Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 931–936

Direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides to 1,3-oxathiolanes

Michael J. Porter,* Fabienne Saez and Amandeep Kaur Sandhu

Department of Chemistry, University College London, Christopher Ingold Building, 20 Gordon Street, London WC1H 0AJ, UK

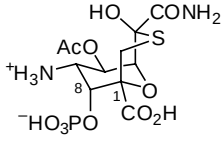
Received 15 August 2005; revised 23 September 2005; accepted 13 October 2005

Available online 7 November 2005

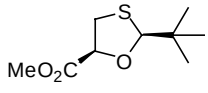
Abstract—*tert*-Butyl 2-hydroxyalkyl sulfides, prepared by reaction of epoxides with 2-methylpropane-2-thiol, are converted directly to 1,3-oxathiolanes upon treatment with pivalaldehyde and boron trifluoride diethyl etherate in the presence of thioanisole.

1. Introduction

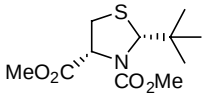
As part of a research programme[1] targeted towards the synthesis of the RNA polymerase inhibitor tagetitoxin **1**,[2] we wished to synthesise the cis-disubstituted 1,3-oxathiolane ester **2-c** as a single enantiomer. It was hoped that subsequent deprotonation and reaction with an appropriate aldehyde would allow stereospecific construction of the C1–C8 bond of tagetitoxin.[3] Literature reports concerning the enolates of related sulfur-containing heterocycles left some doubt as to whether the proposed coupling would be feasible. Seebach et al. reported that the lithium enolate of thiazolidine **3** rapidly decomposed by a β-elimination process and could not be induced to react with electrophiles.[4] Conversely, Pattenden et al. were successful in alkylating the enolate of thiazolidine **4**, which differs from **3** only in the nature of the nitrogen protecting group.[5] It was thus unclear prior to this study whether the enolate of **2-c** would be sufficiently stable to allow reaction with an aldehyde to take place. While **2-c** had not previously been synthesised, it was anticipated that it should be readily prepared by acid-catalysed condensation of the corresponding β-hydroxythiol with pivalaldehyde.



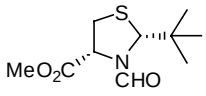
1



2-*c*



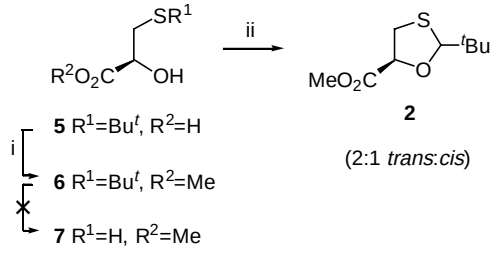
3



4

2. Results and discussion

L-Serine was converted via potassium (*R*)-glycidate to carboxylic acid **5** by literature procedures.[6] Esterification was accomplished with thionyl chloride/methanol to afford ester **6** (Scheme 1).[7]

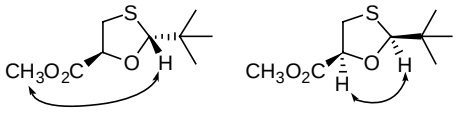


Scheme 1. Reagents and conditions: (i) $SOCl_2$, MeOH, 45%; (ii) ^{t}BuCHO (1 equiv), $BF_3 \cdot OEt_2$ (2 equiv), PhSMe (1 equiv), CH_2Cl_2, 55%.

Keywords: Heterocycles; Sulfur; Protecting groups; *tert*-Butyl sulfides; Lewis acids.
* Corresponding author. Tel.: +44 20 7679 4710; fax: +44 20 7679 7463; e-mail: m.j.porter@ucl.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.026

The next step, removal of the *tert*-butyl protecting group to generate a vicinal hydroxythiol **7**,[7] proved problematic. Treatment of **6** with a range of protic and Lewis acids (including $Hg(OAc)_2$/TFA followed by H_2S;[7b] TFA/Et_3-SiH,[7c] and HBF_4/TFA)[7d] failed to give efficient deprotection, and attempts to generate the corresponding disulfide by treatment with oxidising agents (I_2 or $PhI(OAc)_2$)[7e] were also unsuccessful. We were thus forced to develop a new method for removal of the *tert*-butyl group, and were gratified to discover that treatment of **6** with pivalaldehyde, $BF_3\cdot OEt_2$ and thioanisole in dichloromethane led directly to the formation of the desired 1,3-oxathiolane **2**, which was obtained as a 2:1 mixture of isomers. NOE experiments on this mixture (Fig. 1), together with analysis of ^1H–^1H coupling constants,[8] indicated that the major component was the trans-isomer **2-t**.



