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Preliminary studies on the synthesis of rancinamycins from nitrosugars: first total synthesis of (3*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-cyclohex-1-enecarbaldehyde

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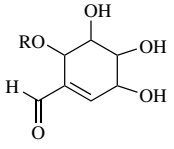
Abstract—The first total synthesis of (3*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-cyclohex-1-enecarbaldehyde from D-glucose is described. The key steps of this synthesis are the stereoselective Michael addition of 2-lithio-1,3-dithiane to 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xilo*-hex-5-enofuranose followed by the enantioselective two-step transformation of 3-*O*-benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-6-nitro-β-L-idofuranose into (1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-2-nitro-cyclohexanecarbaldehyde propylene dithioacetal, which was finally converted into the target compound.

1. Introduction

Carbasugars are a family of polyhydroxylated cyclopentanes and cyclohexanes, structurally similar to that of cyclic monosaccharides, from which they can formally be derived by replacement of the ring oxygen atom with a methylene group.[1] Due to the lack of an easily hydrolysable glycosidic function, these sugar derivatives are stable towards hydrolysis. Additionally, as they are topologically similar to that of normal sugars, particularly in the arrangement of their hydroxy groups, they can mimic sugars in biological systems and thus may act as enzyme inhibitors and have been used as sweeteners, antibiotics and anticancer agents.[2]

The use of the term carbasugar has also been extended to closely related compounds,[3] including unsaturated carbasugars such as rancimamycin III **1d**, a member of a group of secondary metabolites known as rancinamycins **1a**–**d**,[4] which are produced by *Streptomyces lincolnensis* in a sulfur-depleted culture medium and have important antibiotic activity in vitro against *Proteus vulgaris*, *Proteus rettgeri* and *Staphylococcus aureus* (Fig. 1).



1 a) R=CO*i*-Pr
b) R_1=CO*n*-Pr
c) R_1=CO*n*-Bu
d) R=H

Figure 1.

As they have a wide range of pharmacological applications, carbasugars are receiving considerable attention from chemists and biochemists. Much attention has been devoted to the development of regio- and stereoselective synthetic methodologies for their preparation, most of which are based on the conversion of sugars into carbocycles.[5] Several approaches have been developed for the transformation of sugars into enantiomerically pure carbasugars,[5a] including the intramolecular nitroaldol condensation (Henry reaction),[6] which has proven to be a powerful method for the preparation of nitrocycloalkanes, that has recently been used by us for the preparation of cyclohexane α-amino acids, cyclopentane β-amino acids, dehydrohydroxymethylinositols, among other carbasugars.[7]

Herein we describe the first total synthesis of a rancinamycin analogue **1e** from nitrosugars,[8] following a route which includes an improvement of the previously described[9] transformation of nitrosugar **4b** into cyclitol

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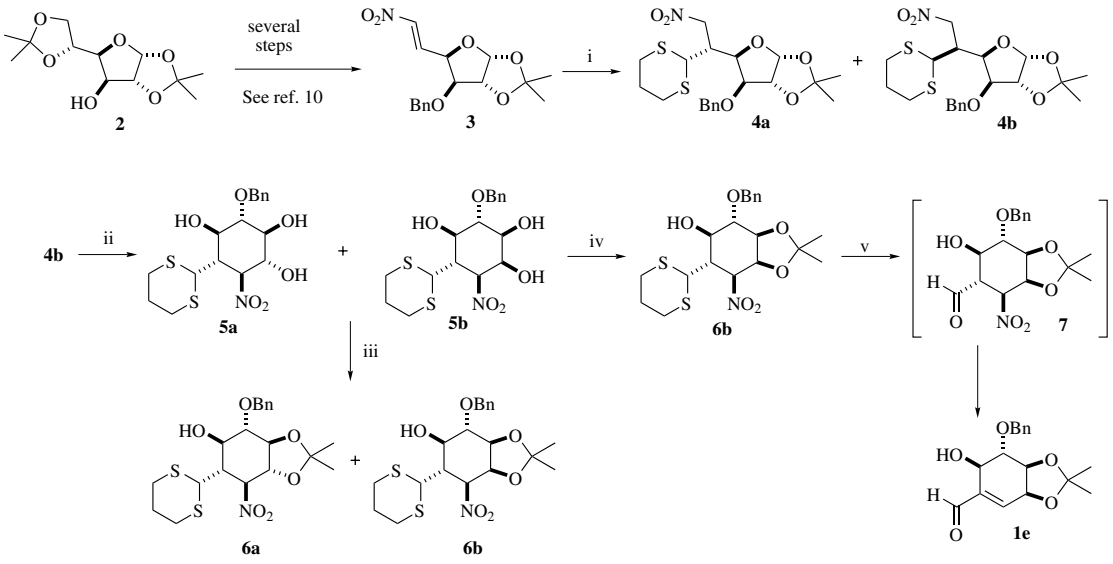


