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4-[(4-Methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone as a convenient precursor for a new formal synthesis of KDO

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Dedicated to Professor Paola Vita Finzi, Università di Pavia, on the occasion of her 70th birthday

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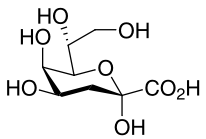
Abstract—The application of 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone, a readily available four-carbon building block, to the synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) is described.

1. Introduction

The biological importance of carbohydrates in living cells justifies the interest in the development of procedures for the synthesis of natural and unnatural sugars containing six, seven or more carbon atoms. The 3-deoxy-D-*manno*-2-octulosonic acid (KDO) **1**, for example, is an essential component of lipopolysaccharides contained in the outer membrane of Gram-negative bacteria.[1–3]



1 (KDO)

Accordingly, the chemical synthesis of this molecule and its analogues has been largely studied to obtain enough substance for biological studies and as a lead in designing potential anti-infection agents. To date, continuous efforts have been invested in developing efficient synthetic approaches to KDO and related compounds including homologation of lower monosaccharides, mainly D-mannose and D-arabinose,[4–7] enzymatic syntheses[8] and, less frequently, de novo syntheses.[9]

We describe here a novel approach to the synthesis of this popular target based on the utilization of 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **2**, a readily available four-carbon building block, which we have recently introduced[10] as a versatile tool for the construction of substituted carbon atom frameworks, since it can be functionalized at either end.

2. Results and discussion

Considering the KDO molecule as the target, we envisaged that the Wittig reaction of (*R*)-2,3-*O*-isopropylidene glyceraldehyde with the stabilized ylide function of **2** could serve a twofold purpose, i.e. (i) the 3-carbon atom elongation of the chain containing a conjugated double bond, in turn susceptible to hydroxylation or epoxidation for the installation of the required oxygenated functions and (ii) the introduction of a stereogenic center of known configuration as a handle to induce asymmetry in the synthetic pathway. In addition the sulfone moiety could be useful both (i) to add the lacking carbon atom through deprotonation and reaction with a suitable one carbon electrophile and (ii) for the final conversion into a carbonyl group by oxidative desulfonylation[11] (Scheme 1).

With this in mind, the reaction between the stabilized ylide **2** and (*R*)-2,3-*O*-isopropylidene glyceraldehyde produced exclusively the *trans* seven-carbon Wittig-adduct **3**,[10] containing both the conjugated double bond and the chiral

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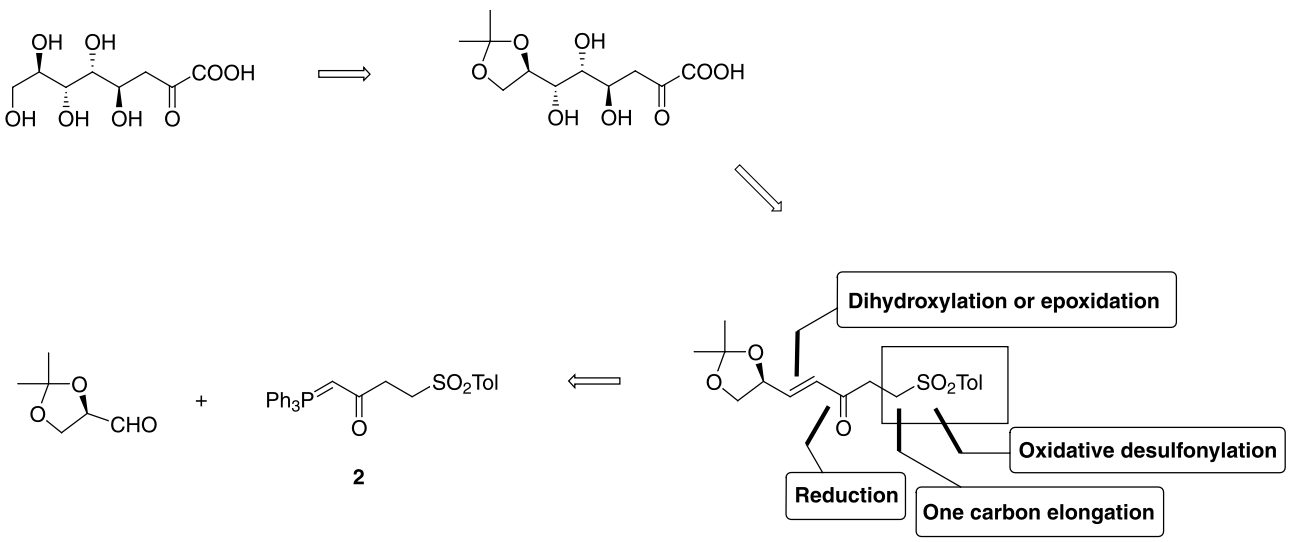


