Facile Diels–Alder dimerisation of a vinyloxepin synthesised using intramolecular ene–yne metathesis

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Dedicated with respect to Professor Siegfried Blechert on the occasion of his 65th birthday

Abstract

The partially-protected D-lyxose derivative **4** was converted into the thioether-substituted lactol **6**, which was subjected to Ohira–Bestmann alkynylation, *O*-allylation and ene–yne metathesis to give a bicyclic vinyloxepin. This underwent high-yielding and completely regio-and stereo Diels–Alder dimerisation at ambient temperature. X-Ray crystallographic analysis of the dimer revealed unexpectedly that epimerisation at the sugar C2-position had taken place during the alkynylation step.

Keywords: Diels–Alder dimerisation, ene–yne metathesis, epimerisation, Ohira–Bestmann reaction, vinyloxepin

Introduction

Since it was first reported 25 years ago, ring-closing ene–yne metathesis[1] has been developed as an atom-economical way of forming 1,3-diene moieties incorporated in carbo- and heterocyclic systems, which have been further shown to participate in Diels–Alder reactions.[2]

We became interested in utilising the ene–yne metathesis reaction of the sugar-derived substrate **1** to assemble vinyloxepin **2**, with the intention of subjecting it to elimination to give trienol **3** (Scheme 1), which was required for intramolecular hetero-Diels–Alder reactivity studies in conjunction with imine dienophiles. This paper presents the results of these studies.
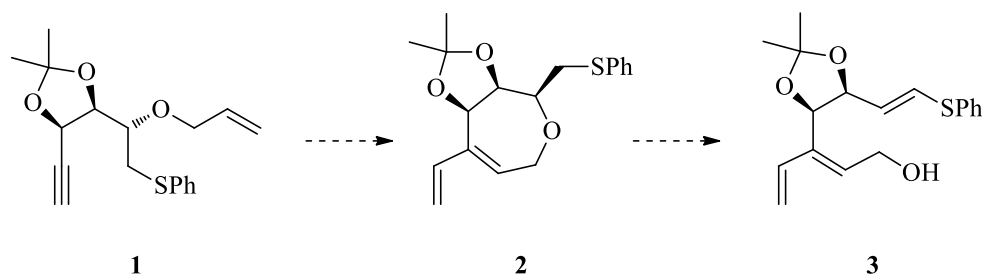
Scheme 1. Planned synthetic route to dienol **3** from enyne **1**.

Results and Discussion

Our synthesis approach began with 2,3-di-*O*-isopropylidene-D-lyxofuranose **4**,[3] which was converted into the bis(thioether) **5**[4] under standard conditions. Selective hydrolysis of the anomeric carbon–sulfur bond gave the bicyclic lactol **6**, which was exposed to the Ohira–Bestmann reagent[5] under basic conditions with the intention of obtaining the homologated, monocyclic terminal alkyne **7**; subsequent *O*-allylation would provide the ether substrate for ene–yne metathesis studies. In the event, esterification of the product of Ohira–Bestmann reaction of **6** gave a 3,5-dinitrobenzoate which was shown by X-ray crystallography to be **10**, which was epimeric at the propargylic stereocentre (Figure 1).[6] Since the structure of the thioglycoside **5** had already been confirmed by X-ray crystallography,[7] the epimerisation must have occurred during the Ohira–Bestmann homologation, giving **8** instead of **7**; such unwanted base–acid reactivity has been documented previously (Scheme 2).[8] Compound **8** was allylated under standard conditions to give ether **9** in nearly quantitative yield.

   In initial experiments, ether **9** was exposed to Grubbs' second-generation catalyst (5 mol %) in dichloromethane (0.05 M) at room temperature for 48 h. Compound **13**, the product of cross-metathesis of the expected vinyloxepin **11** was isolated in 13% yield, together with 21% of unreacted **9**. In an effort to increase the turnover rate of the catalyst,[9] an analogous reaction was conducted under an atmosphere of ethylene; this gave in 70% yield the vinyloxepin **11** and the ethylene–alkyne cross-metathesis product **12** as an inseparable 4:3 mixture (Scheme 3). Similar reactivity in the presence of ethylene has been reported by Mori and co-workers.[10] In further experiments, ether **9** was treated with 10 mol % Grubbs' second-generation catalyst in dichloromethane (0.05 M) under reflux conditions for 3.5 h, giving **11** in 42% yield. However, the product readily decomposed at higher concentrations and elevated temperatures, and as a consequence could be stored only as a dilute solution in dichloromethane for short periods. The decomposition product was determined to be a dimer, the product of a highly stereo- and regioselective Diels–Alder reaction of vinyloxepin **11** with itself. X-ray crystallography confirmed the regiochemistry of the cycloadduct **14** (Figure 2).[11] Dimerisation of 7-membered