Scheme 1. Reagents and conditions: (i) 2-lithio-1,3-dithiane, THF, −78 °C, 2 h, (**4a**:**4b**—1:3), 78% yield; (ii) (a) AcOH (aq) (75%), reflux, 3 h; (b) $NaHCO_3$ (aq) (2%), MeOH, rt, 12 h, (**5a**:**5b**—1:2.5), 87% yield; (iii) $CH_3OC(CH_3)CH_2$, PPTS, CH_2Cl_2, reflux, 3 h, 24% yield of **6a**, 61% yield of **6b**; (iv) $(CH_3O)_2C(CH_3)_2$, PTSA, acetone, rt, 12 h, 87% yield; (v) MeI, $NaHCO_3$ (aq), CH_3CN, 35 °C, 36 h, 53% yield.

6b prior to a new way of removing nitro groups from nitrocarbasugars (Scheme 1).

2. Results and discussion

Nitro-olefin **3**[10] obtained from diacetone-D-glucose **2** was allowed to react with 1.2 equiv of 2-lithio-1,3-dithiane at −78 °C for 2 h, the result being a 78% yield of a 1:3 mixture for compounds **4a** and **4b**, a ratio established by NMR (comparison of the intensity of H_1 protons). The major component **4b** was easily isolated by crystallization and its structure unambiguously established by means of an X-ray experiment (Fig. 2).[11] The above stereoselectivity is due to the presence of a benzyloxy group at position C_3, which means that attack by the dithiane anion on the double bound face leading to the minor component **4a** is difficult. These results improve on a previous similar experiment carried out at −45 °C, in which there were a 60% global yield and a 3:4 ratio of **4a** and **4b**, and the configuration of both epimers was indirectly established.[9]

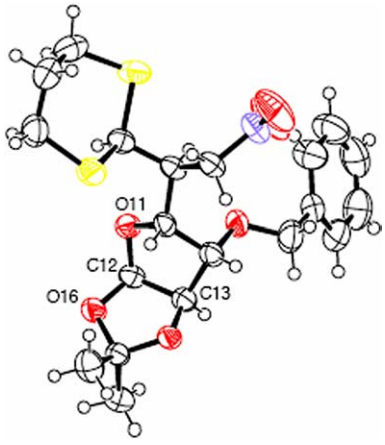
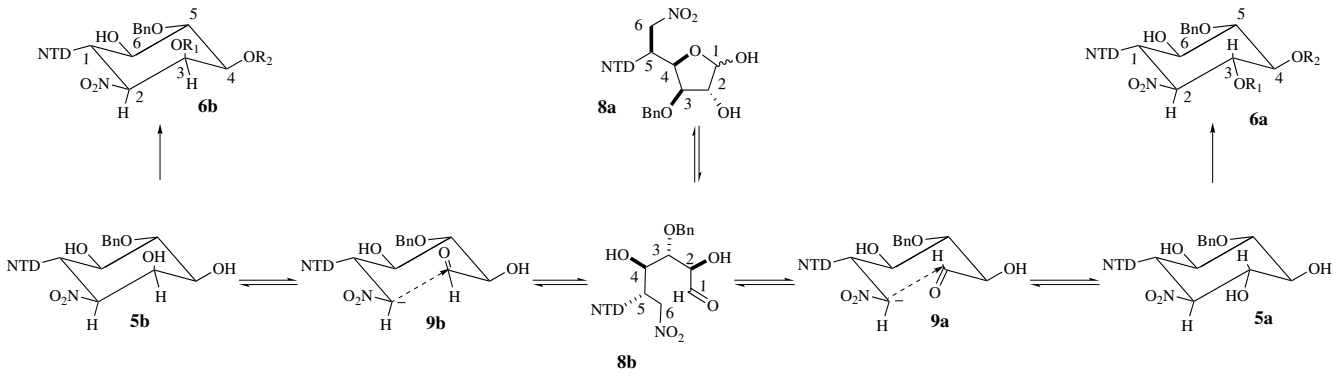


Figure 2. An ORTEP diagram corresponding to the X-ray molecular structure of compound **4b**.