Scheme 1.

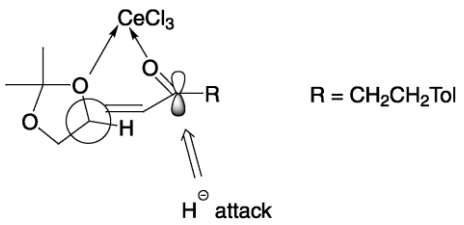
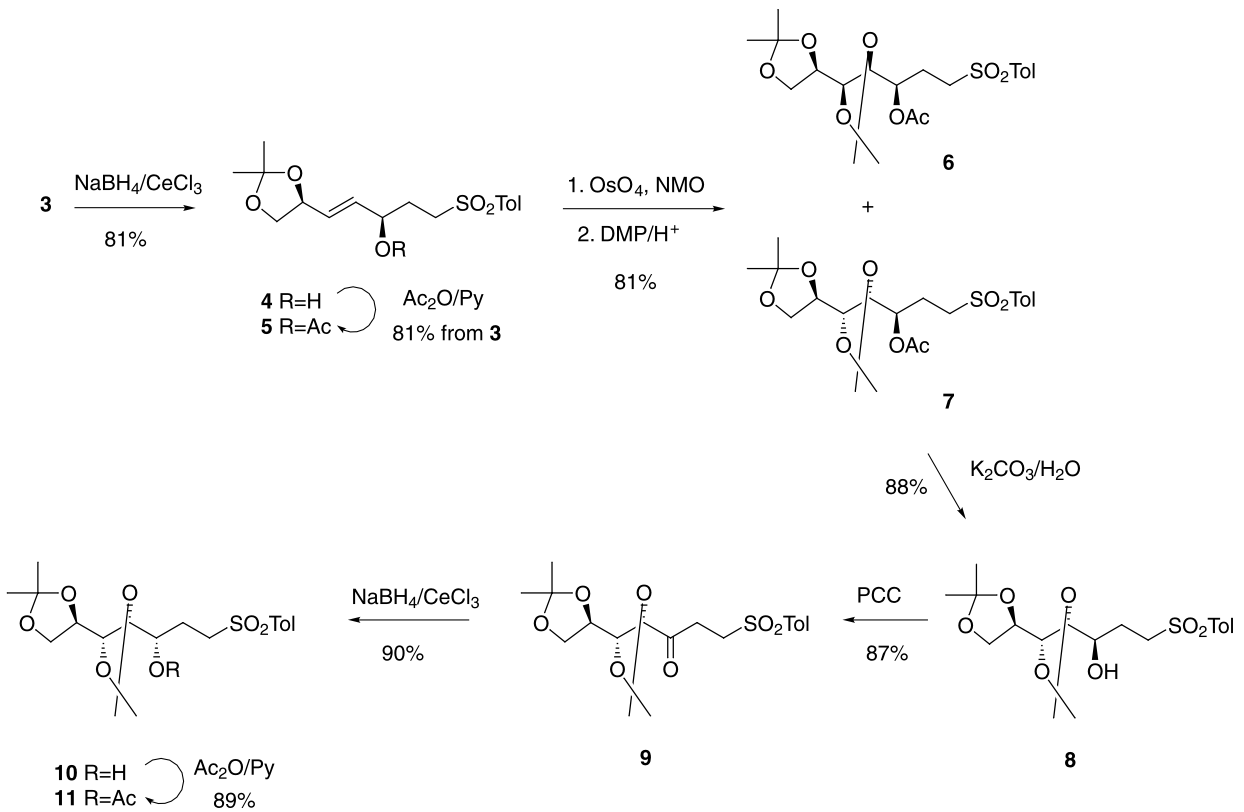


