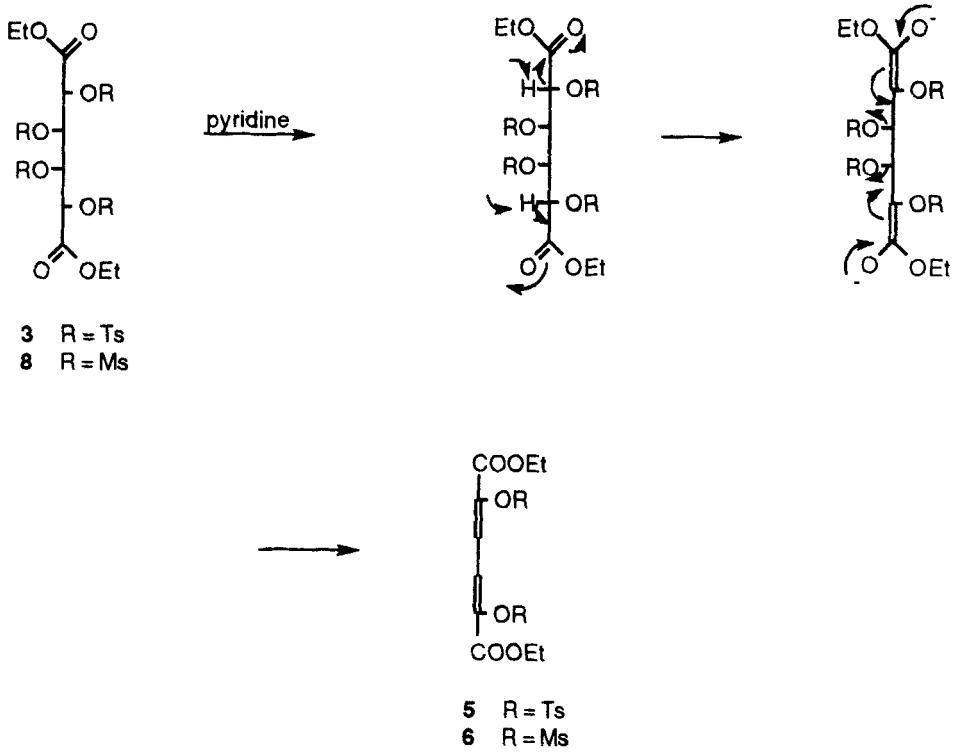


5a



6a

Both compounds are probably formed from the corresponding, but unisolated tetraesters **3** and **8** by a pyridine-induced ß-elimination pathway. There are literature precedents[5-12] for similar processes occurring during the acylation and sulfonylation of various aldonolactones. With these it is known that the protons α to the lactone oxygen are relatively acidic. An E_1 mechanism was proposed[7] earlier for some of these reactions but it was suggested later[11] that an $E_{1c,b}$ process seemed more likely. More recently[12] an $E_{1c,b}$ mechanism has also been proposed to explain the facile elimination of sulfonate groups from some protected aldono-1,4-lactone diesters. This obviated the need to propose



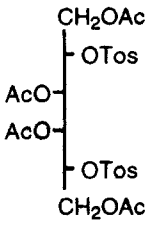
SCHEME

separate mechanisms for *cis* and *trans* pathways and reduced the issue to one of minor differences in the kinetic acidity of the proton α to the lactone carbonyl group. Compounds **5** and **6** may have arisen from **3** or **8** by a similar type of mechanism (scheme).

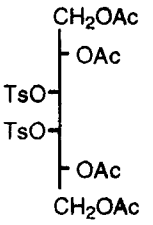
When **2** was reacted with a large excess (15.4 equiv) of benzoyl chloride in pyridine at room temperature for two days, reaction conditions known[6-9,11] to cause the formation of unsaturated benzoyloxy derivatives from aldonolactones, only the known[13] tetrabenzoate **9** was isolated in 91% yield.