The next step was the removal of the 1,2-*O*-isopropylidene group of the major component **4b** with acetic acid. The resulting free sugar was directly treated with 2.5 equiv of sodium hydrogen carbonate in aqueous methanol at room temperature for 12 h, giving a 87% yield of an unisolable syrupy mixture of **5a** and **5b** (TLC). Refluxing of a solution of this mixture with 2-methoxypropene and PPTS in methylene chloride for 3 h allowed isopropylidene nitrocyclohexanes **6a** (not previously described) and **6b**[12] to be isolated from the reaction mixture in 24% and 61% yields, respectively.

The *myo* configuration assigned to the previously uncharacterized inositol derivative **6b** was easily established by taking into account that configurations of stereogenic centres of C_1, C_4, C_5 and C_6 are the same as those of its precursor **4b** and presupposing that this compound predominately adopts the thermodynamically preferred chair-like conformation **6b** (Scheme 2) where H_3 adopts an equatorial disposition and the rest of the hydrogens on the ring adopt axial dispositions. This was easily confirmed from its ^1H NMR spectrum, since all the coupling constants of the ring protons were 7.5–10 Hz, except for coupling constants of H_2 and H_3 ($J_{2,3} = 4.3$ Hz) and H_3 and H_4 ($J_{3,4} = 7.0$ Hz). The *scyllo* configuration of the new minor inositol derivative **6a** was also established from its ^1H NMR data, which revealed that H_1, H_2, H_3, H_4, H_5 and H_6 are all axial (Scheme 2).

The formation of compounds **6a** and **6b** can be explained as indicated in Scheme 2. The intramolecular Henry reaction in the open form **8b** of nitrosugar **8a** gives a



Scheme 2. $R_1 + R_2 = -CMe_2$ NTD = HC(S)(S).

mixture of nitrocyclohexanes **5a** and **5b** via chair transition states of the corresponding nitronates **9a** and **9b**, each having an equatorial nitro group. Compounds **5a** and **5b** can easily revert to compound **8b** by a retro-Henry reaction. As compound **5a** is thermodynamically more stable than **5b**, at the point of equilibrium **5a** should be more favoured with respect to **5b**. Notwithstanding, as stated previously, *myo*-inositol **5b** is the predominant component in the mixture resulting from the cyclization of compound **8b**. Accordingly, the highly remarkable stereoselectivity of this cyclization can be explained by assuming that the formation of **5b** is kinetically favoured, and consequently that the acyclic conformation **9b** is more favoured than **9a**.

When the direct acetonization of the mixture **5a** and **5b** was carried out in acetone at rt, surprisingly only compound **6b** was obtained. This enantioselectivity can be explained as follows: the moderate reaction conditions now used make the selective acetonization of inositol **5b** possible due to the *cis*-configuration of the OH groups at C_3 and C_4. This process is accompanied by the displacement of the equilibrium between compounds **5a** and **5b** to **5b**.

Finally, treatment of compound **6b** with MeI and aqueous hydrogen sodium carbonate produced compound **1e**, which was easily identified from its analytical and spectroscopic data. Formation of this compound is probably the result of the liberation of the masked carbonyl group of **6b** followed by a kinetically and thermodynamically favoured E_1cB elimination of the nitro group of the resulting β-nitro cyclohexanecarbaldehyde **7** in the basic reaction conditions.[13]

3. Conclusion

In conclusion, we have developed the first total synthesis of a rancinamycin-like compound from nitrosugars following a route, which includes the enantioselective transformation of nitrosugar **4b** into carbasugar derivative **6b**.