vinyl oxepins *via* thermal or Lewis acid-catalysed Diels–Alder reaction has previously been reported.[12]
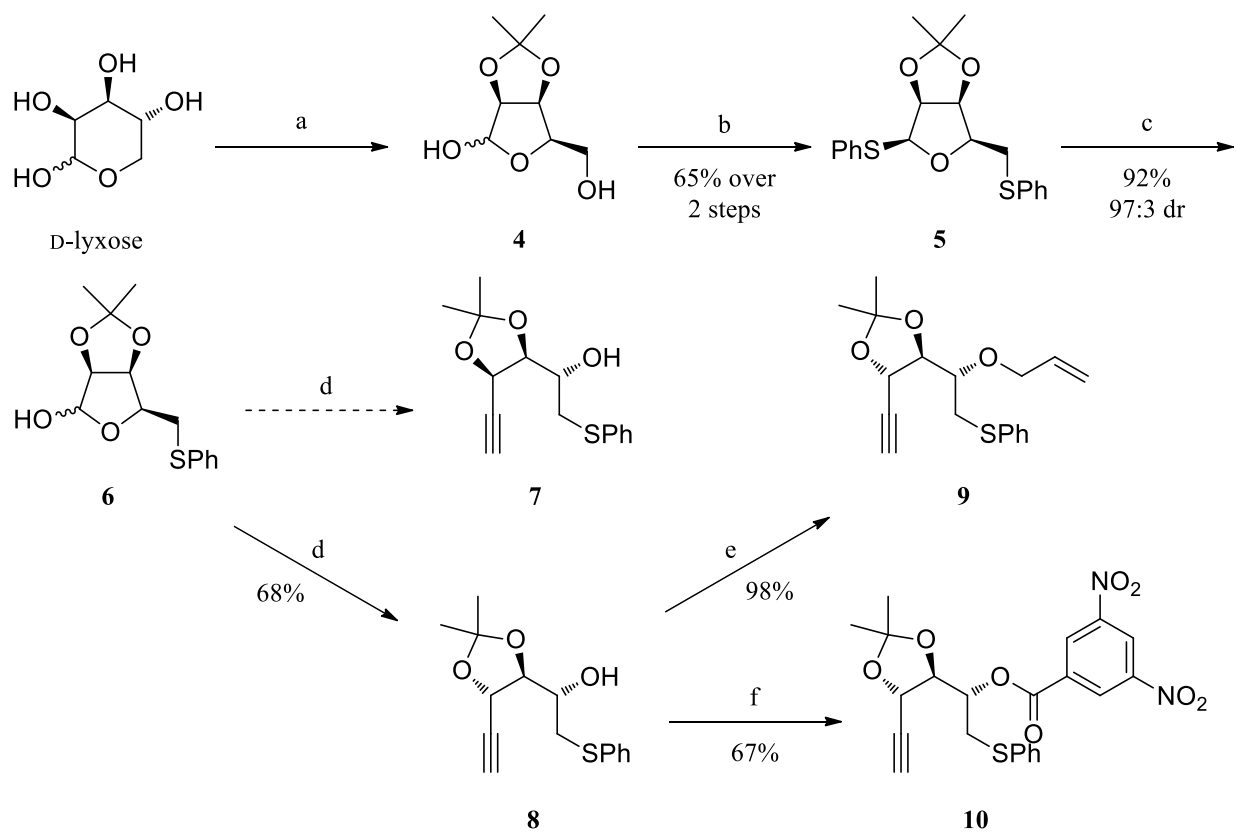
Scheme 2. Synthesis of enyne **9** from D-(–)-lyxose. *Reagents and conditions*: (a) H_2SO_4 (0.17 equiv), acetone, rt, 15h; (b) PhSSPh (2.5 equiv), ^{n}Bu$_3$P (4.0 equiv), pyridine, rt, 17 h; (c) $HgCl_2$ (2.0 equiv), HgO red (2.5 equiv), MeCN/H_2O (10:1), rt; 48 h; (d) K_2CO_3 (3.0 equiv), MeOH, reflux; then Ohira–Bestmann reagent (3.0 equiv), MeOH, added *via* syringe pump over a period of 8 h; (e) NaH (1.5 equiv), DMF, 0 °C; then a solution of **8** (1.0 equiv) and allyl bromide (1.5 equiv) in DMF added, 0 °C→rt, 60 min; (f) 3,5-dinitrobenzoyl chloride (1.1 equiv), Et$_3$N (1.5 equiv), THF, 0 °C→rt, 3 h.
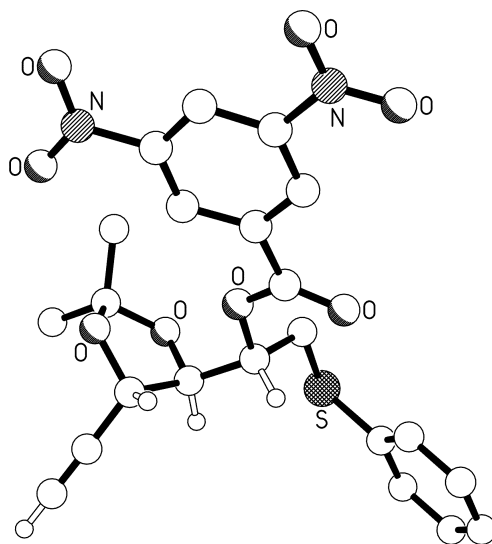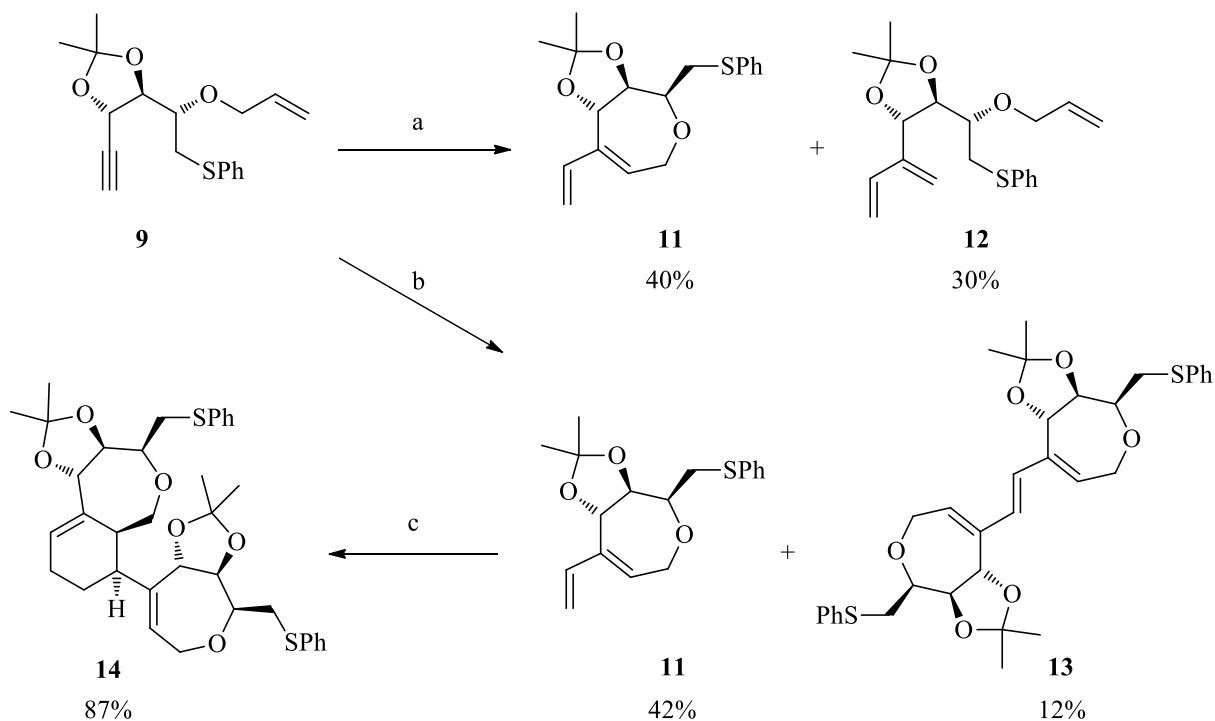
Figure 1. The molecular structure of 3,5-dinitrobenzoate **10**.