It had been suggested earlier[1] that the other major product resulting from the reaction of **2** with *p*-toluenesulfonyl chloride in pyridine was the diester **4**. Compound **10** would have been the expected product from this reaction in view of the enhanced reactivity of the hydroxyl groups on C-2 and C-5, which are adjacent to the two terminal ester functions. Treatment of **2** with *p*-toluenesulfonyl chloride (2 equiv) in pyridine yielded a crystalline ditosylate with the same characteristics noted[1] for the originally proposed **4**. Acylation of the material in the usual manner (acetic anhydride-pyridine) yielded the same

diacetate (mp 200-202°C) as described[1] previously from **4**. Reduction of the ditosylate with sodium borohydride in the presence of an acidic ion-exchange resin and a continuous stream of carbon dioxide, to prevent subsequent formation of epoxides, followed by acylation of the resultant crude product gave the known[14] 1,3,4,6-tetra-*O*-acetyl-2,5-di-*O*-tosylgalactitol (**11**). The material was shown to be different from the alternative isomer **12** prepared from the previously described[15] compound **13** in a conventional manner. These results confirmed structure **10** for the ditosylate.



11



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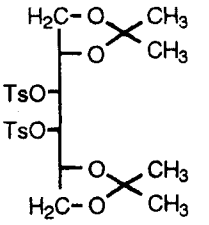

13

Benzoylation of **10** with an excess of benzoyl chloride (15 equiv) in pyridine gave the corresponding dibenzoate derivative **14**. Controlled benzoylation of **2** gave the expected dibenzoate **15** (66%) which on further treatment with *p*-toluenesulfonyl chloride yielded the known[2] diethyl dibenzoyloxyhexa-2,4-diendioate **16**. This result demonstrated the requirement for a good leaving group at positions C-3 and C-4 for elimination to occur, and provided additional evidence for structure **10** and the suggested mechanism.

Some hex-2,4-diendioic acid derivatives have recently[16] become of interest as 5-lipoxygenase inhibitors.

EXPERIMENTAL

General procedures. Melting points were determined with a Reichert thermopan microscope and are uncorrected. Chemical-ionisation (CI) mass spectra, induced with methane gas at 200 °C and emission current 0.5 mAmp, were determined on a VG 7070E spectrometer. ^{1}H NMR spectra were recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si) and ^{13}C NMR spectra were recorded with a Bruker AM 400 (100.6 MHz, FT) spectrometer on solutions in $CDCl_3$ (external standard; 1,4-dioxane at 67.8 ppm). Column chromatography was performed on Silica Gel 60 (Merck) in the solvent mixtures indicated.

Diethyl 2,5-Ditosyloxyhexa-2,4-dienoate (5). A stirred, cooled 0 °C solution of compound **2** (2 g, 7.5 mmol) in dry pyridine (40 mL) was treated portionwise with *p*-toluenesulfonyl chloride (6.3 g, 33 mmol) and then set aside at room temperature for 5 days. The mixture was treated with ice water (2 mL) and after 30 min. poured into ice water (800 mL). The brown precipitate was collected by filtration, washed with water (2x100 mL) and recrystallised from ethanol. Column chromatography (light petroleum-ethyl acetate, 3:1) of the resultant material (2.4 g) gave compound **5** (2 g, 50.5%): mp 134-137 °C; lit.[1] mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 7.87-7.37 (q_{AB}, 8H, arom. H), 6.98 (s, 2H, H-3, H-4), 4.20 (q, 4H, 2x$OC\underline{H}_2CH_3$), 2.45 (s, 6H, arom. CH_3), 1.28 (t, 6H, 2x$OCH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 160.91 (C=O), 146.06, 140.39 (arom. C), 132.28 (C-2 and C-5), 130, 128.47 (arom. C), 121.91 (C-3 and C-4), 62.25 ($O\underline{C}H_2CH_3$), 21.65 ($Ph\underline{C}H_3$), 13.93 ($OCH_2\underline{C}H_3$); M/e 539 (M^++1), 493 (M^++1-C_2H_5OH), 383 (M^+-$C_7H_7SO_2^+$), 155 ($C_7H_7SO_{2+}$), 139 ($C_7H_7SO^+$), 99 (^+CH=CH-$CO_2C_2H_5$), 91 ($C_7H_7^+$).

MS (peak match): Calcd for $(M+H)^+$ $C_{24}H_{26}O_{10}S_2$: 539.1046 amu. Found 539.1045 ± 0.0011 amu.