Figure 1.

center of known configuration for the stereoselective functionalization of the entire molecule. Thus, sodium borohydride reduction of the carbonyl group in the presence of cerium chloride[12] proceeded highly stereoselectively affording the corresponding allylic alcohol **4** as a single diastereoisomer, as indicated by analytical HPLC of the crude product. It is likely that the chiral auxiliary influences the stereochemical outcome in the reductive step, a vinylogous version of Cram's rule being right to explain the observed high level of 1,4-stereocontrol across the existing *E* double bond. Based on literature examples on the addition of nucleophiles to enones bearing a chiral center in



Scheme 2.

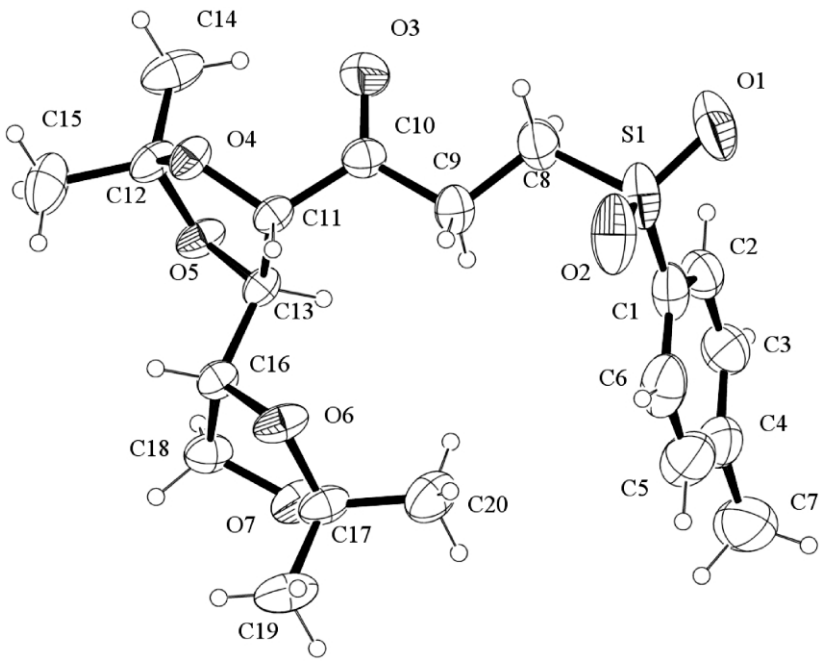


Figure 2. An ORTEP[14] view of compound **9** displaying the thermal ellipsoids at 30% probability.

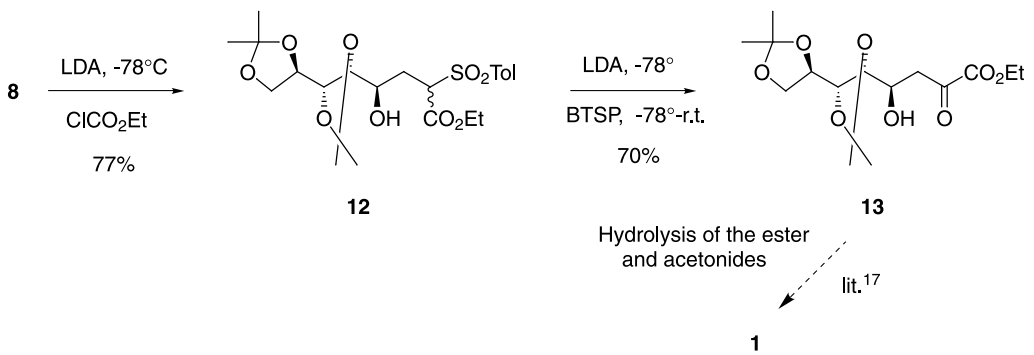
γ-position,[13] we assumed that the α,β-unsaturated ketone **3** reacts via its s-*cis* conformation, the Lewis acid reasonably forcing the enone to adopt this particular conformation through complexation both to the carbonyl oxygen atom and the C-4 oxygen atom of the dioxolanyl substituent. Thus, the hydride attack must occur preferentially from the bottom face of the ketone group (Fig. 1).

