Asymmetric synthesis of tetrahydropyrans with competitive [1,2]-phenylsulfanyl (PhS) migrations

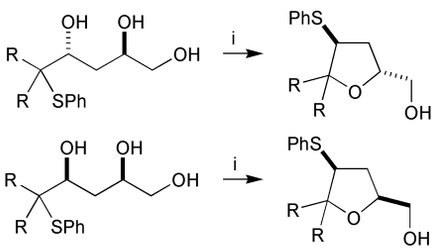
Lorenzo Caggiano,[a] David J. Fox,[b] David House,[c] Zoe A. Jones,[b] Fraser Kerr[d] and Stuart Warren*[b]

[a] *Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Via Venezian 21, 20133 Milano, Italy*
[b] *University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: sw134@cam.ac.uk*
[c] *Dyson Perrins Laboratory, South Parks Road, Oxford, UK OX1 3QY*
[d] *AstraZeneca, Hurdsfield Industrial Estate, Macclesfield, Cheshire, UK SK10 2NA*

Received (in Cambridge, UK) 3rd September 2002, Accepted 30th September 2002
First published as an Advance Article on the web 7th November 2002

Enantiomerically enriched triols were treated with trimethyl orthoacetate and pyridinium toluene-*p*-sulfonate to give a mixture of unrearranged THF and rearranged THP; treatment of the product mixture with toluene-*p*-sulfonic acid equilibrated the mixture to the THP.

In the preceding paper[1] we reported the preparation of three series of enantiomerically enriched 2,4,5-triols (**1**–**6**) with C-1 bearing a phenylsulfanyl group (Fig. 1). We showed that in each case their acid catalysed cyclisation resulted in rearrangement to tetrahydrofuran (THF) products (Scheme 1). The outcome of



Scheme 1 *Reagents*: i, TsOH, CH_2Cl_2, 40 °C.

this rearrangement was proven to be a consequence of thermodynamic control. In this second paper we disclose full details[2] of how the same cyclisation precursors can be converted to the complementary tetrahydropyran (THP) products without the need for a selective protection-deprotection strategy.

We have shown already that it is the secondary hydroxy group at C-4 in these 2,4,5-triols that cyclises to give THFs. In order to prepare the corresponding THPs, an orthogonal protecting group strategy would be required in which the primary and secondary hydroxy group are sequentially protected; the primary hydroxy could then be unmasked and left available for cyclisation. A more elegant solution to this problem would be to protect, in a single step, the secondary hydroxy nucleophile and simultaneously activate the other secondary hydroxy group to nucleophilic displacement. We reasoned that by treatment of these triols with an orthoester under the appropriate conditions, an exchange could be set up between a 5- and a 6-membered orthoester (Scheme 2). As long as the 5-membered orthoester was inert under these reaction conditions it would be possible to trigger the episulfonium ion formation and protect the secondary hydroxy group as its acetate.

Pyridinium toluene-*p*-sulfonate (PPTS) (pK_a ~ 5.5) was chosen as the acid catalyst for this reaction because orthoesters exchange under general acid catalysis[3] but we did not expect such a weak acid to promote direct formation of the episulfonium ion (specific acid catalysis is needed). Hence triol **1** was treated with one equivalent of trimethyl orthoacetate with 25 mol% PPTS as the acid catalyst. In the first instance the product isolated from this reaction was the orthoester **7** formed by exchange of all three molecules of methanol (Scheme 3). However, with longer reaction times we obtained none of this orthoester but two heterocyclic products instead. The two heterocycles were the rearranged[4] THP **8** and the unrearranged[4] THF **9**: both products derive from cyclisation of the primary hydroxy nucleophile but to different ends of the episulfonium ion intermediate (Scheme 4).

This observation was important to our research programme because it constituted the first example of a cyclisation onto the

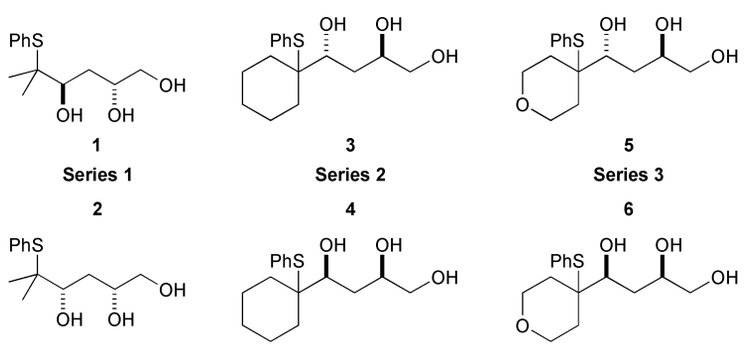
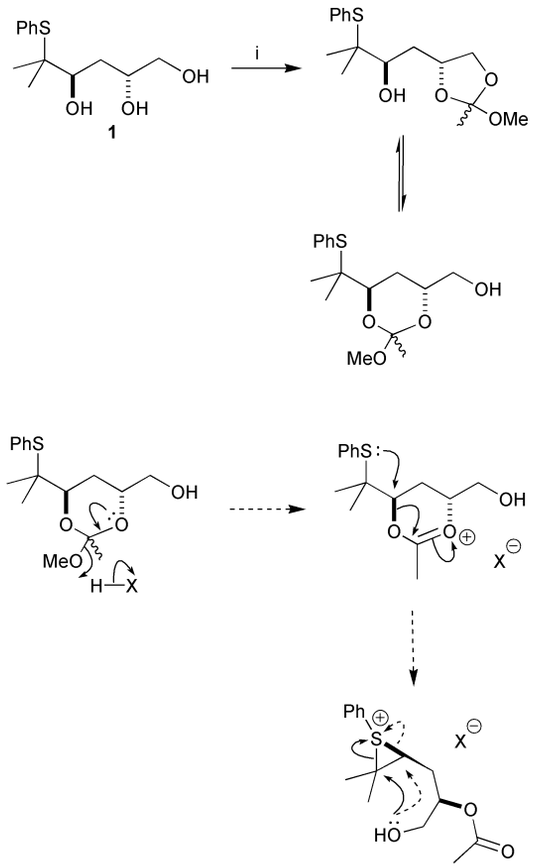
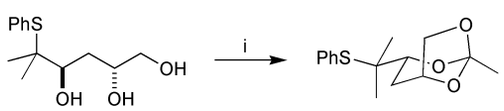


Fig. 1 2,4,5-Triols for cyclisation reactions.