Diethyl 2,5-Dimesyloxyhexa-2,4-diendioate (6). A stirred, cooled (0 °C) solution of **2** (2 g, 7.5 mmol) in dry pyridine (20 mL) was treated dropwise with a solution of methanesulfonyl chloride (2.6 mL) in pyridine (5 mL) and then set aside at room temperature for 8 h. The mixture was poured into ice water (400 mL) and the resultant dried material recrystallised (methanol) to give **6** (1.7 g, 60%): mp 135-137 °C; lit.[2] mp 134 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (s, 2H, H-3, H-4), 4.34 (q, 4H, 2x$OC\underline{H}_2CH_3$), 3.44 (s, 6H, 2xCH_3), 1.37 (t, 6H, 2x$OCH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 161.11 (C=O), 140.53 (C-2 and C-5), 122.60 (C-3 and C-4), 62.71 ($O\underline{C}H_2CH_3$), 39.60 ($SO_2\underline{C}H_3$), 13.95 ($OCH_2\underline{C}H_3$); M/e 387 (M^++1), 341 (M^++1-C_2H_5OH), 307 (M^+-$CH_3SO_2^+$), 279 (M^+-$CH_3SO_2^+$-CO), 155 (M^++1-C_2H_5OH-2xCH_3SO_{2+}), 99 (^+CH=CH-$CO_2C_2H_5$), 79 ($CH_3SO_2^+$).

MS (peak match): Calcd for $(M+H)^+$ $C_{12}H_{18}O_{10}S_2$: 387.04197 amu. Found 387.04193 ± 0.00076 amu.

Diethyl 2,3,4,5-Tetra-*O*-benzoylgalactarate (9). A stirred solution of **2** (1 g, 3.75 mmol) in dry pyridine (13 mL) was treated dropwise with benzoyl chloride (6.7 mL, 57 mmol) and then set aside at room temperature for 48 h. The mixture was processed in the usual manner and recrystallisation (diisopropyl ether) of the product gave **9** (2.3 g, 90%): mp 153.5-155 °C; lit.[11] mp 151-152.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.1-7.5 (m, 20H, arom. H), 6.28 (t, 2H, H-2, H-5), 5.64 (t, 2H, H-3, H-4), 4.1 (q, 4H, $OC\underline{H}_2CH_3$), 1.1 (t, 6H, $OCH_2C\underline{H}_3$).

Diethyl 2,5-Di-*O*-tosylgalactarate (10). A stirred, cooled (0 °C) solution of **2** (8 g, 30 mmol) in dry pyridine (50 mL) was treated portionwise with *p*-toluenesulfonyl

chloride (11.4 g, 60 mmol) and then set aside at room temperature for 2 days. The mixture was processed in the usual manner and recrystallisation (ethanol) of the resultant material gave **10** (6.7 g, 37%): mp 172-173 °C; lit.[2] mp 170-171 °C; ^{1}H NMR ($CDCl_3$+D_2O) δ 7.86-7.34 (q_{AB}, 8H, arom. H), 5.33 (s, 2H, H-2, H-5), 4.22 (s, 2H, H-3, H-4), 4.15 (q, 4H, $OC\underline{H}_2CH_3$), 2.44 (s, 6H, arom. CH_3), 1.19 (t, 6H, $2xOCH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 166.72 (C=O), 145.55, 132.41, 129.75, 128.36 (arom. C),76.41 (C-2 and C-5), 70.62 (C-3 and C-4), 62.24 ($O\underline{C}H_2CH_3$), 21.64 ($Ph\underline{C}H_3$), 13.89 ($OCH_2\underline{C}H_3$).

Diethyl 3,4-Di-*O*-benzoyl-2,5-di-*O*-tosylgalactarate (14). A stirred, cooled (0 °C) solution of **10** (0.5 g, 0.9 mmol) in dry pyridine (3 mL) was treated slowly with benzoyl chloride (1.6 mL, 9.4 mmol) and then set aside overnight at room temperature. The mixture was processed in the usual manner and recrystallisation (ethanol) of the resultant material gave **14** (0.7 g, 97%): mp 210-212 °C; ^{1}H NMR ($CDCl_3$) δ 8 (m, 4H, arom. H), 7.4 (m, 14H, arom. H), 5.92 (t, 2H, $J_{3,4}$=1 Hz, H-2, H-5), 5.14 (t, 2H, $J_{2,5}$=1 Hz, H-3, H-4), 3.90-4.05 ($q_{A,B}$, 4H, $OC\underline{H}_2CH_3$), 2.33 (s, 6H, arom. CH_3), 1.07 (t, 6H, $OCH_2C\underline{H}_3$).

Anal. Calcd for $C_{38}H_{38}O_{14}S_2$ (782.844): C, 58.30; H, 4.89; S, 8.19. Found: C, 58.31; H, 4.72; S, 7.93%.