Scheme 3. Ene–yne metathesis of **9**. *Reagents and conditions*: (a) Grubbs (II) (10 mol%), ethylene atmosphere, CH$_2$Cl$_2$ (0.03 M), rt, 17 h; (b) Grubbs (II) (10 mol%), CH$_2$Cl$_2$ (0.05 M), reflux, 3.5 h; (c) ambient temperature.
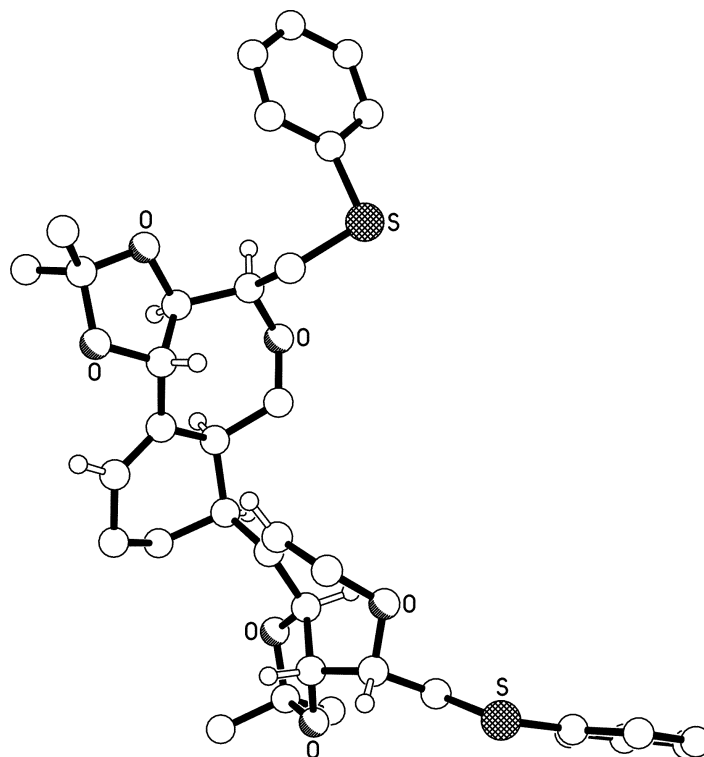
Figure 2. The molecular structure of cycloadduct **14**.

Summary

In summary, the results described herein demonstrate the susceptibility to epimerisation of acetonide-protected sugar lactols under the basic conditions of the Ohira–Bestmann reaction. The facile Diels-Alder dimerisation of diene **11** is unusual; ongoing studies are directed towards the identification of alternative, non-basic reaction sequences for the synthesis of **7**, and its subsequent allylation and ene–yne metathesis reactions.

Experimental Section

General. Standard laboratory techniques were employed when handling air-sensitive reagents. All reactions were performed under a nitrogen atmosphere unless otherwise stated. Melting points were determined using a Stuart Scientific SMP1 or Büchi B-545 melting point apparatus and are uncorrected. Optical rotations were measured on an Optical Activity Ltd, AA-10 Automatic or polAAr 3000 Automatic polarimeter. Infrared spectra were recorded on Perkin–Elmer Spectrum RX FT-IR or Spectrum One FT-IR spectrometers. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultra-Shield AV-400 spectrometer. Chemical shifts (δ_H and δ_C) are

expressed in parts per million (ppm), referenced to the appropriate residual solvent peak. Mass spectra (CI, EI and FAB) were recorded uing a Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier spectrometer. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Thin-layer chromatography was performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck Kieselgel 60 F_{254}), which were developed using standard visualising agents: ultraviolet fluorescence (254 nm) and/or potassium permanganate and vanillin. Flash column chromatography was performed using BDH (40-63 μm) flash chromatography silica gel unless otherwise stated. Standard solvents were distilled under nitrogen prior to use: THF was distilled from sodium-benzophenone ketyl and CH_2Cl_2, MeOH and pyridine from CaH_2. Hexane refers to the fraction of petroleum boiling between 67–70 ºC. All other solvents and reagents were used as received from the supplier unless otherwise noted.

Phenyl 2,3-*O*-isopropylidene-5-*S*-phenyl-1,5-dithio-*β*-D-lyxofuranoside (5). To a stirred suspension of D-(−)-lyxose (1.00 g, 6.66 mmol, 1.0 equiv) in acetone (25 mL) was added concentrated H_2SO_4 (60.4 μL, 1.13 mmol, 0.17 equiv). The reaction mixture was stirred at room temperature for 15 h. Then, neutralised by the addition of Na_2CO_3 (2.5 g). After stirring for 3 h at room temperature, the mixture was filtered and concentrated under reduced pressure to give crude 2,3-*O*-isopropylidene-D-lyxofuranose **4** (1.34 g) as a colourless gum, which was dissolved in dry pyridine (5.6 mL) along with diphenyl disulfide (3.64 g, 16.7 mmol, 2.5 equiv). To this stirred yellow solution at room temperature was added tri-*n*-butylphosphine (6.67 mL, 26.7 mmol, 4.0 equiv) dropwise. During the addition an exotherm was observed and at the end of addition a dark red solution was observed. After 17 h at room temperature, the reaction mixture was quenched with CH_2Cl_2 (50 mL). After 15 min, a pale yellow solution was observed, which was washed with saturated aqueous $NaHCO_3$ solution (50 mL) and water (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a green residue. Purification by chromatography (0→5% Et_2O–hexane) gave phenyl 2,3-*O*-isopropylidene-5-S-phenyl-1,5-dithio-β-D-lyxofuranoside **5** (1.63 g, 65% over 2 steps) as colourless needles; mp 77.0−79.0 °C (Et_2O); R_f 0.27 (20% Et_2O–hexane); $[\alpha]_D^{25}$ −88.5 (*c* 1.04, $CHCl_3$); ν_{max} (film) 3058 (Ar-H, w), 2988 (CH_3, m), 2938 (CH_2, m), 2869 (CH_2, w), 1584 (C=C, m), 1482 (CH_2, s), 1440 (CH_3, m), 1382 (CH_3, m), 1373 (CH_3, m), 1270 (CH_2, m), 1228 (CH_2, m), 1209 (C-O, s), 1160 (C-O, m), 1100 (C-O, vs), 1062 (C-O, s), 1024 (C-O, vs), 976 (CH_2, m), 872 (Ar-H, m), 741 (Ar-H, vs), 692 (Ar-H, vs) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.52 (2H, d, *J* 7.0 Hz, *ortho* PhS), 7.44 (2H, d, *J* 8.0 Hz, *ortho* PhS), 7.34–7.21 (6H, m, *meta* PhS & *para* PhS), 4.92–4.89 (2H, m, H-1 & H-2), 4.79 (1H, dd, *J* 4.5 & 4.0 Hz, H-3), 3.75 (1H, ddd, *J* 7.5, 6.5 & 3.5 Hz, H-4), 3.40–3.38 (2H, m, H-5), 1.60 (3H, s, C(C*H₃*)₂), 1.40 (3H, s, C(C*H₃*)₂); δ_C ($CDCl_3$, 101 MHz) 135.7 (*ipso* PhS), 135.5 (*ipso* PhS), 130.5 (*ortho* PhS), 129.6 (*ortho* PhS), 129.0 (*meta* PhS), 128.9 (*meta* PhS), 126.9 (*para* PhS), 126.4 (*para* PhS), 113.3 (*C*(CH₃)₂), 89.8 (C-1), 82.3 (C-2), 80.3 (C-4), 80.0 (C-3), 31.2 (C-5), 26.0 (C(*C*H₃)₂), 25.2 (C(*C*H₃)₂); *m/z* (CI) 392 ([M+NH₄]⁺, 93%), 375 ([MH]⁺,

100%), 263 ([M−SPh]$^+$, 52%) (Found: [MH]$^+$, 375.1077. $C_{20}H_{23}O_3S_2$ requires [MH]$^+$, 375.1089) (Found: C, 64.23; H, 6.00%. $C_{20}H_{22}O_3S_2$ requires C, 64.14; H, 5.92%).