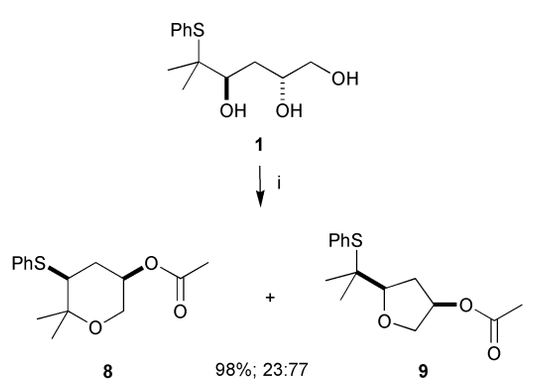
 DOI: 10.1039/b208557g



Scheme 2 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+\cdot TsO^-$, CH_2Cl_2.

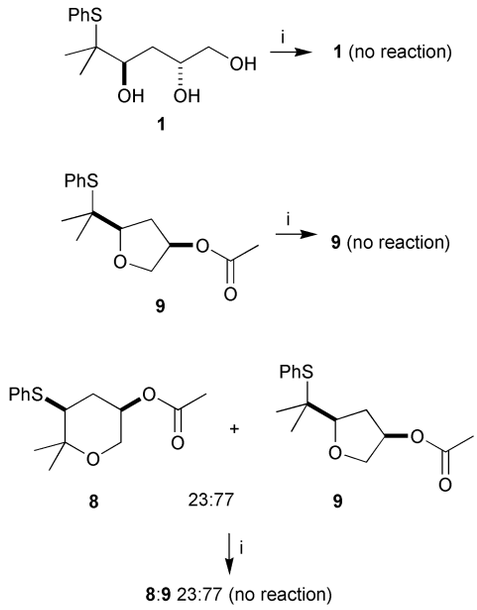


Scheme 3 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+\cdot TsO^-$, CH_2Cl_2, rt, 2 min.



Scheme 4 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+\cdot TsO^-$, CH_2Cl_2, rt, 24 h.

less substituted end of an episulfonium ion (where the alternative cyclisation would not give a seven-membered ring).[5] This raised the question of whether these reactions were therefore under kinetic control.[6] We were able to address this question by performing a series of control experiments (Scheme 5). Firstly we took a sample of the triol and treated it with PPTS, without adding trimethyl orthoacetate, and showed that no reaction occurred. Secondly the 23:77 THP **8**:THF **9** mixture isolated from the cyclisation reaction was resubmitted to the PPTS acid catalyst: no equilibration of the mixture occurred. Finally we confirmed the second experiment by showing that a pure sample of the unrearranged THF **9** was not converted to the THP **8** by PPTS. At this point we could conclude that this orthoester promoted cyclisation is in fact under kinetic control.



Scheme 5 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+\cdot TsO^-$, CH_2Cl_2, rt, 24 h.

That this cyclisation was irreversible was further substantiated by ^1H NMR spectroscopy; we were able to perform the rearrangement reaction in a 400 MHz NMR spectrometer at 50 °C and record ^1H NMR spectra at regularly timed intervals (Fig. 2). This experiment proved very revealing: the bicyclic

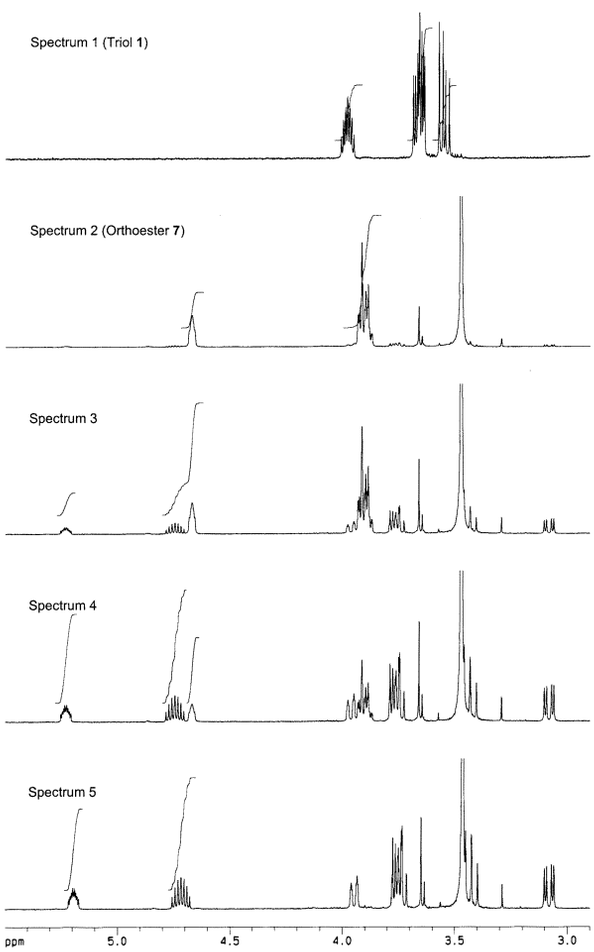
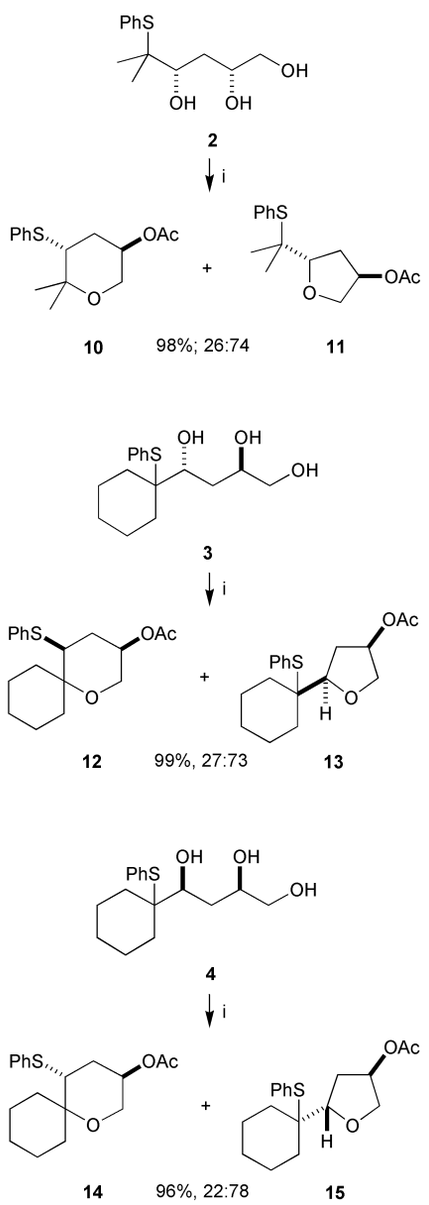


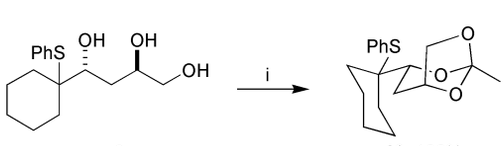
Fig. 2 ^1H NMR spectra recorded in $CDCl_3$ at 50 °C at specified intervals to show the rearrangement of triol **1** under kinetic conditions. Spectrum 1 shows triol **1** (OH couplings removed); spectrum 2 shows the bicyclic orthoester **7**; and spectra 3–5 show the rearranged THP **8** (δ_H ~ 4.7) and unrearranged THF **9** (δ_H ~ 5.2) forming under kinetic control.

orthoester **7**, which we had previously observed, formed more quickly than we could record the first spectrum! Over a 12-hour period we were able to watch the slow decay of this intermediate and the gradual appearance of the two heterocyclic products **8** and **9**. The ratio of the two products was constant over the 12-hour monitoring period. It is worth noting that as the NMR experiment was performed at 50 °C the THP **8** is the major product, whereas at room temperature the THF **9** predominates.