2-*t* (major) **2-*c*** (minor)

Figure 1. Selected nuclear Overhauser enhancements in **2-t** and **2-c**.

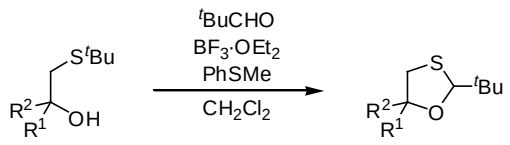
Attempts to improve the yield of the reaction by use of other Lewis or Brønsted acids ($ZnCl_2$, $InCl_3$, $ZrCl_4$, Dowex-50) were unsuccessful, with only boron trifluoride, of the acids investigated, giving the desired product. Replacement of pivalaldehyde with other aldehydes or ketones also proved unsuccessful, while omission of the thioanisole gave a much slower reaction, with appreciable quantities of starting material still present after 40 h.

Our attention next turned to the scope of this transformation. A range of racemic or achiral *tert*-butyl 2-hydroxyalkyl sulfides was prepared by opening of the corresponding mono- or 1,1-disubstituted epoxides with 2-methylpropane-2-thiol under basic conditions.[9] These compounds were subjected to the deprotection–cyclisation conditions developed for compound **6**: the results are summarised in Table 1.

Sulfides derived from monosubstituted epoxides (**8a**–**8g**) were converted to the corresponding 1,3-oxathiolanes **9a**–**9g** as mixtures of diastereomers, which were in general not separable by column chromatography. In the case of **9a**, as for **2**, the trans-isomer was the major one; in all other cases, the cis-isomer predominated. Achiral sulfide **8h**, which incorporates a tertiary alcohol, could also be converted to the corresponding 1,3-oxathiolane in high yield under the same conditions.

Given the ready interconversion of 1,3-oxathiolane stereoisomers in the presence of $BF_3\cdot OEt_2$,[8] the product ratios observed may reflect the relative thermodynamic stability of the two diastereomers. Indeed, previous equilibration studies have indicated that the cis-isomer of 2,5-dialkyl-1,3-oxathiolanes is the more stable.[8] By contrast, Brønsted acid-catalysed condensation of methyl 3-mercapto-2-hydroxypropanoate with acetaldehyde was reported to give the trans-isomer, analogous to **2-t**, as the major isolated product.[10]

Table 1. Conversion of *tert*-butyl sulfides to 1,3-oxathiolanes



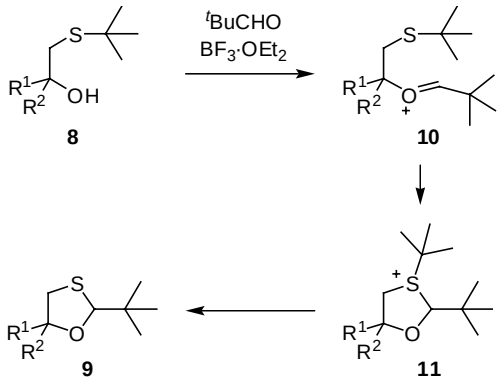
8a-8h **9a-9h**

Sulfide	R^1	R^2	Time (h)	Yield (%) (trans:cis)[a]
8a	CO_2Et	H	4	67 (2.2:1)
8b	*n*-C_3H_7	H	4	15 (1:2.5)[b]
8c	CH_2Ph	H	22	47 (1:3.8)
8d	CH_2OPh	H	5	74 (1:3.1)
8e	CH_2OBn	H	24	82 (1:3.0)
8f	$CH_2OCH_2CH{=}CH_2$	H	25	36 (1:2.9)
8g	$(CH_2)_6CH{=}CH_2$	H	5	12 (1:3.7)
8h	CH_2OPh	CH_2OPh	23	91

[a] Isolated yields of mixtures of diastereomers. The figures in parentheses represent the trans:cis isomeric ratio in the crude reaction mixture, as determined by ^1H NMR spectroscopy.
[b] Isolated yield of cis-isomer.

Yields of oxathiolanes were moderate to good, with the exceptions of **9b**, whose volatility made isolation troublesome, and of **9g**, where isolation of a pure product was hampered by problems in separating the oxathiolane product from non-polar impurities.

The mechanism for this combined deprotection–cyclisation transformation is presumed to be that outlined in Scheme 2. Condensation of the alcohol functionality of **8** with pivalaldehyde, catalysed by the Lewis acid, gives cation **10**, which is attacked in an intramolecular fashion by the sulfur atom to afford **11**. Loss of a *tert*-butyl cation, which is scavenged by thioanisole, leads to the observed product **9**.