2,3-*O*-Isopropylidene-5-*S*-phenyl-5-thio-D-lyxofuranose (6). To a stirred colourless solution of phenyl 2,3-O-isopropylidene-5-S-phenyl-1,5-dithio-β-D-lyxofuranoside **5** (100 mg, 0.267 mmol, 1.0 equiv) in MeCN/water (1.9 mL, 10:1) at room temperature was added $HgCl_2$ (145 mg, 0.534 mmol, 2.0 equiv), followed by red HgO (145 mg, 0.668 mmol, 2.5 equiv). The orange suspension was stirred at room temperature for 45 h. The reaction mixture was filtered through a pad of celite, washing with CH_2Cl_2 (3 x 5 mL). The combined filtrate and washings were washed with 20% aqueous KI solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a colourless semi-solid. Purification by chromatography (0→20% EtOAc–hexane) gave 2,3-*O*-isopropylidene-5-S-phenyl-5-thio-D-lyxofuranose **6** (64.2 mg, 85%, 93:7 dr) as a colourless oil; R$_f$ 0.48 (50% EtOAc–hexane); [α]$_D^{26}$ −33.9 (*c* 1.89, CHCl$_3$); ν$_{max}$ (neat) 3426 (O-H, br m), 3057 (Ar-H, w), 2987 (CH$_3$, m), 2939 (CH$_2$, m), 1584 (C=C, m), 1481 (CH$_2$, m), 1439 (CH$_3$, m), 1373 (CH$_3$, s), 1271 (CH$_2$, m), 1234 (CH$_2$, m), 1210 (C-O, s), 1161 (C-O, m), 1125 (C-O, m), 1066 (C-O, vs), 1025 (C-O, s), 1012 (C-O, s), 979 (CH$_2$, m), 866 (Ar-H, s), 739 (Ar-H, s), 691 (Ar-H, s) cm^{-1}; δ$_H$ (CDCl$_3$, 400 MHz) 7.42 (2H, d, *J* 7.0 Hz, *ortho* PhS), 7.31 (2H, dd app. t, *J* 7.5 Hz, *meta* PhS), 7.22 (1H, t, *J* 7.5 Hz, *para* PhS), 5.41 (1H, d, *J* 2.5 Hz, H-1 major anomer), 4.98 (1H, dd, *J* 12.0 & 3.5 Hz, H-1 minor anomer), 4.80 (1H, dd, *J* 6.0 & 3.5 Hz, H-3 major anomer), 4.76 (1H, dd, *J* 6.0 & 3.5 Hz, H-3 minor anomer), 4.63 (1H, d, *J* 6.0 Hz, H-2 major anomer), 4.52 (1H, dd, *J* 6.0 & 3.5 Hz, H-2 minor anomer), 4.33 (1H, ddd app. td, *J* 7.0 & 3.5 Hz, H-4, major anomer), 3.91 (1H, d, *J* 12.0 Hz, OH minor anomer), 3.67 (1H, ddd, *J* 9.0, 6.0 & 3.0 Hz, H-4 minor anomer), 3.27 (1H, dd, *J* 13.5 & 7.0 Hz, H-5), 3.24 (1H, dd, *J* 13.5 & 7.0 Hz, H-5), 2.39 (1H, d, *J* 2.5 Hz, OH major anomer), 1.56 (3H, s, C(C*H*$_3$)$_2$ minor anomer), 1.50 (3H, s, C(C*H*$_3$)$_2$ major anomer), 1.40 (3H, s, C(C*H*$_3$)$_2$ minor anomer), 1.35 (3H, s, C(C*H*$_3$)$_2$ major anomer); δ$_C$ (CDCl$_3$, 101 MHz) 135.8 (*ipso* PhS), 129.5 (*ortho* PhS), 128.9 (*meta* PhS), 126.3 (*para* PhS), 112.7 (*C*(CH$_3$)$_2$), 101.2 (C-1), 85.5 (C-2), 79.9 (C-3), 78.9 (C-4), 32.1 (C-5), 26.1 (C(*C*H$_3$)$_2$), 24.9 (C(*C*H$_3$)$_2$); *m/z* (CI) 300 ([M+NH$_4$]$^+$, 61%), 283 ([MH]$^+$, 100%), 265 ([M−OH]$^+$, 96%) (Found: [MH]$^+$, 283.1003. $C_{14}H_{19}O_4S$ requires [MH]$^+$, 283.1004) (Found: C, 59.62; H, 6.60%. $C_{14}H_{18}O_4S$ requires C, 59.55; H, 6.43%).

(3*S*,4*S*,5*S*)-3,4-Isopropylidenedioxyhex-1-yne-5-ol-6-thiobenzene (8). To a stirred suspension of 2,3-*O*-isopropylidene-5-*S*-phenyl-5-thio-D-lyxofuranose **6** (100 mg, 0.354 mmol, 1.0 equiv) and potassium carbonate (147 mg, 1.06 mmol, 3.0 equiv) in dry MeOH (0.93 mL) heated under reflux, was added a solution of dimethyl 1-diazo-2-oxopropylphosphonate (204 mg, 1.06 mmol, 3.0 equiv) in dry MeOH (0.74 mL) dropwise over a period of 8 h *via* a syringe pump. The reaction mixture was filtered through a glass frit to remove the residual inorganics. The filtrate was concentrated under reduced pressure to give a brown residue, which was dissolved in water (5 mL) and then extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated under reduced pressure to give a yellow oil. Purification by chromatography (0→10% Et$_2$O–hexane) gave (3*S*,4*S*,5*S*)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene

8 (61 mg, 62%) as a colourless oil; R_f 0.37 (50% Et_2O–hexane); $[\alpha]_D^{26}$ −33.3 (*c* 0.72, $CHCl_3$); ν_{max} (neat) 3479 (O-H, br m), 3289 (≡CH, m), 3059 (Ar-H, w), 2989 (CH_3, m), 2935 (CH_2, m), 2122 (C≡C, w), 1584 (C=C, m), 1482 (CH_2, m), 1440 (CH_3, m), 1383 (CH_3, s), 1247 (CH_2, s), 1213 (C-O, s), 1158 (C-O, m), 1111 (C-O, m), 1059 (C-O, vs), 1026 (C-O, s), 879 (Ar-H, m), 741 (Ar-H, s), 691 (Ar-H, s) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.43 (2H, d, *J* 7.0 Hz, *ortho* PhS), 7.32 (2H, dd app. t, *J* 7.5 Hz, *meta* PhS), 7.24 (1H, tt, *J* 7.5 & 1.0 Hz, *para* PhS), 4.62 (1H, dd, *J* 7.5 & 2.0 Hz, H-3), 4.26 (1H, dd, *J* 7.5 & 3.0 Hz, H-4), 3.76 (1H, ddd, *J* 14.0, 7.0 & 3.0 Hz, H-5), 3.16 (1H, dd app, d, *J* 7.0 Hz, H-6), 3.13 (1H, dd app. d, *J* 6.5 Hz, H-6), 2.56 (1H, d, *J* 2.0 Hz, H-1), 2.50 (1H, br d, *J* 7.5 Hz, OH), 1.49 (3H, s, C(CH_3)$_2$), 1.45 (3H, s, C(CH_3)$_2$); δ_C ($CDCl_3$, 101 MHz) 134.9 (*ipso* PhS), 130.3 (*ortho* PhS), 129.1 (*meta* PhS), 126.8 (*para* PhS), 111.0 (*C*(CH_3)$_2$), 82.2 (C-4), 80.5 (C-2), 75.1 (C-1), 68.1 (C-5), 66.7 (C-3), 38.2 (C-6), 26.6 (C(*C*H_3)$_2$), 26.0 (C(*C*H_3)$_2$); *m/z* (CI) 574 ([2M+NH$_4$]$^+$, 2%), 296 ([M+NH$_4$]$^+$, 43%), 279 ([MH]$^+$, 57%), 263 ([M−CH$_3$]$^+$, 15%), 221 ([M−OC(CH$_3$)$_2$+H]$^+$, 100%) (Found: [MH]$^+$, 279.1048. $C_{15}H_{19}O_3S$ requires [MH]$^+$, 279.1055) (Found: C, 64.84; H, 6.65%. $C_{15}H_{18}O_3S$ requires C, 64.72; H, 6.52%).

(3*S*,4*R*,5*S*)-3,4-Isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene (9). To a stirred suspension of sodium hydride (511 mg, 12.8 mmol, 1.5 equiv, 60% dispersion in mineral oil) in dry DMF (21 mL) at 0 °C, was added a solution (3*S*,4*S*,5*S*)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene **8** (2.37 g, 8.51 mmol, 1.0 equiv) and allyl bromide (1.11 mL, 12.8 mmol, 1.5 equiv) in dry DMF (21 mL). Effervescence observed during addition. Then the reaction mixture was allowed to warm to room temperature. After 60 min, at room temperature the reaction mixture was quenched with MeOH (5 mL). Concentrated under reduced pressure to give a pale yellow semi-solid residue, which was dissolved in $CHCl_3$ (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (100 mL). Aqueous layer was extracted with $CHCl_3$ (3 x 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography (0→5% Et_2O–hexane) gave (3*S*,4*R*,5*S*)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene **9** (2.66 g, 98%) as a colourless oil; R_f 0.62 (50% Et_2O–hexane); $[\alpha]_D^{24}$ −42.9 (*c* 1.12, $CHCl_3$); ν_{max} (neat) 3287 (≡CH, w), 3078 (Ar-H, w), 2988 (CH_3, w), 2935 (CH_2, w), 2119 (C≡C, w), 1584 (C=C, w), 1481 (CH_2, w), 1459 (CH_3, w), 1382 (CH_3, m), 1373 (CH_3, m), 1246 (CH_2, m), 1212 (C-O, m), 1157 (C-O, m), 1121 (C-O, m), 1060 (C-O, vs), 1025 (C-O, m), 990 (=CH, m), 924 (=CH$_2$, m), 866 (Ar-H, m), 739 (Ar-H, s), 690 (Ar-H, s) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.42 (2H, dd, *J* 8.0 & 1.5 Hz, *ortho* PhS), 7.32 (2H, dd app. t, *J* 8.0 Hz, *meta* PhS), 7.22 (1H, tt, *J* 7.5 & 1.0 Hz, *para* PhS), 5.88 (1H, dddd app. ddt, *J* 17.0, 10.5 & 6.0 Hz, *H*C=CH$_2$), 5.21 (1H, ddd app. dq, *J* 17.0 & 1.5 Hz, *trans* HC=C*H*$_2$), 5.17 (1H, ddd app. dq, *J* 10.5 & 1.5 Hz, *cis* HC=C*H*$_2$), 4.59 (1H, dd, *J* 7.5 & 2.0 Hz, H-3), 4.35 (1H, dd, *J* 7.5 & 3.5 Hz, H-4), 4.19 (1H, ddt, *J* 12.5, 5.5 & 1.5 Hz, C*H*$_2$CH=CH$_2$), 4.03 (1H, ddt, *J* 12.5, 6.0 & 1.5 Hz, C*H*$_2$CH=CH$_2$), 3.59 (1H, ddd app. td, *J* 6.5 & 3.5 Hz, H-5), 3.21 (1H, dd, *J* 13.5 & 6.5 Hz, H-6), 3.17 (1H, dd, *J* 13.5 & 6.5 Hz, H-6), 2.55 (1H, d, *J* 2.0 Hz, H-1), 1.47 (3H, s, C(C*H*$_3$)$_2$), 1.45 (3H, s, C(C*H*$_3$)$_2$); δ_C ($CDCl_3$, 101 MHz) 135.9 (*ipso* PhS), 134.2 (H*C*=CH$_2$), 129.8 (*ortho* PhS), 129.0 (*meta* PhS), 126.4 (*para* PhS), 117.8 (HC=*C*H$_2$), 110.7 (*C*(CH$_3$)$_2$), 81.9

(C-4), 80.8 (C-2), 75.7 (C-5), 74.9 (C-1), 72.1 ($CH_2CH=CH_2$), 66.3 (C-3), 34.5 (C-6), 26.6 (C(CH_3)$_2$), 26.0 (C(CH_3)$_2$); m/z (CI) 336 ([M+NH$_4$]$^+$, 33%), 319 ([MH]$^+$, 6%), 303 ([M−CH$_3$]$^+$, 4%), 261 ([M−OCH$_2$CH=CH$_2$]$^+$, 100%) (Found: [M+NH$_4$]$^+$, 336.1635. $C_{18}H_{26}NO_3S$ requires [M+NH$_4$]$^+$, 336.1633) (Found: C, 68.00; H, 6.87%. $C_{18}H_{22}O_3S$ requires C, 67.89; H, 6.96%).