Following the rearrangement of triol **1**, we also cyclised triols **2**–**4** (**2** and **4** being the diastereoisomers of **1** and **3**) under the same conditions and observed in each case a mixture of the THP (**10**, **12** and **14**) and THF (**11**, **13** and **15**) products. The unrearranged THFs were always the major products (Scheme 6). For the 2,4-*anti* triol **3** a bicyclic orthoester intermediate **16** could again be isolated if short reaction times were used (Scheme 7). For the *syn* triols however (**2** and **4**) it was not



Scheme 6 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+ \cdot TsO^-$, CH_2Cl_2, rt, 24 h.



Scheme 7 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+ \cdot TsO^-$, CH_2Cl_2, rt, 2 min.

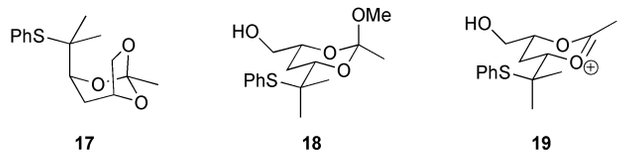
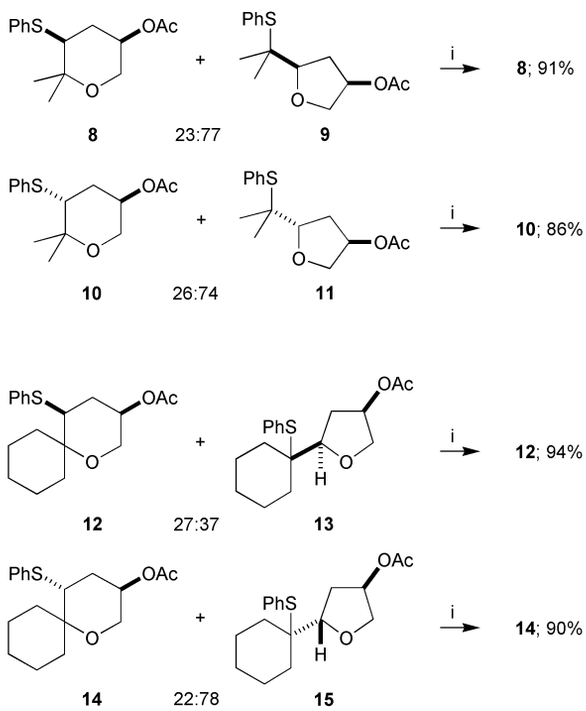


Fig. 3 Possible intermediates in the rearrangement of triol **2**.

possible to isolate a bicyclic orthoester intermediate. The possible intermediate **17** (Fig. 3) for the rearrangement of triol **2** has an extremely large axial group so the transition state for the formation of this species may be very high in energy and hence the rate of formation very low. This suggests the reaction may proceed through the direct breakdown of orthoester **18** into the monocyclic oxenium intermediate **19** (Fig. 3).

At first sight a reaction that produces THF–THP mixture would seem of little synthetic use. On the contrary, this result can be exploited synthetically: treatment of the THF–THP mixtures with a strong acid (toluene-*p*-sulfonic acid) leads to equilibration of the mixture to the rearranged THPs. Indeed this was observed in all four cases; complete equilibration occurred to give the THPs **8**, **10**, **12** and **14**, protected as their acetates (Scheme 8). This two-step procedure can therefore give

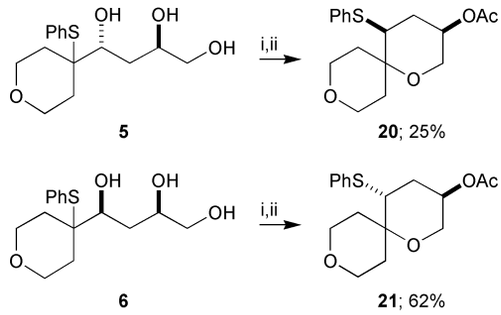


Scheme 8 *Reagents*: i, TsOH, CH_2Cl_2, 40 °C, 24 h.

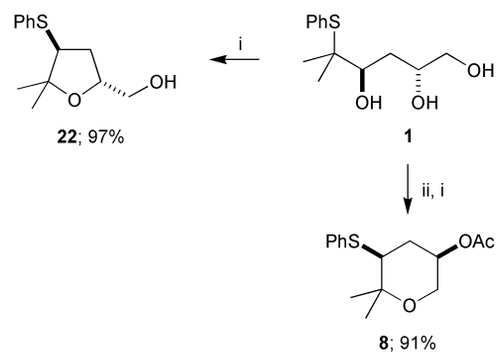
the THP products (which are complementary to the THF products of the one-step toluene-*p*-sulfonic acid cyclisation) without the need for any purification of the intervening mixture.

For the rearrangement of the two remaining triols, **5** and **6**, no attempt was made to separate the unrearranged THFs, instead the crude reaction mixture from the orthoester-triggered cyclisation was filtered through a plug of silica and treated with Amberlyst® to give the THPs **20** and **21** respectively (Scheme 9).

In summary we have demonstrated, in this and the preceding paper,[1] a rapid approach to enantiomerically enriched THPs or THFs from common triol precursors depending on the choice of reagent (Scheme 10). For THF synthesis (*e.g.* **1** → **22**) the episulfonium ion is formed directly, under specific acid catalysis. Use of the orthoester route promotes episulfonium ion formation under general acid catalysis and results in THP–THF mixtures that can be equilibrated to THP (*e.g.* **1** → **8**).



Scheme 9 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+ \cdot TsO^-$, CH_2Cl_2, rt, 24 h; ii, Amberlyst®, CH_2Cl_2, 40 °C, 48 h.