Based on this assumption, we assigned the absolute configuration at the C-3 carbon atom in compound **4** as *R*, this assignment being confirmed at a later stage of the synthesis. Transformation of the allylic alcohol **4** into the acetate **5** by treatment with acetic anhydride and pyridine (Scheme 2) and subsequent oxidation of **5** with the osmium tetroxide/*N*-methylmorpholine *N*-oxide system gave a 4:1 mixture of isomeric diols which was protected as isopropylidene derivatives by a standard procedure and separated by flash-chromatography, the major isomer **7** being a solid.

Unfortunately, we were unable to obtain suitable crystals for X-ray analysis in spite of numerous attempts of crystallization in a variety of solvents. To assign the stereochemistry we oxidized the alcohol **8**, obtained by removal of the acetyl group, with pyridinium chlorochromate to the ketone **9**. X-Ray analysis allowed us to unequivocally assign the absolute configuration of the three contiguous asymmetric centers as 2*R*,3*R*,4*S* (Fig. 2).

Moreover, sodium borohydride reduction of the carbonyl group of the ketone **9** in the presence of cerium chloride[12] afforded the corresponding alcohol **10** as a single diastereoisomer, which gave rise by acetylation to the corresponding acetyl derivative **11**, an epimer of **7**. The stereochemical outcome of the reduction could be predicted on the basis of a chelate Felkin–Ahn model,[15] the hydride attack occurring preferentially from the *re* face to produce the *S* configuration at the newly created stereogenic centre.

The attractive intermediate **8** possesses both the correct framework and stereochemistry for KDO **1**. Thus, the reaction of the bisanion of **8**, prepared by action of LDA at −78°C, with ethyl chloroformate (Scheme 3) produced a mixture of epimeric esters **12**, a fact of no consequence because the final oxidative desulfonylation generated the required carbonyl group. This operation was carried out



Scheme 3.

following Hwu's protocol[11] involving the action of bistrimethylsilylperoxide[16a] on the bisanion produced by means of LDA on the mixture of epimeric esters **12** which was eventually transformed into the known diacetonide-protected KDO ethyl ester **13** already taken to KDO by Whitesides et al.[17] thus establishing a new formal synthesis of this target. Our own methodology advantageously compares with the reported one, allowing to obtain the key intermediate **13** in 25% overall yield based on **3**.

3. Conclusions

Our results emphasize once more the versatility of the synthon **2** as a tool for the construction of functionalized carbon frameworks and this strategy may be extended to the synthesis of unnatural sugars with seven or more carbon atoms. In particular, the versatile intermediate **2** has been conveniently used to develop a new formal synthesis of KDO, which is complementary to the already reported chemical syntheses of this target.

4. Experimental

4.1. General remarks

Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FT-IR Paragon 500 spectrometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were taken on a Bruker AC spectrometer at 200 and 50 MHz, respectively, for solutions in $CDCl_3$ unless otherwise noted. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard and coupling constants are given in Hertz. Optical rotations were measured with a Perkin–Elmer 241 MC Polarimeter. Diastereomeric ratios were determined through HPLC analyses: in normal phase on silica gel and isopropanol–water 80:20 as eluant, in reverse phase on C18 and acetonitrile–water concentration gradient. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40–60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230–400 mesh). All reactions were performed under N_2 or Ar atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Compound **3** was prepared according to the literature.[10]