(*S*)-1-((4*R*,5*S*)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(phenylthio)ethyl 3,5-dinitrobenzoate (10). To a stirred colourless solution of (3*S*,4*S*,5*S*)-3,4-isopropylidenedioxy-hex-1-yne-5-ol-6-thiobenzene **8** (47 mg, 0.169 mmol, 1.0 equiv) in dry THF (0.66 mL) at 0 °C was added triethylamine (35.4 μL, 0.253 mmol, 1.5 equiv), followed by 3,5-dinitrobenzoyl chloride (42.8 mg, 0.186 mmol, 1.1 equiv). Solution turned yellow in colour on addition of the 3,5-dinitrobenzoyl chloride. Reaction mixture was allowed to warm to room temperature. After 3 h at room temperature, the reaction mixture was partitioned between Et$_2$O (2 mL) and water (2 mL). The layers were separated and the aqueous layer was extracted with Et$_2$O (2 mL). The combined organic layers were washed with brine (2 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to give a yellow semi-solid. Purification by chromatography (0→5% Et$_2$O–hexane) gave (*S*)-1-((4*R*,5*S*)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(phenylthio)ethyl 3,5-dinitrobenzoate **10** (53.8 mg, 67%) pale yellow fine needles; R$_f$ 0.46 (50% Et$_2$O–hexane); [α]$_D^{19}$ −69.0 (*c* 1.58, CHCl$_3$); ν_{max} (neat) 3288 (≡CH, m), 2994 (CH$_3$, w), 2948 (CH$_2$, w), 2121 (C≡C, w), 1713 (C=O, s), 1582 (C=C, w), 1545 (NO$_2$, vs), 1482 (CH$_2$, m), 1460 (CH$_3$, w), 1438 (CH$_3$, w), 1389 (CH$_3$, m), 1375 (≡CH, m), 1341 (NO$_2$, vs), 1277 (C-O, vs), 1246 (C-O, vs), 1214 (C-O, s), 1174 (C-O, s), 1096 (C-N, m), 1064 (C-O, vs), 1044 (C-O, s), 1026 (C-O, s), 972 (≡CH, m), 921 (C-N, s), 851 (Ar-H, m), 833 (Ar-H, s), 743 (Ar-H, s), 729 (Ar-H, vs), 719 (Ar-H, vs), 693 (Ar-H, vs), 666 (≡CH, vs) cm^{-1}; δ$_H$ (CDCl$_3$, 400 MHz) 9.22 (1H, t, *J* 2.0 Hz, *para* Ar(NO$_2$)$_2$), 9.03 (2H, d, *J* 2.0 Hz, *ortho* Ar(NO$_2$)$_2$), 7.42 (2H, dd, *J* 8.0 & 1.0 Hz, *ortho* PhS), 7.23 (2H, dd app. t, *J* 8.0 Hz, *meta* PhS), 7.10 (1H, td, *J* 7.5 & 1.0 Hz, *para* PhS), 5.50 (1H, ddd, *J* 8.5, 5.0 & 3.5 Hz, H-1), 4.54–4.49 (2H, m, H-4 & H-5), 3.44 (1H, dd, *J* 14.5 & 8.0 Hz, C*H*$_2$SPh), 3.36 (1H, dd, *J* 14.5 & 5.0 Hz, C*H*$_2$SPh), 2.62 (1H, d, *J* 2.0 Hz, C≡C*H*), 1.53 (3H, s, C(C*H*$_3$)$_2$), 1.49 (3H, s, C(C*H*$_3$)$_2$); δ$_C$ (CDCl$_3$, 101 MHz) 161.8 (C=O), 148.6 (*meta* Ar(NO$_2$)$_2$), 134.6 (*ipso* PhS), 134.6 (*ipso* Ar(NO$_2$)$_2$), 130.4 (*ortho* Ar(NO$_2$)$_2$), 129.5 (*ortho* PhS), 129.1 (*meta* PhS), 126.9 (*para* PhS), 122.5 (*para* Ar(NO$_2$)$_2$), 111.8 (*C*(CH$_3$)$_2$), 80.9 (C-4), 80.1 (*C*≡CH), 75.7 (C≡*C*H), 74.0 (C-1), 66.7 (C-5), 34.5 (*C*H$_2$SPh), 26.6 (C(CH$_3$)$_2$), 26.1 (C(CH$_3$)$_2$); m/z (CI) 490 ([M+NH$_4$]$^+$, 18%), 472 ([M]$^+$, 9%), 415 ([M−OC(CH$_3$)$_2$+H]$^+$, 100%) (Found: [M+NH$_4$]$^+$, 490.1295. $C_{22}H_{24}N_3O_8S$ requires [M+NH$_4$]$^+$, 490.1284) (Found: C, 56.02; H, 4.30; N, 5.75%. $C_{22}H_{20}N_2O_8S$ requires C, 55.93; H, 4.27; N, 5.93%).

(*Z*,3a*R*,4*S*,8a*S*)-3a,4,6,8a-Tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-*c*]oxepine (11) and ((3a*R*,4*S*,7*Z*,8a*S*)-3a,4,6,8a-tetrahydro-8-((1*E*)-2-((*Z*,3a*R*,4*S*,8a*S*)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-*c*]oxepin-8-yl)vinyl)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-*c*]oxepine (13). To a stirred colourless solution of (3*S*4*R*,5*S*)-3,4-isopropylidenedioxy-5-allyloxy-hex-1-yne-6-thiobenzene **9** (135 mg, 0.424 mmol, 1.0 equiv) in dry CH$_2$Cl$_2$ (8.5 mL) was added Grubbs II catalyst (36.0 mg, 0.042 mmol, 0.1 equiv). Then, the reaction mixture was heated under reflux