Scheme 10 *Reagents*: i, TsOH, CH_2Cl_2; ii, $(MeO)_3CMe$, $C_5H_6N^+ \cdot TsO^-$, CH_2Cl_2.

Experimental

Dichloromethane was freshly distilled before use from calcium hydride. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$). Preparative HPLC was performed using a Zorbax SIL prepacked silica column (21.2 mm id × 25 cm) with a Gilson model 303 pump and a Cecil Instruments CE 212A UV detection system measuring the absorbance at 254 nm. Analytical HPLC was performed using either a Zorbax RX-C8 prepacked reverse phase silica column or a Daicel Chiralpak AD column with a Spectra-Physics SP8800 pump, a Spectra-Physics SP8450 UV detection system and a ChromJet single channel integrator.

Proton and carbon NMR spectra were recorded on Bruker DPX 250, AM 400, DRX 400 or DRX 500 Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants *J* are quoted in Hz and are not rationalised. The symbol † after the proton NMR chemical shift indicates that the signal disappears after a D_2O "shake". Carbon NMR spectra were recorded with broad band proton decoupling and Attached Proton Test. The symbols $^+$ and $^-$ after the carbon NMR chemical shift indicate odd and even numbers of attached protons respectively.

Melting points were measured on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. Electron Impact (EI) mass spectra were recorded on a Kratos double focusing magnetic sector instrument using a DS503 data system for high-resolution analysis. Fast atom bombardment (FAB) mass spectra were obtained from a Kratos MS 890 instrument. Electrospray (+ES) mass spectra were recorded using a Brucker Bio-Apex FT-ICR instrument and LCMS using a Hewlett Packard HPLC system, eluting with an acetonitrile-water gradient, in conjunction with positive and negative ion electrospray mass spectrometry.

Optical rotations were recorded on a Perkin–Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D$ are given in units of 10^{-1} deg dm^2 g^{-1}.

(1*RS*,3*SR*,5*SR*)-1-Methyl-3-(1-methyl-1-phenylsulfanylethyl)-2,7,8-trioxabicyclo[3.2.1]octane 7

Anti-triol **1** (50 mg, 195 μmol) was dissolved in dry dichloromethane (2 cm^3) and pyridinium toluene-*p*-sulfonate (12.3 mg, 48.8 μmol, 25 mol%) was added. The reaction vessel was sealed with a septum and trimethyl orthoacetate (26 μl, 24.6 mg, 205 μmol) was injected in one portion. The reaction was stirred at room temperature for 5 minutes. The reaction mixture was then filtered through a short plug of silica, eluting with dichloromethane, and the solvent was evaporated under reduced pressure to give the *orthoester* **7** as an oil (54 mg, 99%); R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.24; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3008, 2931, 2898, 1474, 1438, 1401, 1334, 1144, 1124, 1082, 1046, 991, 964 and 912; δ_H(400 MHz; $CDCl_3$) 7.57–7.52 (2 H, m, PhS), 7.38–7.25 (3 H, m, PhS), 4.74–4.65 (1 H, br m, CH_{eq}), 3.96–3.85 (3 H, m, CH_{ax}, CH_AH_B and CH_AH_B), 2.13 (1 H, tdd, *J* 13.2, 3.8 and 1.3 Hz, $CH_{ax}H_{eq}$), 1.69 (1 H, ddd, *J* 13.4, 4.0 and 2.1 Hz, $CH_{ax}H_{eq}$), 1.56 (3 H, s, $MeCO_3$), 1.22 (3 H, s, Me_A) and 1.21 (3 H, s, Me_B); δ_C(62.9 MHz; $CDCl_3$) 137.6$^+$ (*m*-PhS), 131.3$^-$ (*i*-PhS), 128.7$^+$ (*p*-PhS), 128.3$^+$ (*o*-PhS), 118.9$^-$ (CO_3), 73.4$^+$ (CH–O), 72.8$^+$ (CH–O), 68.8$^-$ (CH_2O), 50.6$^-$ (CSPh), 29.0$^-$ (CH_2), 25.2$^+$ (Me), 23.8$^+$ (Me) and 21.8$^+$ (Me); *m*/*z* (EI) 280 (43%, M$^+$), 220 (17), 151 (23, Me_2CSPh^+), 129 (100, M$^+$ − Me_2CSPh) and 111 (61); (Found: M$^+$, 280.1132. $C_{15}H_{20}O_3S$ requires *M*, 280.1133).

(3*RS*,5*SR*)-2,2-Dimethyl-3-phenylsulfanyltetrahydropyran-5-yl ethanoate 8 and (3*RS*,5*SR*)-5-(1-Methyl-1-phenylsulfanylethyl)-tetrahydrofuran-3-yl ethanoate 9