Scheme 2. Proposed mechanism for deprotection–cyclisation.

An alternative mechanism in which acid-catalysed removal of the *tert*-butyl group to yield a hydroxythiol is followed by condensation with pivalaldehyde was ruled out by a control experiment carried out in the absence of pivalaldehyde; in this case, no reaction occurred and the starting material was recovered unchanged.

We have investigated the possibility of generating the lithium enolate of **2** with LDA (for initial studies a mixture of **2-c** and **2-t** was employed) and reacting it with an aldehyde electrophile. Under all conditions tested to date[11] (temperatures from −90 to −78 °C, in the presence or absence of DMPU and lithium bromide as additives; trapping by addition of isobutyraldehyde, or in situ with benzaldehyde), decomposition of the starting material **2** occurred, but none of the desired adduct was formed. These results suggest that the lithium enolate of oxathiolane ester **2**, like that of thiazolidine **3**, decomposes more rapidly than it reacts with aldehyde electrophiles, presumably through β-elimination.

3. Conclusions

We have developed a mild method for the direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides into 1,3-oxathiolanes in a single step. This method circumvents the difficulties encountered in removal of the *tert*-butyl group to form a thiol. A variety of functional groups is tolerated, and yields of up to 91% are obtained for the reaction.

4. Experimental

4.1. General

Reactions were performed under an atmosphere of nitrogen or argon. Methanol and ethanol were dried by distillation from the corresponding magnesium alkoxides. Dichloromethane was dried by passage through an alumina column. Triethylamine was distilled from calcium hydride prior to use. Other reagents were used as obtained from commercial sources.

All new compounds or mixtures of stereoisomeric compounds were judged to contain <5% impurities by ^{1}H NMR.

The relative stereochemistries of compounds **9a–9g** were ascertained by the observation of nuclear Overhauser enhancements in each diastereomer.

4.2. Synthesis of sulfides 6 and 8a–8h

4.2.1. Methyl (2*S*)-3-*tert*-butylsulfanyl-2-hydroxypropanoate (6). (2*S*)-3-*tert*-Butylsulfanyl-2-hydroxypropanoic acid[6b] (**5**, 2.0 g, 11 mmol) was added to a solution of thionyl chloride (8.3 mL, 11.4 mmol) in methanol (50 mL), and the mixture was heated to reflux for 18 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (silica, hexane/ethyl acetate 2:1) afforded **6** (0.98 g, 45%); as a colourless oil; $[\alpha]_D^{25}$ +28.3 (*c* 0.92, EtOH); ν_{max}/cm^{-1} (film) 3444, 2960, 1743, 1460, 1365, 1215, 1096; δ_H (300 MHz; $CDCl_3$) 1.33 (9H, s), 2.87 (1H, dd, J=13.1, 6.0 Hz), 3.01 (1H, dd, J=13.1, 4.3 Hz), 3.81 (3H, s), 4.39 (1H, dd, J=6.0, 4.4 Hz); δ_C (75 MHz; $CDCl_3$) 31.0 (CH_3), 38.5 (CH_2), 44.6 (C), 52.7 (CH_3), 70.3 (CH), 173.7 (C); *m/z* (CI+) 193 (MH^+, 35%), 137 (100).

4.2.2. Ethyl 3-*tert*-butylsulfanyl-2-hydroxypropanoate (8a). A solution of sodium ethoxide was prepared by adding sodium (11.86 mg, 0.5 mmol) to dry ethanol (0.26 mL) at 0–5 °C. 2-Methylpropane-2-thiol (0.43 mL, 3.8 mmol) was then added and the resultant solution was stirred for 30 min at room temperature. A solution of ethyl glycidate (400 mg, 3.4 mmol) in dry ethanol (6.9 mL) was added dropwise to the ethoxide/thiol solution, and heated under reflux for 2 h. The reaction mixture was quenched with water (10 mL) and the ethanol removed in vacuo. The aqueous layer was then extracted with diethyl ether (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (silica, petroleum ether/ethyl acetate 85:15) afforded **8a** (193 mg, 27%) as a colourless oil; ν_{max}/cm^{-1} (film) 3444, 2962, 2931, 2902, 1732, 1461; δ_H (300 MHz; $CDCl_3$) 1.31 (3H, t, J=7.2 Hz), 1.32 (9H, s), 2.85 (1H, dd, J=13.0, 5.8 Hz), 3.02 (1H, dd, J=13.0, 4.3 Hz), 4.26 (2H, q, J=7.1 Hz), 4.37–4.40 (1H, m); δ_C (75 MHz; $CDCl_3$) 14.2, 30.9, 33.0, 42.4, 62.0, 69.9, 173.1; *m/z* (CI+) 207 (MH^+, 10%), 188 (11), 151 (100), 133 (81), 105 (25); HRMS (CI+) found 207.1048; $C_9H_{19}O_2S$ (MH^+) requires 207.1055.