4.1.1. (3*R*)3-Acetoxy-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-[(4′-methylphenyl)sulfonyl]-1-pentene (5). To a well-stirred and cooled (−10°C) solution of ketone **3**[10] (0.75 g, 2.21 mmol) in MeOH (10 mL) containing $CeCl_3{\cdot}7H_2O$ (0.82 g, 2.21 mmol), $NaBH_4$ (0.1 g, 2.60 mmol) was added in one portion. Stirring was continued for 30 min, then the excess of $NaBH_4$ was destroyed with acetone. The reaction mixture was concentrated in vacuo, diluted with aqueous NaCl (7 mL), and extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried and evaporated to afford the alcohol **4** (0.60 g, 81%) as a light yellow oil, which was sufficiently pure (HPLC analysis) to be used in the next step without further purification. The crude alcohol was dissolved in CH_2Cl_2 (8 mL) containing pyridine (0.18 mL, 2.35 mmol) and a catalytic amount of 4-*N*,*N*′-dimethylaminopyridine. Acetic anhydride (0.24 mL, 2.35 mmol) was added, the mixture stirred at room temperature for 3 h, then washed with H_2O (10 mL) and $NaHCO_3$ solution (10 mL, sat. aq.). The organic phase was separated, dried and the solvent evaporated. The residual oil was purified by flash chromatography (eluent EtOAc–cyclohexane 1:1), affording the title compound **5** (0.65 g, 81%) as an oil; [Found: C, 59.80; H, 6.70. $C_{19}H_{26}O_6S$ requires C, 59.67; H, 6.85%]; $[\alpha]_D^{20}$=+9.5 (*c* 0.35, $CHCl_3$). ν_{max} (liquid film) 1720, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.39 (3H, s, *Me*), 1.41 (3H, s, *Me*), 2.01 (3H, s, CO*Me*), 1.95–2.10 (2H, m, CH_2CHOAc), 2.42 (3H, s, Ph*Me*), 3.05–3.17 (2H, m, CH_2SO_2), 3.50–3.60 (1H, m, CH_aH_bO), 4.05–4.15 (1H, m, CH_aH_bO), 4.40–4.50 (1H, m, HC═CH–C*H*O), 5.20–5.30 (1H, m, C*H*OAc), 5.60–5.75 (2H, m, *H*C═C*H*), 7.40 (2H, d, *J*=7.8 Hz, arom.), 7.80 (2H, d, *J*=7.8 Hz, arom.); δ_C (50 MHz, $CDCl_3$) 20.9, 21.5, 25.7, 26.5, 27.3, 27.4, 52.2, 69.2, 75.7, 109.5, 128.0, 129.8, 131.3, 131.8, 135.7, 144.8, 169.7.

4.1.2. (2*R*,3*R*,4*S*,5*R*)5-*O*-Acetyl-1,2,3,4-bis-*O*-isopropylidene-7-[(4′-methylphenyl)sulfonyl]-heptan-1,2,3,4,5-pentaol (7). A solution of *N*-methylmorpholine *N*-oxide (0.67 g, 4.49 mmol) in *tert*-butyl alcohol–H_2O mixture (50:5) (30 mL) containing a catalytic amount of OsO_4 was added dropwise to a stirred solution of **5** (0.61 g, 1.59 mmol) in THF (5 mL) (CAUTION: care should be taken in handling osmium tetroxide.[18] The vapor is toxic, causing damage to eyes, respiratory tract and skin). The reaction mixture was stirred at room temperature for 18 h, the solvent was evaporated, the residue dissolved in a mixture of acetone (10 mL) and 2,2-dimetoxy-propane (10 mL), and *p*-toluenesulfonic acid was added in small portions until pH=5. After stirring the reaction mixture at room temperature for 3 h, triethylamine was added until pH=8, then the solvent was concentrated in vacuo. Purification of the residual oil by flash cromatography (eluent EtOAc–cyclohexane 1:3) allowed to obtain the title compound **7** (0.47 g, 65%), the more abundant isomer, as a white solid, mp 81–82°C (ether–petroleum ether 1:1); [Found: C, 58.25; H, 7.15. $C_{22}H_{32}O_8S$ requires C, 57.88; H, 7.06%]; $[\alpha]_D^{20}$=+12.66 (*c* 0.30, $CHCl_3$); ν_{max} (KBr) 3300, 1735, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.38 (6H, s, 2*Me*), 1.40 (3H, s, *Me*), 1.60 (3H, s, *Me*), 2.09 (3H, s, CO*Me*), 2.05–2.20 (2H, m, CH_2CHOAc), 2.50 (3H, s, Ph*Me*), 3.10–3.21 (2H, m, CH_2SO_2), 3.70–3.80 (1H, m, CH_aH_bO), 3.85–3.95 (2H, m, C*H*O), 3.96–4.04 (m, 1H, C*H*O), 4.09–4.20 (m, 1H, CH_aH_bO), 5.10–5.20 (1H, m, C*H*OAc), 7.40 (2H, d, *J*=7.8 Hz, arom.), 7.80 (2H, d, *J*=7.8 Hz, arom.); δ_C (50 MHz, $CDCl_3$) 21.1, 21.7, 23.9, 25.4, 26.6, 27.2, 27.3, 52.6, 67.7, 71.4, 79.3, 81.0, 110.0, 110.2, 128.1, 130.0, 136.0, 144.9, 170.2.