By the method described for compound **7**, *anti*-triol **1** (100 mg, 390 μmol), pyridinium toluene-*p*-sulfonate (24.5 mg, 97.5 μmol, 25 mol%) and trimethyl orthoacetate (52 μl, 49.2 mg, 410 μmol) in dry dichloromethane (2.5 cm^3) gave a crude product after 24 h. Purification by column chromatography [silica, light petroleum (bp 40–60 °C)–diethyl ether, 4:1] gave the *3,5-syn-tetrahydropyran* **8** (23 mg, 20%) as an oil, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.23; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2960, 2973, 2877, 1740 (C=O), 1583, 1477, 1456, 1369, 1240, 1138, 1088, 1073, 1051 and 1039; δ_H(200 MHz; $CDCl_3$) 7.48–7.18 (5 H, m, PhS), 4.75 (1 H, tt, *J* 10.4 and 5.2 Hz, $CH_{ax}OAc$), 3.77 (1 H, ddd, *J* 11.1, 5.4 and 2.0 Hz, $CH_{ax}H_{eq}O$), 3.44 (1 H, t, *J* 10.7 Hz, $CH_{ax}H_{eq}O$), 3.08 (1 H, dd, *J* 12.8 and 4.2 Hz, $CH_{ax}SPh$), 2.31 (1 H, dtd, *J* 12.7, 4.7 and 2.0 Hz, $CH_{ax}H_{eq}$), 2.01 (3 H, s, Ac), 1.81 (1 H, td, *J* 12.8 and 11.3 Hz, $CH_{ax}H_{eq}$), 1.41 (3 H, s, Me_A) and 1.31 (3 H, s, Me_B); δ_C(100.6 MHz; $CDCl_3$) 170.1$^-$ (C=O), 134.8$^-$ (*i*-PhS), 132.1$^+$, 129.2$^+$, 127.4$^+$ (*p*-PhS), 75.1$^-$ (C–O), 68.1$^+$ (CHOH), 62.4$^-$ (CH_2O), 53.2$^+$ (CSPh), 33.6$^-$ (CH_2), 28.7$^+$ (Me), 21.0$^+$ (Me) and 17.9$^+$ (Me); *m*/*z* (EI) 280 (24%, M$^+$), 220 (7, M$^+$ – AcOH), 191 (7), 181 (12), 162 (40), 136 (84), 109 (27, PhS$^+$) and 69 (100) (Found: M$^+$, 280.1124. $C_{15}H_{20}O_3S$ requires *M*, 280.1133) and the unrearranged *3,5-syn-tetrahydrofuran* **9** (86 mg, 74%) as an oil; R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.29; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2934, 2857, 1733 (C=O), 1605, 1474, 1376, 1239, 1078, 1024, 909 and 872; δ_H(200 MHz; $CDCl_3$) 7.60–7.21 (5 H, m, PhS), 5.22 (1 H, dddd, *J* 7.6, 4.9, 3.2 and 1.9 Hz, CHOAc), 3.99 (1 H, dt, *J* 10.5, and 1.5 Hz, CH_AH_BO), 3.76 (1 H, dd, *J* 10.5 and 4.6 Hz, CH_AH_B–O), 3.71 (1 H, d, *J* 8.0 Hz, CH–O), 2.38 (1 H, dt, *J* 14.4 and 7.5 Hz, CH_AH_B), 2.06 (3 H, s, Ac), 1.96 (1 H, dddd, *J* 14.4, 8.4, 3.2 and 1.3 Hz, CH_AH_B), 1.27 (3 H, s, Me_A) and 1.24 (3 H, s, Me_B); δ_C(100.6 MHz; $CDCl_3$) 170.9$^-$ (C=O), 137.8$^+$ (*m*-PhS), 131.1$^-$ (*i*-PhS), 128.9$^+$ (*p*-PhS), 128.5$^+$ (*o*-PhS), 84.5$^+$ (CH–O), 74.7$^+$ (CH–O), 73.0$^-$ (CH_2O), 50.4$^-$ (C–SPh), 34.2$^-$ (CH_2), 25.4$^+$ (Me), 24.2 (Me) and 21.1$^+$ (Me); *m*/*z* (EI) 280 (45%, M$^+$), 220 (15, M$^+$ − AcOH), 162 (46), 136 (100), 110 (28, PhSH$^+$), 109 (33, PhS$^+$) and 77 (11, Ph$^+$); (Found: M$^+$, 280.1124. $C_{15}H_{20}O_3S$ requires *M*, 280.1133).

(3*RS*,5*SR*)-2,2-Dimethyl-3-phenylsulfanyltetrahydropyran-5-yl ethanoate 8

Toluene-*p*-sulfonic acid (1.9 mg, 10 μmol) was added to a stirred solution of the unrearranged THF **9** (50 mg, 170 μmol) in dichloromethane (5 cm^3). The reaction temperature was raised to 50 °C to initiate reflux and heating continued for 24 hours. The mixture was cooled to room temperature and then filtered through a short plug of silica, eluting with dichloromethane, and the solvent was evaporated under reduced pressure to give the ^{3,5}*syn-tetrahydropyran* **8** as an oil (46 mg, 91%), which was spectroscopically identical to an authentic sample.

(3*RS*,5*RS*)-2,2-Dimethyl-3-phenylsulfanyltetrahydropyran-5-yl ethanoate 10 and (3*RS*,5*RS*)-5-(1-Methyl-1-phenylsulfanylethyl)-tetrahydrofuran-3-yl ethanoate 11

By the method described for compound **7**, *syn*-triol **2** (50 mg, 195 μmol), pyridinium toluene-*p*-sulfonate (12.3 mg, 48.8 μmol, 25 mol%) and trimethyl orthoacetate (26.1 μl, 24.6 mg, 205 μmol) in dry dichloromethane (2 cm^3) gave a crude product after 24 h. Purification by column chromatography [silica, light petroleum (bp 40–60 °C)–diethyl ether, 4:1] gave the ^{3,5}*anti-tetrahydropyran* **10** (14 mg, 25%) as an oil, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.14; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2963, 2926, 1733 (C=O), 1582, 1480, 1438, 1373, 1222, 1116, 1086, 1060 and 967; δ_H(250 MHz; $CDCl_3$) 7.44–7.36 (2 H, m, PhS), 7.34–7.20 (3 H, m, PhS), 4.87 (1 H, br s, $CH_{eq}OAc$), 3.87–3.65 (2 H, m, $CH_{ax}H_{eq}O$ and $CH_{ax}H_{eq}O$), 3.42 (1 H, dd, *J* 12.5 and 4.4 Hz, $CH_{ax}SPh$), 2.21–1.92 (2 H, m, $CH_{ax}CH_{eq}$ and $CH_{ax}CH_{eq}$), 2.08 (3 H, s, Ac), 1.43 (3 H, s, Me_A) and 1.31 (3 H, s, Me_B); δ_C(100.6 MHz; $CDCl_3$) 170.5$^-$ (C=O), 135.1$^-$ (*i*-PhS), 131.5$^+$, 129.1$^+$, 127.1$^+$ (*p*-PhS), 75.5$^-$ (C–O), 68.7$^+$ (CHOH), 63.1$^-$ (CH_2OH), 50.0$^+$ (C–SPh), 32.3$^-$ (CH_2), 29.1$^+$ (Me), 21.3$^+$ (Me) and 17.5$^+$ (Me); *m*/*z* (EI) 280 (100%, M^+), 219 (23), 162 (53); (Found: M^+, 280.1131. $C_{15}H_{20}O_3S$ requires *M*, 280.1133) and the unrearranged ^{3,5}*anti-tetrahydrofuran* **11** (42 mg, 74%) as an oil, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.20; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2928, 1736, 1461, 1366, 1128, 1088, 1023 and 980; δ_H(250 MHz; $CDCl_3$) 7.58–7.53 (2 H, m, PhS), 7.38–7.25 (3 H, m, PhS), 5.37–5.26 (1 H, m, C*H*OAc), 4.11 (1 H, dd, *J* 10.4 and 4.4 Hz, CH_AH_BO), 4.04 (1 H, dd, *J* 9.7 and 6.3 Hz, CH_AH_BO), 3.84 (1 H, br d, *J* 10.4 Hz, CH–O), 2.26–2.04 (2 H, m, CH_AH_B and CH_AH_B), 2.07 (3 H, s, Ac), 1.24 (3 H, s, Me_A) and 1.22 (3 H, s, Me_B); δ_C(100.6 MHz; $CDCl_3$) 170.7$^-$ (C=O), 137.7$^+$ (*m*-PhS), 131.2$^-$ (*i*-PhS), 128.9$^+$ (*p*-PhS), 128.5$^+$ (*o*-PhS), 84.6$^+$ (CH–O), 75.3$^+$ (CH–O), 73.6$^-$ (CH_2O), 51.2$^-$ (CSPh), 34.1$^-$ (CH_2), 25.4$^+$ (Me), 24.8 (Me) and 21.2$^+$ (Me); *m*/*z* (EI) 280 (M^+, 100%); (Found: M^+, 280.1121. $C_{15}H_{20}O_3S$ requires *M*, 280.1133).