4.2.3. 1-*tert*-Butylsulfanylpentan-2-ol (8b) (general procedure A). 1,2-Epoxypentane (1.12 g, 13.0 mmol) was dissolved in methanol (130 mL). 2-Methylpropane-2-thiol (1.46 mL, 13.0 mmol) and triethylamine (0.91 mL, 6.5 mmol) were added and the resulting mixture was heated under reflux for 5 h. The solvent was then removed in vacuo to give the crude product. Flash chromatography (silica, petroleum ether/ethyl acetate 95:5) afforded **8b** as a colourless oil (1.76 g, 77%); ν_{max}/cm^{-1} (film): 3385, 2929, 2872, 1460, 1363, 1163; δ_H (300 MHz; $CDCl_3$) 0.92 (3H, broad t, J=7.0 Hz), 1.32 (9H, s), 1.37–1.53 (4H, m), 2.35 (1H, s), 2.50 (1H, dd, J=12.8, 8.6 Hz), 2.76 (1H, dd, J=12.7, 3.6 Hz), 3.61–3.69 (1H, m); δ_C (75 MHz; $CDCl_3$) 14.1, 19.0, 31.1, 36.6, 38.7, 42.4, 69.8; *m/z* (EI) 176 (M^+, 93%), 133 (43), 119 (52); HRMS (EI) found 176.1239; $C_9H_{20}OS$ (M^+) requires 176.1235.

4.2.4. 1-*tert*-Butylsulfanyl-3-phenylpropan-2-ol (8c). Prepared in 72% yield from 2-benzyloxirane by general procedure A, using ethanol as solvent; colourless oil; ν_{max}/cm^{-1} (film) 3418, 2899, 2864, 1456, 1366, 1163, 1032; δ_H (300 MHz; $CDCl_3$) 1.31 (9H, s), 2.26 (1H, broad s), 2.58 (1H, dd, J=12.8, 7.8 Hz), 2.75 (1H, dd, J=12.8, 4.4 Hz), 2.84 (2H, app. d, J=6.4 Hz), 3.87–3.96 (1H, m), 7.20–7.26 (3H, m), 7.29–7.35 (2H, m); δ_C (75 MHz; $CDCl_3$) 31.1, 35.6, 42.5, 42.9, 71.3, 126.6, 128.5, 129.4, 138.0; *m/z* (EI) 224 (M^+, 21%), 206 (100), 150 (83), 133 (70), 117 (100); HRMS (EI) found 224.1239; $C_{13}H_{20}OS$ (M^+) requires 224.1235.

4.2.5. 1-*tert*-Butylsulfanyl-3-phenoxypropan-2-ol (8d).[12] Prepared in 97% yield from glycidyl phenyl ether by general procedure A, using ethanol as solvent; yellow oil; ν_{max}/cm^{-1} (film) 3395, 2926, 2864, 1601, 1495, 1245; δ_H (300 MHz; $CDCl_3$) 1.38 (9H, s), 2.51 (1H, broad s), 2.78 (1H, dd, J=13.0, 6.9 Hz), 2.89 (1H, dd, J=13.0, 5.6 Hz), 3.97–4.14 (3H, m), 6.90–6.99 (3H, m), 7.26–7.32 (2H, m); δ_C (75 MHz; $CDCl_3$) 31.0, 32.3, 42.7, 69.3, 70.6, 114.6, 121.2, 129.5, 158.5; *m/z* (FAB+) 240 (M^+, 20%), 222 (22),

149 (29), 133 (49), 94 (100); HRMS (FAB+) found 240.1186; $C_{13}H_{20}O_2S$ (M^+) requires: 240.1184.