4.1.3. (2*R*,3*R*,4*S*,5*R*)1,2,3,4-Bis-*O*-isopropylidene-7-[(4′-methylphenyl)sulfonyl]-heptan 1,2,3,4,5-pentaol (8). A solution of **7** (0.5 g, 1.1 mmol) and sodium carbonate (0.18 g, 1.7 mmol) in a 1:1 mixture of MeOH–H_2O (15 mL) was stirred at room temperature for 24 h. Most of the solvent

was evaporated in vacuo and the residual slurry extracted with EtOAc (3×15 mL). After usual work-up, the title compound **8** (0.4 g, 88%) was obtained as an oil which was used without further purification in the next step. ν_{max} (liquid film) 3450, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.25 (3H, s, *Me*), 1.35 (3H, s, *Me*), 1.37 (3H, s, *Me*), 1.41 (3H, s, *Me*), 2.04–2.09 (2H, m, CH_2CHOH), 2.44 (3H, s, Ph*Me*), 3.25–3.35 (2H, m, CH_2SO_2), 3.57–3.63 (1H, m, CH_aH_bO), 3.65–3.69 (3H, m, 2C*H*O and OH), 4.06–4.15 (1H, m, CH_aH_bO), 4.15–4.20 (1H, m, C*H*OH), 7.40 (2H, d, *J*=7.8 Hz, arom.), 7.80 (2H, d, *J*=7.8 Hz, arom.).

4.1.4. (2*R*,3*R*,4*S*)1,2,3,4-Bis-*O*-isopropylidene-7-[(4′-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroxy-heptan-5-one (9). A solution of the alcohol **8** (0.4 g, 0.96 mmol) in dry CH_2Cl_2 (4 mL) was quickly added to a well-stirred suspension of PCC (0.3 g, 1.38 mmol), sodium acetate (0.12 g, 1.4 mmol) and 4 Å molecular sieves (0.25 g) in dry CH_2Cl_2 (4 mL). After 3 h, ether (40 mL) was added and the mixture passed through a short column of florisil. Evaporation of the solvent in vacuo afforded the title compound **9** (0.34 g, 87%) as a white solid, mp 98–99°C (hexane); [Found: C, 58.35; H, 6.70. $C_{20}H_{28}O_7S$ requires C, 58.23; H, 6.84%]; $[\alpha]_D^{20}$=+1.41 (*c* 0.55, $CHCl_3$); ν_{max} (KBr) 1705, 1600 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 1.40 (3H, s, *Me*), 1.42 (3H, s, *Me*), 1.60 (6H, s, 2*Me*), 2.44 (3H, s, Ph*Me*), 3.15–3.20 (2H, m, CH_2SO_2), 3.39–3.42 (2H, m, CH_2CO), 3.95–4.01 (1H, m, CH_aH_bO), 4.15–4.18 (3H, m, 2C*H*O and CH_aH_bO), 4.39 (1H, d, *J*=7.0 Hz, OC*H*–CO), 7.40 (2H, d, *J*=7.8 Hz, arom.), 7.80 (2H, d, *J*=7.8 Hz, arom.).