for 3½ h. Filtered through a pad of silica eluting with hexane (25 mL) and then Et$_2$O/hexane (1:1, 5 x 10 mL). The filtrate was concentrated under reduced pressure without heating to almost dryness to give a brown liquid. Purification by chromatography (0→20% Et$_2$O–hexane) gave **(Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo [4,5-c]oxepine (11).** (56.4 mg, 42%) as a colourless oil; R$_f$ 0.33 (20% Et$_2$O–hexane); [α]$_D^{22}$ −46.3 (c 0.605, CHCl$_3$); ν$_{max}$ (film) 2986 (CH$_3$, w), 2931 (CH$_2$, w), 2883 (CH$_3$, w), 1584 (C=C, w), 1481 (CH$_2$, m), 1439 (CH$_3$, m), 1372 (CH$_3$, m), 1236 (CH$_2$, s), 1167 (C-O, m), 1141 (C-O, m), 1113 (C-O, s), 1082 (C-O, vs), 1026 (C-O, m), 992 (=CH, m), 912 (=CH$_2$, m), 869 (Ar-H, m), 738 (Ar-H, s), 691 (Ar-H, s) cm^{-1}; δ$_H$ (CDCl$_3$, 400 MHz) 7.41 (2H, dd, J 7.5 & 1.0 Hz, *ortho* PhS), 7.31 (2H, dd app. t, J 7.5 Hz, *meta* PhS), 7.20 (1H, tt, J 7.5 & 1.0 Hz, *para* PhS), 6.38 (1H, dd, J 17.5 & 11.0 Hz, CH=CH$_2$), 5.79 (1H, br dd, J 5.5 & 3.0 Hz, H-7), 5.56 (1H, d, J 17.5 Hz, *trans* CH=CH$_2$), 5.11 (1H, d, J 11.0 Hz, *cis* CH=CH$_2$), 4.96 (1H, br d, J 9.0 Hz, H-8a), 4.45 (1H, dd, J 17.5 & 5.5 Hz, H-6), 4.33 (1H, dd, J 9.5 & 7.0 Hz, H-3a), 4.27–4.22 (2H, m, H-4 & H-6), 3.48 (1H, dd, J 13.5 & 3.0 Hz, CH$_2$SPh), 3.03 (1H, dd, J 13.5 & 9.5 Hz, CH$_2$SPh), 1.48 (3H, s, C(CH$_3$)$_2$), 1.45 (3H, s, C(CH$_3$)$_2$); δ$_C$ (CDCl$_3$, 101 MHz) 138.5 (C-8), 136.7 (*ipso* PhS), 135.2 (CH=CH$_2$), 129.2 (*ortho* PhS), 128.9 (*meta* PhS), 127.9 (C-7), 126.0 (*para* PhS), 115.6 (CH=CH$_2$), 109.9 (C(CH$_3$)$_2$), 79.4 (C-3a), 75.7 (C-8a), 75.6 (C-4), 67.2 (C-6), 34.2 (CH$_2$SPh), 27.1 (C(CH$_3$)$_2$), 26.8 (C(CH$_3$)$_2$); m/z (CI) 336 ([M+NH$_4$]$^+$, 24%), 319 ([MH]$^+$, 39%), 289 ([M−CH$_2$CH$_3$]$^+$, 7%) 261 ([M−OC(CH$_3$)$_2$+H]$^+$, 100%) (Found: [MH]$^+$, 319.1358. C$_{18}$H$_{23}$O$_3$S requires [MH]$^+$, 319.1368) and **((3aR,4S,7Z,8aS)-3a,4,6,8a-tetrahydro-8-((1E)-2-((Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepin-8-yl)vinyl)-2,2-dimethyl-4-((phenylthio)methyl)-[1,3]dioxolo[4,5-c]oxepine (13).** (15.3 mg, 12%) as a colourless oil; R$_f$ 0.13 (20% Et$_2$O–hexane); [α]$_D^{21}$ −109.7 (c 0.62, CHCl$_3$); ν$_{max}$ (film) 2985 (CH$_3$, w), 2931 (CH$_2$, w), 2874 (CH$_3$, w), 1584 (C=C, w), 1481 (CH$_2$, m), 1439 (CH$_3$, m), 1371 (CH$_3$, m), 1234 (CH$_2$, s), 1166 (C-O, m), 1142 (C-O, m), 1112 (C-O, s), 1081 (C-O, vs), 1024 (C-O, m), 972 (=CH, m), 868 (Ar-H, s), 735 (Ar-H, vs), 690 (Ar-H, vs) cm^{-1}; δ$_H$ (CDCl$_3$, 400 MHz) 7.41 (4H, d, J 8.0 Hz, *ortho* PhS), 7.31 (4H, dd app. t, J 7.5 Hz, *meta* PhS), 7.20 (2H, t, J 7.5 Hz, *para* PhS), 6.60 (2H, s, CH=CH), 5.82 (2H, br d, J 4.0 Hz, H-7), 4.95 (2H, br d, J 9.0 Hz, H-8a), 4.46 (2H, dd, J 18.0 & 5.5 Hz, H-6), 4.33 (2H, dd, J 8.5 & 7.5 Hz, H-3a), 4.28–4.24 (4H, m, H-4 & H-6), 3.48 (2H, dd, J 13.5 & 1.5 Hz, CH$_2$SPh), 3.03 (2H, dd, J 13.5 & 9.5 Hz, CH$_2$SPh), 1.48 (6H, s, C(CH$_3$)$_2$), 1.45 (6H, s, C(CH$_3$)$_2$); δ$_C$ (CDCl$_3$, 101 MHz) 138.3 (C-8), 136.7 (*ipso* PhS), 129.2 (*ortho* PhS), 128.9 (*meta* PhS), 128.5 (CH=CH), 127.4 (C-7), 126.0 (*para* PhS), 109.8 (C(CH$_3$)$_2$), 79.4 (C-3a), 75.7 (C-8a), 75.6 (C-4), 67.3 (C-6), 34.2 (CH$_2$SPh), 27.1 (C(CH$_3$)$_2$), 26.8 (C(CH$_3$)$_2$); m/z (CI) 626 ([M+NH$_4$]$^+$, 9%), 609 ([MH]$^+$, 6%), 551 ([M−OC(CH$_3$)$_2$+H]$^+$, 22%) (Found: [MH]$^+$, 609.2358. C$_{34}$H$_{41}$O$_6$S$_2$ requires [MH]$^+$, 609.2345) (Found: C, 67.16; H, 6.54%. C$_{34}$H$_{40}$O$_6$S$_2$ requires C, 67.08; H, 6.62%).

(3aR,4S,6aS,7S,10bS)-7-((3aR,4S,8aS,Z)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-8-yl)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,6a,7,8,9,10b-octahydrobenzo[c][1,3]dioxolo[4,5-e]oxepine (14). The colourless oil of (Z,3aR,4S,8aS)-3a,4,6,8a-tetrahydro-2,2-dimethyl-4-((phenylthio)methyl)-8-vinyl-[1,3]dioxolo[4,5-c]oxepine **11**