Work is currently in progress to extend this route to the panel of hexoses in order to prepare a wide range of rancinamicyns **1** for chemical and biological studies, determination of the stereochemistries of all its 14 described isomers. Additionally, we are exploring the broad synthetic potential of this route for the preparation of other cyclohexane derivatives, including polyhydroxylated cyclohexane β-amino acids, carbasugars and shikimic acid derivatives.

4. Experimental

Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on a MIDAC Prospect-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DPX-250 apparatus. Mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer. Elemental analyses were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and ethyl acetate/hexane mixtures as eluants; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 14. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

4.1. 3-*O*-Benzyl-5,6-dideoxy-5-*C*-(1,3-dithian-2-yl)-1,2-*O*-isopropylidene-6-nitro-β-L-idofuranonse 4b

A 1.6 M solution of *n*-butyllithium in dry THF (6.8 mL, 10.81 mmol) was added dropwise under argon to a solution of 1,3-dithiane (1.36 g, 11.28 mmol) in dry THF (60 mL) cooled to −78 °C. After the addition, the reaction mixture was stirred at −78 °C for 1 h and then a solution of 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-nitro-α-D-*xylo*-hex-5-enofuranose **3** (3.02 g, 9.40 mmol) in dry THF (14 mL) was added dropwise and the new reaction mixture was stirred for 2 h. After aqueous ammonium chloride saturated solution (50 mL) was added, the aqueous layer was extracted with methylene chloride (3 × 50 mL) and the pooled organic layers were dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The resulting crude syrup was washed three times with hot hexane and then methanol was added to deposit 3-*O*-benzyl-

5,6-dideoxy-5-*C*-(dithian-2-yl)-1,2-*O*-isopropylidene-6-nitro-β-L-idofuranose **4b** (2.32 g, 5.26 mmol, 56% yield) as a white solid. Crystallization from ethyl ether/hexane provided colourless crystals, mp 155–157 °C. $[\alpha]_D^{20} = -35.0$ (*c* 1.75 in $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.33$ (s, 3H, CH_3); 1.52 (s, 3H, CH_3); 1.80–1.95 (m, 1H, *H*C-CH_2S); 2.00–2.13 (m, 1H, *H*C-CH_2S); 2.71–2.91 (m, 4H, $2 \times CH_2$-S); 3.42–3.51 (m, 1H, H_5); 4.03 (d, 1H, $J_{3,4} = 3.1$ Hz, H_3); 4.17 (d, 1H, $J_{5,7} = 6.2$ Hz, S-C*H*-S); 4.43 (d, 1H, $J_{gem} = 11.4$ Hz, CH_2Ph); 4.53–4.61 (m, 4H, $H_2 + H_4 + H_6 +$ CH_2Ph); 4.74 (dd, 1H, $J_{5,6'} = 5.2$ Hz, $J_{6,6'} = 14.5$ Hz, $H_{6'}$); 5.90 (d, 1H, $J_{1,2} = 3.6$ Hz, H_1); 7.28–7.42 (m, 5H, 5 × Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 25.3$, 26.2; 26.7; 29.3; 29.4; 41.3; 46.9; 71.2; 74.1; 78.0; 81.3; 81.5; 104.2; 111.8; 128.0; 128.4; 136.6. MS (CI): *m*/*z* (%) = 442 (36, MH^+); 244 (100); 197 (45). IR (KBr, cm^{-1}): 1552, 1382 (NO_2). Found: C, 54.42; H, 6.20; N, 3.27; S, 14.39. $C_{20}H_{27}NO_6S_2$ requires C, 54.40; H, 6.16; N, 3.17; S, 14.52.

4.2. Conversion of 4b into (1*S*,2*S*,3*R*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-2-nitro-cyclohexanecarbaldehyde propylene dithioacetal 6a and (1*S*,2*S*,3*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-2-nitro-cyclohexanecarbaldehyde propylene dithioacetal 6b

A solution of **4b** (0.43 g, 0.98 mmol) in 75% aqueous acetic acid solution (25 mL) was refluxed for 3 h and then the solvent was evaporated to dryness and coevaporated with toluene (3 × 10 mL). After the solid residue was dissolved in methanol (30 mL), a 2% aqueous sodium bicarbonate solution was added (10 mL, 2.44 mmol). This mixture was stirred overnight, and then acidified with DOWEX® 50 WX4-50, filtered and concentrated in vacuo to a syrup that was submitted to flash column chromatography (ethyl acetate/hexane 1:1.5) to isolate an 87% yield of a 1:2.5 mixture of **5a** and **5b** (0.34 g, 0.85 mmol).