(3*RS*,5*RS*)-2,2-Dimethyl-3-phenylsulfanyltetrahydropyran-5-yl ethanoate 10

By the method described for compound **8**, toluene-*p*-sulfonic acid (1.9 mg, 10 μmol) and the unrearranged THF **11** (30 mg, 101 μmol) in dichloromethane (3 cm^3) gave the ^{3,5}*anti-tetrahydropyran* **10** as an oil (26 mg, 86%), which was spectroscopically identical to an authentic sample.

(3*RS*,5*RS*)-5-Phenylsulfanyl-1-oxaspiro[5.5]undecan-3-yl ethanoate 12 and (3*RS*,5*RS*)-5-(1-Phenylsulfanylcyclohexyl)-tetrahydrofuran-3-yl ethanoate 13

By the method described for compound **7**, *anti*-triol **3** (82 mg, 277 μmol), pyridinium toluene-*p*-sulfonate (18.2 mg, 72.4 μmol) and trimethyl orthoacetate (37 μl, 34.8 mg, 290 μmol) in dry dichloromethane (5 cm^3) gave a crude product after 24 h. Purification by column chromatography [silica, light petroleum (bp 40–60 °C)–diethyl ether, 4:1] gave the ^{3,5}*syn-tetrahydropyran* **12** (19 mg, 21%) as an oil, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.32; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3060, 2937, 2860, 1732 (C=O), 1583, 1479, 1446, 1370, 1244, 1077, 1039 and 895; δ_H(400 MHz; $CDCl_3$) 7.43–7.37 (2 H, m, PhS), 7.33–7.21 (3 H, m, PhS), 4.76 (1 H, tt, *J* 10.4 and 5.2 Hz, $CH_{ax}OAc$), 3.78 (1 H, ddd, *J* 11.2, 5.4 and 1.9 Hz, $CH_{ax}H_{eq}O$), 3.37 (1 H, t, *J* 10.5 Hz, $CH_{ax}H_{eq}O$), 3.01 (1 H, dd, *J* 12.6 and 4.3 Hz, $CH_{ax}SPh$), 2.29 (1 H, dtd, *J* 12.8, 4.7 and 1.9 Hz, $CH_{ax}H_{eq}$), 2.23–2.16 (1 H, m), 2.15–2.03 (1 H, m), 2.01 (3 H, s, Ac), 1.89 (1 H, td, *J* 12.7 and 11.1 Hz, $CH_{ax}H_{eq}$), 1.74–1.31 (6 H, m) and 1.29–1.14 (2 H, m); δ_C(100.6 MHz; $CDCl_3$) 170.1$^-$ (C=O), 135.3$^-$ (*i*-PhS), 131.9$^+$, 129.1$^+$, 127.2$^+$, 75.4$^-$ (C–O), 68.2$^+$ (CHOH), 61.2$^-$ (CH_2O), 53.7$^+$ (CSPh), 36.0$^-$, 33.0$^-$, 25.8$^-$, 24.6$^-$, 21.4$^-$, 21.1$^+$ (Ac) and 20.4$^-$; *m*/*z* (EI) 320 (31%, M^+), 260 (12, M^+ − AcOH), 223 (100), 162 (37), 136 (58) and 109 (12, PhS^+); (Found: M^+, 320.1444. $C_{18}H_{24}O_3S$ requires *M*, 320.1446) and the unrearranged ^{3,5}*syn-tetrahydrofuran* **13** (62 mg, 70%) as an oil, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.24; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2934, 2857, 1733 (C=O), 1605, 1474, 1376, 1239, 1078, 1024, 909 and 872; δ_H(400 MHz; $CDCl_3$) 7.56–7.50 (2 H, m, PhS), 7.36–7.22 (3 H, m, PhS), 5.21 (1 H, dddd, *J* 7.6, 5.0, 3.2 and 2.0 Hz, CHOAc), 3.94 (1 H, dt, *J* 10.5 and 1.5 Hz, CH_AH_BO), 3.71 (1 H, dd, *J* 10.5 and 4.7 Hz, CH_AH_BO), 3.68 (1 H, t, *J* 8.1 Hz, CH–O), 2.39 (1 H, dt, *J* 14.5 and 7.6 Hz, CH_AH_B), 2.15 (1 H, dddd, *J* 14.2, 8.4, 3.2 and 1.3 Hz, CH_AH_B), 2.06 (3 H, s, OAc), 2.02–1.80 (2 H, m), 1.77–1.48 (6 H, m) and 1.32–1.18 (2 H, m); δ_C(100.6 MHz; $CDCl_3$) 171.3$^-$ (C=O), 137.7$^+$, 131.7$^-$ (*i*-PhS), 129.1$^+$, 128.9$^+$, 84.5$^+$ (CH–O), 74.9$^+$ (*C*HOAc), 73.1$^-$ (CH_2O), 55.7$^-$ (C–SPh), 33.7$^-$ (CH_2, THF), 32.2$^-$, 29.9$^-$, 26.3$^-$, 22.0$^-$, 22.0$^-$ and 21.5 (Me); *m*/*z* (EI) 320 (59), 220 (55), 191 (100, $C_6H_{10}SPh^+$) and 151 (77); (Found: M^+, 320.1457. $C_{18}H_{24}O_3S$ requires *M*, 320.1446).

(3*RS*,5*RS*)-5-Phenylsulfanyl-1-oxaspiro[5.5]undecan-3-yl ethanoate 12

By the method described for compound **8**, toluene-*p*-sulfonic acid (1.9 mg, 10 μmol) and the unrearranged THF **13** (50 mg, 156 μmol) in dichloromethane (5 cm^3) gave the ^{3,5}*syn-tetrahydropyran* **12** as an oil (47 mg, 94%), which was spectroscopically identical to an authentic sample.