4.1.5. (2*R*,3*R*,4*S*,5*S*)5-*O*-Acetyl-1,2,3,4-bis-*O*-isopropylidene-7-[(4′-methylphenyl)sulfonyl]-heptan-1,2,3,4,5-pentaol (11). To a well-stirred and cooled (−10°C) solution of ketone **9** (0.11 g, 0.26 mmol) in MeOH (10 mL) containing $CeCl_3{\cdot}7H_2O$ (0.10 g, 0.26 mmol), $NaBH_4$ (0.01 g, 0.26 mmol) was added in one portion. Stirring was continued for 30 min, then the excess of $NaBH_4$ was destroyed with acetone. The reaction mixture was concentrated in vacuo, diluted with sodium chloride solution (5 mL, sat. aq.) and extracted with EtOAc (3×15 mL). Usual work-up of the dried organic extracts afforded **10** (0.10 g, 90%) as a light yellow oil. The crude alcohol **10** was dissolved in CH_2Cl_2 (4 mL) containing pyridine (0.029 mL, 0.35 mmol), acetic anhydride (0.03 mL, 0.35 mmol) and a catalytic amount of 4-*N*,*N*′-dimethylaminopyridine. After stirring at room temperature for 3 h, the reaction mixture was washed with H_2O (10 mL) and $NaHCO_3$ solution (10 mL, sat. aq.). The organic phase was separated, dried and evaporated in vacuo. The residual oil was purified by flash cromatography (eluent EtOAc–cyclohexane 1:1), affording the title compound **11** (0.097 g, 89%) as an oil; [Found: C, 57.70; H, 7.18. $C_{22}H_{32}O_8S$ requires C, 57.88; H, 7.06%]; $[\alpha]_D^{20}$=+4.31 (*c* 1.16, $CHCl_3$); ν_{max} (liquid film) 1720, 1600 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 1.35 (3H, s, *Me*), 1.36 (3H, s, *Me*), 1.40 (3H, s, *Me*), 1.41 (3H, s, *Me*), 2.15 (3H, s, CO*Me*), 2.15–2.18 (2H, m, CH_2CHOAc), 2.44 (3H, s, Ph*Me*), 3.15–3.25 (2H, m, CH_2SO_2), 3.60–3.66 (1H, m, CH_aCH_bO), 3.95–4.05 (1H, m, C*H*O), 4.10–4.15 (2H, m, 2C*H*O), 4.15–4.20 (1H, m, CH_aH_bO), 5.05–5.12 (1H, m, C*H*OAc), 7.40 (2H, d, *J*=7.8 Hz, arom.), 7.80 (2H, d, *J*=7.8 Hz, arom.).

4.1.6. (2*R*/*S*,4*R*,5*S*,6*R*,7*R*)Ethyl 2-[(4′-methylphenyl)sulfonyl]-4,5,6,7,8-pentahydroxy-5,6,7,8-bis-*O*-isopropylidene-octanoate (12). A solution of diisopropylamine (0.24 mL, 1.73 mmol) in dry THF (5 mL) was treated with *n*-butyl lithium (1.08 mL, 1.6 M in hexane) at −78°C. After stirring for 15 min, a solution of **8** (0.3 g, 0.72 mmol) in dry THF (1 mL) was added in one portion. The dark red solution was stirred for 20 min, then freshly distilled ethyl chloroformate (0.082 g, 0.86 mmol) in dry THF (1 mL) was added. The mixture was stirred at −78°C for 30 min, then the temperature was slowly raised at −20°C and stirring was continued for 15 min at this temperature. The reaction mixture was diluted with ammonium chloride solution (10 mL, sat. aq.), extracted with EtOAc (3×10 mL), the organic extracts dried and evaporated. The residual oil was purified by flash chromatography (eluent EtOAc–cyclohexane 2:1) to give the title compound **12** (0.27 g, 77%) as an epimeric mixture (positive response to $FeCl_3$ test); [Found: C, 56.85; H, 7.10. $C_{23}H_{34}O_9S$ requires C, 56.77; H, 7.04%]; ν_{max} (liquid film) 3450, 1720, 1690, 1645, 1600 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.20–1.40 (15H, m), 2.00–2.05 (2H, m), 2.44 (3H, s), 3.50–4.40 (10H, m), 7.40 (2H, m), 7.80 (2H, m).