(54.1 mg, 0.170 mmol, 1.0 equiv) was left for 48 h at room temperature under vacuum to dimerise. Purification by chromatography (0→15% Et$_2$O–hexane) gave **(3a*R*,4*S*,6a*S*,7*S*,10b*S*)-7-((3a*R*,4*S*,8a*S*,*Z*)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-*c*]oxepin-8-yl)-2,2-dimethyl-4-(phenylthiomethyl)-3a,4,6,6a,7,8,9,10b-octahydrobenzo[*c*][1,3]dioxolo[4,5-*e*]oxepine (14).** (47.0 mg, 87%) as a colourless, granular solid; R$_f$ 0.13 (20% Et$_2$O–hexane); [α]$_D^{24}$ −39.5 (*c* 0.405, CHCl$_3$); ν$_{max}$ (film) 2985 (CH$_3$, w), 2919 (CH$_2$, m), 2887 (CH$_3$, w), 2850 (CH$_2$, m), 1583 (C=C, w), 1481 (CH$_2$, m), 1456 (CH$_3$, w), 1439 (CH$_3$, m), 1427 (CH$_2$, w), 1381 (CH$_3$, m), 1240 (CH$_2$, s), 1216 (CH$_2$, s), 1168 (C-O, m), 1142 (C-O, m), 1117 (C-O, s), 1109 (C-O, s), 1075 (C-O, vs), 1054 (C-O, s), 1042 (C-O, s), 1026 (C-O, s), 1004 (C-O, m), 985 (=CH, m), 871 (Ar-H, s), 737 (Ar-H, vs), 698 (=CH, m), 689 (Ar-H, vs), 676 (=CH, s) cm^{-1}; δ$_H$ (CDCl$_3$, 400 MHz) 7.41 (4H, d, *J* 7.5 Hz, *ortho* PhS), 7.33–7.29 (4H, m, *meta* PhS), 7.22–7.17 (2H, m, *para* PhS), 5.99 (1H, br s, H-10), 5.40 (1H, br s, H-7'), 4.77 (1H, br d, *J* 7.5 Hz, H-8a'), 4.63 (1H, d, *J* 9.5 Hz, H-10b), 4.41 (1H, dd, *J* 17.0 & 5.0 Hz, H-6'), 4.26 (1H, dd, *J* 10.0 & 6.0 Hz, H-3a), 4.24–4.10 (4H, m, H-3a', H-4', H-4 & H-6'), 3.58–3.33 (4H, m, H-6 & C*H*$_2$SPh), 3.15–2.89 (4H, m, H-6a, H-7 & C*H*$_2$SPh), 2.19 (2H, br s, H-9), 1.67–1.56 (2H, m, H-10), 1.48 (3H, s, C(C*H*$_3$)$_2$), 1.47 (3H, s, C(C*H*$_3$)$_2$), 1.45 (3H, s, C(C*H*$_3$)$_2$), 1.41 (3H, s, C(C*H*$_3$)$_2$); δ$_C$ (CDCl$_3$, 101 MHz) 139.9 (C-10a), 136.7 (*ipso* PhS), 136.4 (*ipso* PhS), 133.2 (C-8'), 129.6 (*ortho* PhS), 129.3 (*ortho* PhS), 128.9 (*meta* PhS), 126.7 (C-10), 126.1 (*para* PhS), 126.0 (*para* PhS), 123.5 (C-7'), 110.1 (*C*(CH$_3$)$_2$), 109.9 (*C*(CH$_3$)$_2$), 80.1 (C-4'), 78.5 (C-3a), 77.1 (C-10b), 76.1 (C-8a'), 75.7 (C-4), 75.1 (C-3a'), 68.5 (C-6), 67.8 (C-6'), 40.1 (C-6a), 37.2 (C-8), 34.2 (*C*H$_2$SPh), 32.5 (*C*H$_2$SPh), 27.3 (C(*C*H$_3$)$_2$), 27.0 (C(*C*H$_3$)$_2$), 26.9 (C(*C*H$_3$)$_2$), 26.8 (C(*C*H$_3$)$_2$), 23.9 (C-7 & C-10); *m/z* (CI) 654 ([M+NH$_4$]$^+$, 88%), 637 ([MH]$^+$, 19%), 596 ([M−OC(CH$_3$)$_2$+NH$_4$]$^+$, 14%), 579 ([M−OC(CH$_3$)$_2$+H]$^+$, 72%) (Found: [MH]$^+$, 637.2639. C$_{36}$H$_{45}$O$_6$S$_2$ requires [MH]$^+$, 637.2658) (Found: C, 68.05; H, 6.94%. C$_{36}$H$_{44}$O$_6$S$_2$ requires C, 67.89; H, 6.96%).

Acknowledgements

References and Notes

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6. Crystal data for 10: $C_{22}H_{20}N_2O_8S$, M = 472.46, orthorhombic, $P2_12_12_1$ (no. 19), a = 7.22546(10), b = 12.76286(16), c = 23.8828(3) Å, V = 2202.41(5) $Å^3$, Z = 4, D_c = 1.425 g cm^{-3}, μ(Cu-Kα) = 1.769 mm^{-1}, T = 173 K, yellow needles, Oxford Diffraction Xcalibur PX Ultra diffractometer; 4266 independent measured reflections (R_{int} = 0.0223), F^2 refinement, R_1(obs) = 0.0268, wR_2(all) = 0.0693, 4016 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 145°], 298 parameters. The absolute structure of 10 was determined by a combination of R-factor tests [R_1^+ = 0.0268, R_1^- = 0.0423] and by use of the Flack parameter [x^+ = +0.000(12)]. CCDC 795020.

7. Crystal data for 5: $C_{20}H_{22}O_3S_2$, M = 374.50, monoclinic, $P2_1$ (no. 4), a = 7.9938(3), b = 9.0867(2), c = 13.5097(3) Å, β = 102.364(3)°, V = 958.55(5) $Å^3$, Z = 2, D_c = 1.298 g cm^{-3}, μ(Mo-Kα) = 0.293 mm^{-1}, T = 173 K, colourless platy needles, Oxford Diffraction Xcalibur 3 diffractometer; 6046 independent measured reflections (R_{int} = 0.0286), F^2 refinement, R_1(obs) = 0.0358, wR_2(all) = 0.0690, 4286 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 66°], 226 parameters. The absolute structure of 5 was determined by a combination of R-factor tests [R_1^+ = 0.0358, R_1^- = 0.0370] and by use of the Flack parameter [x^+ = +0.02(4), x^- = +0.98(4)]. CCDC 795019.

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11. Crystal data for 14: $C_{36}H_{44}O_6S_2$, M = 636.83, monoclinic, $P2_1$ (no. 4), a = 15.976(3), b = 5.6023(11), c = 18.523(6) Å, β = 105.09(2)°, V = 1600.7(7) $Å^3$, Z = 2, D_c = 1.321 g cm^{-3}, μ(Mo-Kα) = 0.212 mm^{-1}, T = 173 K, colourless platy needles, Oxford Diffraction Xcalibur 3 diffractometer; 5739 independent measured reflections (R_{int} = 0.0470), F^2 refinement, R_1(obs) = 0.1153, wR_2(all) = 0.3641, 3657 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 58°], 398 parameters. The absolute structure of 14 could not be determined by either R-factor tests [R_1^+ = 0.1153, R_1^- = 0.1156] or by use of the Flack parameter [x^+ = +0.0(3), x^- = +1.0(3)] and so was assigned based on the known stereochemistries at C(2) and C(28). CCDC 795021.

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