(3*RS*,5*RS*)-5-Phenylsulfanyl-1-oxaspiro[5.5]undecan-3-yl ethanoate 14 and (3*RS*,5*RS*)-5-(1-Phenylsulfanylcyclohexyl)-tetrahydrofuran-3-yl ethanoate 15

By the method described for compound **7**, *syn*-triol **4** (45 mg, 152 μmol), pyridinium toluene-*p*-sulfonate (9.6 mg, 38 μmol) and trimethyl orthoacetate (20 μl, 19.2 mg, 160 μmol) in dry dichloromethane (2.5 cm^3) gave a crude product (46 mg, 95%) as an oil after 24 hours. The two components of this product were not successfully separated by column chromatography or by HPLC. Basic characterisation was performed on a 1:3.6 mixture of the ^{3,5}*anti-tetrahydropyran* **14** and the unrearranged ^{3,5}*anti*-tetrahydrofuran **15**, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.26; δ_H(400 MHz; $CDCl_3$) 7.57–7.52 (4 H, m, PhS), 7.41–7.18 (6 H, m, PhS), 5.32–5.26 (1 H, br m, THF CHOAc), 4.93–4.87 (1 H, br m, THP CHOAc), 4.08–4.02 (2 H, m, THF CH–O and CH_AH_BO), 3.79 (1 H, br d, *J* 10.2 Hz, THF CH_AH_BO), 3.78–3.67 (2 H, m, THP $CH_{ax}H_{eq}O$ and $CH_{ax}H_{eq}O$), 3.35 (1 H, dd, *J* 11.4 and 5.2 Hz, THP $CH_{ax}SPh$), 2.32 (1 H, ddd, *J* 13.8, 9.9 and 5.8 Hz, THF CH_AH_B), 2.21–1.20 (23 H, m), 2.10 (3 H, s, THP Ac) and 2.09 (3 H, s, THF Ac); δ_C(100.6 MHz; $CDCl_3$) 170.7$^-$ (THF C=O), 170.6$^-$ (THP C=O), 137.1$^+$ (THF), 135.5$^-$ (THP *i*-PhS), 131.5$^-$ (THF), 131.2$^+$ (THP), 129.0$^+$ (THP), 128.5$^+$ (THF), 126.9$^+$ (THP), 83.9$^+$ (THF CH–O), 75.9$^-$ (THP C–O), 75.2$^+$ (THF CH–O), 73.3$^-$ (THF CH_2O), 68.8$^+$ (THP CH–O), 62.1$^-$ (THP CH_2O), 55.9$^-$ (THF CSPh), 50.5$^+$ (THP CHSPh), 36.2$^-$ (THP), 33.3$^-$ (THF), 32.3$^-$ (THF), 31.6$^-$ (THP), 30.5$^-$ (THF), 25.9$^-$ (THF), 25.4$^-$ (THP), 24.4$^-$ (THP), 21.7$^-$ (THF), 21.6$^-$ (THF), 21.4$^+$ (THP Ac), 21.2$^-$ (THP), 21.2$^+$ (THF Ac) and 20.8$^-$ (THP).

(3*RS*,5*RS*)-5-Phenylsulfanyl-1-oxaspiro[5.5]undecan-3-yl ethanoate 14

By the method described for compound **8**, toluene-*p*-sulfonic acid (2.7 mg, 14.3 μmol) and the 1:3.6 mixture of THP **14** and THF **15** (46 mg, 144 μmol) in dichloromethane (2.5 cm^3) gave the ^{3,5}*anti-tetrahydropyran* **14** as an oil (43 mg, 93%), R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.26; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3052, 2937, 2860, 1732 (C=O), 1583, 1479, 1439, 1374, 1241, 1177, 1113, 1092, 1064, 1044, 990, 966, 909 and 811; δ_H(400 MHz; $CDCl_3$) 7.42–7.36 (3 H, m, PhS), 7.32–7.18 (2 H, m, PhS), 4.92–4.87 (1 H, m, $CH_{eq}OAc$), 3.78–3.67 (2 H, m, $CH_{ax}H_{eq}O$ and $CH_{ax}H_{eq}O$), 3.35 (1 H, dd, *J* 11.4 and 5.2 Hz, $CH_{ax}SPh$), 2.16–2.01 (4 H, m), 2.07 (3 H, s, Ac), 1.66–1.35 (7 H, m) and 1.28–1.15 (1 H, m); δ_C(100.6 MHz; $CDCl_3$) 170.6$^-$ (C=O), 135.5$^-$ (*i*-PhS), 131.2$^+$, 129.0$^+$, 126.9$^+$, 75.9$^-$ (C–O), 68.8$^+$ (CH–O), 62.1$^-$ (CH_2O), 50.5$^+$ (CHSPh), 36.2$^-$, 31.6$^-$, 25.8$^-$, 24.4$^-$, 21.4$^+$ (Ac), 21.2$^-$ and 20.8$^-$; *m*/*z* (EI) 320 (40%, M^+), 260 (13, M^+ − AcOH), 223 (100), 162 (48) and 136 (66); (Found: M^+, 320.1439. $C_{18}H_{24}O_3S$ requires *M*, 320.1446).

(1*RS*,3*SR*,5*SR*)-1-Methyl-3-(1-cyclohexyl-1-phenylsulfanyl)-2,7,8-trioxabicyclo[3.2.1]octane 16

By the method described for compound **7**, *anti*-triol **3** (65 mg, 219 μmol), pyridinium toluene-*p*-sulfonate (14.4 mg, 57.5 μmol) and trimethyl orthoacetate (29 μl, 27.6 mg, 230 μmol) in dry dichloromethane (2.5 cm^3) gave the *orthoester* **16** as an oil (68 mg, 97%) after 5 minutes, R_f[light petroleum (bp 40–60 °C)–diethyl ether, 4:1] 0.25; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2934, 2896, 2857, 1472, 1448, 1400, 1292, 1152, 1121, 1094, 1074, 991, 909 and 870; δ_H(400 MHz; $CDCl_3$) 7.57–7.52 (2 H, m, PhS), 7.35–7.25 (3 H, m, PhS), 4.73–4.66 (1 H, br m, CH_{eq}), 3.92–3.83 (3 H, m, CH_{ax}, CH_AH_B and CH_AH_B), 2.32 (1 H, br td, *J* 13.2 and 2.8 Hz, $CH_{ax}H_{eq}$), 1.98–1.41 (9 H, m,), 1.75 (1 H, ddd, *J* 13.5, 3.9 and 2.1 Hz, $CH_{ax}H_{eq}$), 1.50 (3 H, s, $MeCO_3$) and 1.31–1.17 (1 H, m); δ_C(100.1 MHz; $CDCl_3$) 136.3$^+$ (*m*-PhS), 130.6$^-$ (*i*-PhS), 127.5$^+$ (*p*-PhS), 127.4$^+$ (*o*-PhS), 117.9$^-$ (CO_3), 72.3$^+$ (CH–O), 72.0$^+$ (CH–O), 67.9$^-$ (CH_2O), 54.8$^-$ (CSPh), 30.0$^-$, 29.2$^-$, 27.3$^-$, 24.9$^-$, 20.9$^+$ (Me), 20.6$^-$ and 20.6$^-$; *m*/*z* (EI) 320 (15%, M^+), 267 (6), 220 (10), 191 (29, $C_6H_{10}SPh^+$), 151 (46) and 131 (100); (Found: M^+, 320.1441. $C_{18}H_{24}O_3S$ requires *M*, 320.1446).