4.1.7. (4*R*,5*S*,6*R*,7*R*)Ethyl 2-oxo-4,5,6,7,8-pentahydroxy-5,6,7,8-bis-*O*-isopropylidene-octanoate (13). A solution of diisopropylamine (0.07 mL, 0.5 mmol) in dry THF (4 mL) was treated with *n*-butyl lithium (0.31 mL, 1.6 M in hexane) at −78°C. After stirring for 15 min, a solution of **12** (0.1 g, 0.20 mmol) in dry THF (1 mL) was added in one portion. The dark red solution was stirred for 15 min, then neat bis-(trimethylsilyl)peroxyde (BTMSPO)[16a] (0.89 g, 5 mmol) was added (CAUTION: the reaction must be carried out in safety cupboards and behind blast shields.[16b] Indeed, it has been reported that BTMSPO could give rise to explosions especially in the presence of metal needles, cannulas, etc.). The color of the solution turned to light brown while stirring was continued at room temperature for 12 h. The reaction mixture was poured in ice-cold ammonium chloride solution (10 mL, sat. aq.), extracted with EtOAc (2×10 mL), the extracts dried and evaporated. The residual oil was purified by flash chromatography (eluent EtOAc–cyclohexane 1:1) to give the title compound **13**[17] (0.05 g, 70%) as an oil; [Found: C, 55.60; H, 7.40. $C_{16}H_{26}O_8$ requires C, 55.48; H, 7.57%]; ν_{max} (liquid film) 3450, 1745, 1730 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (12H, s, 4*Me*), 1.35 (3H, t, *J*=7.0 Hz, CH_3CH$_2$O), 3.05 (1H, dd, *J*=16.5, 7.7 Hz, COCH_aH_b), 3.20 (1H, dd, *J*=16.5, 4.8 Hz, COCH_aH_b), 3.40 (1H, s, OH, exchange with D_2O), 3.67–3.74 (1H, m, CH_aH_bO), 3.80 (1H, t, *J*=7.4 Hz, OC*H*–CHOH), 3.85–3.90 (1H, m, C*H*OH), 4.00–4.20 (2H, m, C*H*O and CH_aH_bO), 4.19–4.25 (1H, m, C*H*O), 4.30 (2H, q, *J*=7.0 Hz, CH$_3$CH_2O).

4.2. X-Ray crystal structure analysis of 9

$C_{20}H_{28}O_7S$, M_r=412.48, colorless crystal (0.15×0.32×0.40 mm^3), monoclinic, space group $P2_1$ (no. 4) with *a*=5.6088(3), *b*=20.3082(17), *c*=9.5794(8) Å, β=92.785(5)°, *V*=1089.8(1) $Å^3$, *Z*=2, D_c=1.257 g cm^{-3}, 5941 reflections measured, 2843 independent, R_{int}=0.048, (θ<24°, *T*=295 K, Mo Kα radiation, λ=0.71073 Å) on a Nonius Kappa CCD diffractometer. The structure was

solved by direct methods (SIR92)[19] and refined on F^2 (SHELXL-97).[20] Refinement converged at a final *wR*2 value of 0.1192 (all reflections), *R*1=0.0455 (for 2534 reflections with $I>2\sigma(I)$), *S*=1.128, Flack[21] parameter=−0.1(1). All non-H atoms were refined anisotropically, all hydrogen atoms were included on calculated positions, riding on their carrier atoms. A final difference Fourier showed no residual density outside −0.17 and 0.19 $Å^{-3}$. An ORTEP[14] view of one of the molecules is shown in Fig. 2.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic data Centre as supplementary publication number CCDC 184660. Copies of the data can be obtained, free of charge, on application to CCDC, Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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