4.2.1. Conversion of 5a and 5b into 6a and 6b. A 0.8 M solution of the above mixture of nitrocyclohexanes **5a** and **5b**, 2-methoxypropene (30 equiv) and a catalytic amount of PPTS (0.5 equiv) in dry dichloromethane was refluxed for 3 h. The usual work-up led to a syrup that was subjected to preparative TLC (ethyl acetate/hexane 1:3) to obtain a 24% yield of inositol **6a** and a 61% yield of inositol **6b**.

Compound **6a**: $[\alpha]_D^{20} = -43.9$ (*c* 1.94, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.45$ (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 1.81–1.92 (m, 1H, *H*C-CH_2S); 2.07–2.14 (m, 1H, *H*C-CH_2S); 2.73 (dt, 1H, $J_{1,1'} = 1.6$ Hz, $J_{1,6} = 10.6$ Hz, $J_{1,2} = 10.6$ Hz, H_1); 2.83–2.96 (m, 5H, $2 \times CH_2$-S + OH); 3.51 (t, $J_{4,5} = 9.8$ Hz, $J_{3,4} = 9.8$ Hz, 1H, H_4); 3.64 (dd, 1H, $J_{5,6} = 7.8$ Hz, $J_{4,5} = 9.8$ Hz, H_5); 3.93 (dd, 1H, $J_{3,4} = 9.8$ Hz, $J_{2,3} = 10.6$ Hz, H_3); 3.94 (ddd, 1H, $J_{6,OH} = 2.7$ Hz, $J_{5,6} = 7.8$ Hz, $J_{1,6} = 10.6$ Hz, H_6); 4.43 (d, 1H, $J_{1,1'} = 1.6$ Hz, S-C*H*-S); 4.70 (d, 1H, $J_{gem} = 11.3$ Hz, CH_2Ph); 4.90 (t, 1H, $J_{1,2} = 10.6$ Hz, $J_{2,3} = 10.6$ Hz, H_2); 4.94 (d, 1H, $J_{gem} = 11.3$ Hz, CH_2Ph); 7.29–7.37 (m, 5H, 5 × Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 25.7$; 26.5; 26.8; 31.6; 31.9; 48.0; 49.6; 72.2; 73.0; 77.2; 78.1; 80.2; 84.0; 113.4; 127.9; 128.0; 128.4; 137.7. MS (CI): *m*/*z* (%) = 442 (100, MH^+); 384 (45, $MH^+ - C_3H_6O$). IR (KBr, cm^{-1}): 3510 (OH); 1557, 1372 (NO_2). Found: C, 54.60; H, 6.22; N, 3.16; S, 14.27. $C_{20}H_{27}NO_6S_2$ requires C, 54.40; H, 6.16; N, 3.17; S, 14.52.

Compound **6b**: $[\alpha]_D^{20} = -60.5$ (*c* 3.75, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.31$ (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 1.80–1.91 (m, 1H, *H*C-CH_2S); 2.07–2.15 (m, 1H, *H*C-CH_2S); 2.81–3.01 (m, 6H, $2 \times CH_2$-S + H_1 + OH); 3.90 (t, 1H, $J_{4,5} = 4.3$ Hz, $J_{5,6} = 4.3$ Hz, H_5); 4.24–4.29 (m, 1H, H_6); 4.50 (d, 1H, $J_{1,1'} = 3.1$ Hz, S-C*H*-S); 4.53 (ddd, 1H, $J_{4,6} = 1.2$ Hz, $J_{4,5} = 4.3$ Hz, $J_{3,4} = 7.0$ Hz, H_4); 4.60 (d, 1H, $J_{gem} = 11.7$ Hz, CH_2Ph); 4.81 (dd, 1H, $J_{2,3} = 4.3$ Hz, $J_{3,4} = 7.0$ Hz, H_3); 4.83 (d, 1H, $J_{gem} = 11.7$ Hz, CH_2Ph); 5.27 (dd, 1H, $J_{2,3} = 4.3$ Hz, $J_{1,2} = 10.9$ Hz, H_2); 7.29–7.38 (m, 5H, 5 × Ar-H). ^{13}C NMR ($CDCl_3$): $\delta = 23.7$; 25.7; 25.9; 30.4; 31.1; 45.2; 49.7; 68.0; 72.4; 73.8; 76.4; 76.5; 81.9; 110.9; 127.9; 128.0; 128.4; 137.1. MS (CI): *m*/*z* (%) = 442 (100, MH^+); 384 (16, $MH^+ - C_3H_6O$). IR (KBr, cm^{-1}): 3529 (OH); 1557, 1382 (NO_2). Found: C, 54.82; H, 6.34; N, 3.03; S, 14.10. $C_{20}H_{27}NO_6S_2$ requires C, 54.40; H, 6.16; N, 3.17; S, 14.52.