(3*R*,5*R*)-3-Acetoxy-5-phenylsulfanyl-1,9-dioxaspiro[5.5]-undecane 20

Pyridinium toluene-*p*-sulfonate (22.7 mg, 89 μmol, 25 mol%) was added to a stirred solution of triol **5** (107 mg, 360 μmol) in dry dichloromethane (4 cm^3). The flask was sealed with a septum before injecting trimethyl orthoacetate (45.4 mg, 49 μl, 378 μmol), in one portion. Stirring was continued at room temperature until the reaction was judged complete by TLC (*ca*. 3 hours). The reaction mixture was filtered through a short silica plug, eluting with dry dichloromethane (4 × 25 cm^3). The solvent was removed under reduced pressure to give a dark yellow oil as the crude product. Amberlyst® (0.25 g) was added to a solution of the crude product in dry dichloromethane (10 cm^3) at 35 °C. Once the unrearranged product was deemed to be consumed using TLC (48 hours) the reaction mixture was allowed to cool to room temperature and the filtered residue was purified using column chromatography [silica, light petroleum (40–60 °C)–diethyl ether, 4:1] to give the *tetrahydropyran* **20** as an oil (30 mg, 25%); R_f(diethyl ether) 0.62; $[\alpha]_D$ +1.5 (*c*. 1.2 in $CHCl_3$; 78% ee); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3201 (O–H), 2890 (C–H), 1728 (C=O) and 1105 (C–O); δ_H(400 MHz; $CDCl_3$) 7.40 (2 H, dd, *J* 8.0 and 1.5 Hz, PhS), 7.32–7.26 (3 H, m, PhS), 4.93–4.90 (1 H, m, C*H*OAc), 3.81–3.70 (5 H, m, CH_2O), 3.60 (1 H, td, *J* 12.0 and 2.0 Hz, $OCH_{ax}CH_{eq}$), 3.35 (1 H, dd, *J* 12.0 and 4.5 Hz, CHSPh), 2.40 (1 H, ddd, *J* 13.5, 12.0 and 5.5 Hz, $CH_{ax}CH_{eq}$), 2.14 (1 H, dtd, *J* 14.5, 4.0 and 2.0 Hz, $CH_{ax}CH_{eq}$), 2.07 (3 H, s, CH_3CO), 2.06–1.94 (2 H, m, CH_2), 1.87 (1 H, ddd, *J* 14.5, 12.5 and 5.0 Hz, $CH_{ax}CH_{eq}$) and 1.45 (1 H, dd, *J* 14.0 and 2.0 Hz, $CH_{ax}CH_{eq}$); δ_C(100.6 MHz; $CDCl_3$) 170.4$^-$ (C=O), 134.8$^-$ (*i*-PhS), 131.3$^+$ (PhS), 128.9$^+$ (PhS), 126.9$^+$ (*p*-PhS), 73.8$^-$ (OC_q), 68.3$^+$ (OCH), 63.0$^-$ (OCH_2), 62.7$^-$ (OCH_2), 62.2$^-$ (OCH_2), 50.2$^+$ (CHSPh), 35.7$^-$ (CH_2), 31.0$^-$ (CH_2), 25.2$^-$ (CH_2) and 21.2$^+$ (CH_3); *m*/*z* (EI) 322 (23%, M^+), 280 (2), 251 (3), 201 (5), 151 (9), 163 (5), 119 (37) and 69 (100); (Found: M^+, 322.1233. $C_{17}H_{22}O_4S$ requires *M*, 322.1239).

(3*R*,5*S*)-3-Acetoxy-5-phenylsulfanyl-1,9-dioxaspiro[5.5]-undecane 21

By the method described for compound **20**, pyridinium toluene-*p*-sulfonate (11.8 mg, 47 μmol, 25 mol%), triol **6** (56 mg, 188 μmol) and trimethyl orthoacetate (23.7 mg, 25 μl, 197 μmol) in dry dichloromethane (2 cm^3) gave a crude product after 3 hours. Treatment of this product with Amberlyst® (0.25 g) in dry dichloromethane (10 cm^3) at 35 °C gave a second product after 48 hours. Purified by column chromatography [silica, light petroleum (40–60 °C)–diethyl ether, 4:1] gave the *tetrahydropyran* **21** as an oil (24 mg, 62%); R_f(diethyl ether) 0.58; $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3220 (O–H), 2890 (C–H), 2815 (C–H), 1725 (C=O) and 1105 (C–O); δ_H(400 MHz; $CDCl_3$) 7.47–7.29 (5 H, m, PhS), 4.82 (1 H, tt, *J* 10.5 and 5.0 Hz, C*H*OAc), 3.89–3.76 (4 H, m, CH_2O), 3.63 (1 H, td, *J* 12.5 and 2.0 Hz, $OCH_{ax}CH_{eq}$), 3.41 (1 H, dd, *J* 11.0 and 10.0 Hz, $OCH_{ax}CH_{eq}$), 3.06 (1 H, dd, *J* 12.5 and 4.0 Hz, CHSPh), 2.46 (1 H, dt, *J* 13.5 and 9.5 Hz, $CH_{ax}CH_{eq}$), 2.36 (1 H, dtd, *J* 13.5, 6.5 and 2.0 Hz, $CCH_{ax}CH_{eq}$), 2.01 (3 H, s, CH_3CO) and 1.97–1.81 (4 H, m, CH_2); δ_C(100.6 MHz; $CDCl_3$) 170.1$^-$ (C=O), 134.0$^-$ (*i*-PhS), 131.1$^+$ (PhS), 128.2$^+$ (PhS), 126.5$^+$ (*p*-PhS), 72.5$^-$ (OC_q), 66.9$^+$ (OCH), 62.3$^-$ (OCH_2), 61.6$^-$ (OCH_2), 60.5$^-$ (OCH_2), 52.2$^+$ (CHSPh), 38.8$^-$ (CH_2), 31.6$^-$ (CH_2), 21.7$^-$ (CH_2) and 20.0$^+$ (CH_3); *m*/*z* (EI) 322 (29%, M^+), 251 (2), 201 (4), 151 (9), 119 (47) and 69 (100); (Found: M^+, 322.1226. $C_{17}H_{22}O_4S$ requires *M*, 322.1239).

Acknowledgements

We thank the EPSRC for grants to LC and DH and Astra-Zeneca for extra support to DH.

Notes and References

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