Diethyl 2,5-Di-*O*-benzoylgalactarate (15). A stirred, cooled (0 °C) solution of **2** (1 g, 3.7 mmol) in dry pyridine (10 mL) was treated dropwise with benzoyl chloride (0.9 mL, 7.4 mmol), set aside overnight at room temperature and processed in the usual manner. Recrystallisation of the crude material (1.5 g) from ethanol yielded **15** (1.2 g, 66%): mp 192-195 °C; ^{1}H NMR ($CDCl_3$+D_2O) δ 8.1-7.5 (m, 10H, arom. H), 5.76 (s, 2H, H-2, H-5), 4.32 (s, 2H, H-3, H-4), 4.26 (q, 4H, $OC\underline{H}_2CH_3$), 1.25 (t, 6H, $OCH_2C\underline{H}_3$).

Anal. Calcd for $C_{24}H_{26}O_{10}$ (474.467): C, 60.76; H, 5.52. Found: C, 60.43; H, 5.61%.

Diethyl 2,5-Dibenzoyloxyhexa-2,4-diendioate (16). A stirred, cooled (0 °C) solution of **15** (0.2 g, 0.4 mmol) in dry pyridine (3 mL) was treated with *p*-toluenesulfonyl chloride (1.14 g, 6 mmol) in portions over 30 min. The mixture was then set aside at room temperature for 5 days, treated with ice water (50 mL). The resultant mixture was extracted with dichloromethane (2x25 mL) and the combined extracts washed successively with 1 N HCl, saturated aqueous sodium hydrogen carbonate, water, dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation (diisopropyl ether) of the residue gave **16** (0.09 g, 27%) mp 142-144 °C);lit.[2] mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 8.3-7.8 (m, 10H, arom. H), 7.44 (s, 2H, H-3, H-4), 4.35 (q, 4H, $OC\underline{H}_2CH_3$), 1.31 (t, 6H, $OCH_2C\underline{H}_3$).

1,3,4,6-Tetra-*O*-acetyl-2,5-di-*O*-tosylgalactitol (11) from compound 10. A stirred, cooled (0 °C) solution of **10** (0.96 g, 1.68 mmol) in a mixture of methanol (15 mL), 1,2-dimethoxyethane (10 mL) and water (1 mL), containing Amberlyst XN-1010 ion-exchange resin, H^+ form (0.45 g) was treated portionwise over 20 min. with sodium borohydride (0.378 g, 10 mmol). A slow stream of CO_2 was passed continuously through the mixture during the addition and thereafter for 10 min. The mixture was filtered and the filtrate treated with acetic acid (4 mL) and concentrated *in vacuo*. Methanol (3x10 mL) was distilled *in vacuo* from the residue. The resultant material was treated with pyridine (20 mL) and acetic anhydride (8 mL) and processed in the usual manner. Recrystallisation (2-propanol) of the crude product gave **11** (0.42 g, 38%): mp 159-161 °C; lit.[11] mp 161-162 °C; ^{1}H NMR ($CDCl_3$) δ 7.81-7.35 (q_{AB}, 8H, arom. H), 5.2 (m, 4H, H-2, H-3, H-4, H-5), 4.26-4.05 (m, 4H, H-1, H-1', H-6, H-6'), 2.45 (s, 6H, arom. CH_3), 2.11-1.91 (2s, each 6H, acetyl H).

1,2,5,6-Tetra-*O*-acetyl-3,4-di-*O*-tosylgalactitol (12). A stirred solution of **13**[15] (0.30 g, 0.5 mmol) in aqueous 80% acetic acid (30 mL) and 1,2-dimethoxyethane (10 mL) was maintained overnight at 40 °C. The mixture was concentrated *in vacuo* and the residue acetylated with a mixture of pyridine (3 mL) and acetic anhydride (1 mL) for 24 h at room temperature and processed as usual to give **12** (0.13 g, 70%) after recrystallisation from ethanol: mp 184-185 °C; ^{1}H NMR ($CDCl_3$) δ 7.81-7.33 (q_{AB}, 8H, arom. H), 5.2 (m, 4H, H-2, H-3, H-4, H-5), 4.05 (d, 4H, H-1, H-1', H-6, H-6'), 2.45 (s, 6H, arom. CH_3), 2.07-1.93 (2s, each 6H, acetyl H).

Anal. Calcd for $C_{28}H_{34}O_{14}S_2$ (658.659): C, 51.05; H, 5.20. Found: C, 50.86; H, 5.34%.

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