4.2.2. Conversion of 5a and 5b into 6b. A mixture of **5a** and **5b**, 2,2-dimethoxypropane (0.07 M), acetone (0.1 M) and PTSA (0.2 equiv) and anhydrous copper sulfate was stirred at rt for 12 h. The work-up furnished a syrup that was subjected to flash column chromatography (ethyl acetate/hexane 1:3) giving an 87% yield of *myo*-inositol **6b** as a white foam.

4.3. (3*S*,4*S*,5*S*,6*R*)-5-Benzyloxy-6-hydroxy-3,4-(isopropylidendioxy)-cyclohex-1-enecarbaldehyde 1e

Iodomethane (10 equiv) was added to a 0.1 M solution of **6b** and saturated aqueous sodium bicarbonate solution (0.5 M) in acetonitrile, and the mixture was heated to 35 °C for 36 h. The liquids were removed in vacuo and the solid residue subjected to flash column chromatography (ethyl acetate/hexane 1:3), providing a 53% yield of **1e** as a yellow oil. $[\alpha]_D^{20} = -29.7$ (*c* 1.63, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.48$ (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 3.11 (br s, 1H, OH); 3.64 (dd, 1H, $J_{3,4} = 9.1$ Hz, $J_{4,5} = 10.7$ Hz, H-4); 4.00 (dd, 1H, $J_{5,6} = 5.5$ Hz, $J_{4,5} = 10.7$ Hz, H_5); 4.45 (dt, 1H, $J_{2,3} = 1.4$ Hz, $J_{3,6} = 1.4$ Hz, $J_{3,4} = 9.1$ Hz, H_3); 4.79–4.95 (m, 3H, $H_6 + CH_2Ph$); 7.06 (d, 1H, $J_{3,2} = 1.4$ Hz, H_2); 7.28–7.45 (m, 5H, 5 × Ar-H); 9.51 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta = 26.6$; 26.7; 72.7; 73.4; 75.6; 79.6; 81.7; 112.5; 127.6; 127.8; 128.3; 138.1; 141.3; 145.7; 193.1. MS (CI): *m*/*z* (%) = 305 (100, MH^+); 247 (65, $MH^+ - C_3H_6O$). IR (KBr, cm^{-1}): 3456 (OH); 1688 (CO). Found: C, 67.15; H, 6.74; $C_{17}H_{21}O_5$ requires C, 67.09; H, 6.62.

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11. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 289417 **4b**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)1223-336-033; email: deposit@ccdc.cam.ac.uk]. Crystallographic data for **4b**. $C_{20}H_{27}NO_6S_2$, $M = 441.55$, $T = 293(2)$ K. Orthorhombic, space group $P2_12_12_1$ with $a = 5.193(5)$, $b = 11.133(5)$, $c = 37.150(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2148(2)$ Å^3, D_c ($Z = 4$) = 'not measured'. $F(000) = 936$, absorption coefficient = 0.284 mm^{-1}. Data were obtained on a Smart-CCD-1000 BRUKER diffractometer (graphite crystal monochromator, $\lambda = 0.71069$ Å) using the $\omega = 2\theta$ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93) using all data; $wR^2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.
12. Previous specific rotation attributed to compound **6b** $\{[\alpha]_D^{24} = -9.3$ (c 1.14, $CHCl_3$)$\}$ is incorrect. See Ref. 9.
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