4.2.6. 1-Benzyloxy-3-*tert*-butylsulfanylpropan-2-ol (8e).[13] Prepared in 53% yield from benzyl glycidyl ether by general procedure A; colourless oil; ν_{max}/cm^{-1} (film) 3443, 2961, 2924, 2862, 2899, 1454, 1364; δ_H (300 MHz; $CDCl_3$) 1.33 (9H, s), 2.40 (1H, broad s), 2.67 (1H, dd, J= 12.8, 7.1 Hz), 2.75 (1H, dd, J=12.8, 5.9 Hz), 3.49 (1H, dd, J=9.6, 6.3 Hz), 3.58 (1H, dd, J=9.6, 4.0 Hz), 3.87–3.95 (1H, m), 4.57 (2H, s), 7.27–7.38 (5H, m); δ_C (75 MHz; $CDCl_3$) 31.0, 32.3, 42.4, 69.7, 73.1, 73.5, 127.8, 128.5, 137.9; *m/z* (CI+) 255 (MH^+, 32%), 289 (28), 236 (100), 199 (20), 181 (69), 147 (40); HRMS (CI+) found 255.1412; $C_{14}H_{23}O_2S$ (MH^+) requires 255.1419.

4.2.7. 1-Allyloxy-3-*tert*-butylsulfanylpropan-2-ol (8f). Prepared in 80% yield from allyl glycidyl ether by general procedure A; colourless oil; ν_{max}/cm^{-1} (film) 3445, 2961, 2899, 2862, 1645, 1460, 1366; δ_H (300 MHz; $CDCl_3$) 1.32 (9H, s), 2.54 (1H, broad s), 2.66 (1H, dd, J=12.8, 7.0 Hz), 2.74 (1H, dd, J=12.8, 5.9 Hz), 3.44 (1H, dd, J=9.6, 6.4 Hz), 3.54 (1H, dd, J=9.6, 4.0 Hz), 3.84–3.92 (1H, m), 4.01–4.04 (2H, m), 5.17–5.31 (2H, m), 5.84–5.97 (1H, m); δ_C (75 MHz; $CDCl_3$) 31.0, 32.3, 42.4, 69.7, 72.3, 73.0, 117.3, 134.5; *m/z* (CI+) 205 (MH^+, 10%), 159 (20), 149 (45), 131 (100), 97 (38); HRMS (CI+) found 205.1259; $C_{10}H_{21}O_2S$ (MH^+) requires 205.1262.

4.2.8. 1-*tert*-Butylsulfanyldec-9-en-2-ol (8g). Prepared in 98% yield from 1,2-epoxydec-9-ene by general procedure A, using ethanol as solvent; pale yellow oil; ν_{max}/cm^{-1} (film) 3404, 2928, 2856, 1639, 1458, 1364, 1163; δ_H (300 MHz; $CDCl_3$) 1.31–1.40 (10H, m), 1.33 (9H, s), 2.00–2.07 (2H, m), 2.50 (1H, dd, J=12.8, 8.6 Hz), 2.77 (1H, dd, J=12.8, 3.6 Hz), 3.59–3.67 (1H, m), 4.90–5.02 (2H, m), 5.80 (1H, ddt, J=17.0, 10.3, 6.7 Hz); δ_C (75 MHz; $CDCl_3$) 25.7, 28.9, 29.0, 29.5, 31.2, 33.8, 36.6, 36.7, 42.4, 70.0, 114.2, 139.2; *m/z* (FAB+) 245 (MH^+, 100%), 227 (23), 187 (25), 171 (68); HRMS (FAB+) found 245.1928; $C_{14}H_{29}OS$ (MH^+) requires 245.1939.

4.2.9. 2-(*tert*-Butylsulfanylmethyl)-1,3-diphenoxypropan-2-ol (8h). 1,3-Diphenoxy-2-methylenepropane[14] (802 mg, 3.3 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution was cooled to 0 °C. MCPBA (70–75%, 902 mg, 3.7 mmol) and saturated aqueous $NaHCO_3$ (5 mL) were added and the resulting mixture was stirred for 5 h at room temperature. The mixture was cooled to 0 °C and another equivalent of MCPBA was added. After stirring at room temperature for 21 h, the mixture was cooled to 0 °C and treated with a further equivalent of MCPBA and saturated aqueous $NaHCO_3$ (2 mL). After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite® and the filtrate was washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (silica, petroleum ether/ethyl acetate 94:6) afforded 2,2-di(phenoxymethyl)-oxirane (415 mg, 49%); ν_{max}/cm^{-1} (film) 3057, 3040, 2930, 1587, 1497, 1242; δ_H (300 MHz; $CDCl_3$) 3.02 (2H, s), 4.24 (2H, d, J=10.6 Hz), 4.28 (2H, d, J=10.6 Hz), 6.92–7.01 (6H, m), 7.26–7.33 (4H, m); δ_C (75 MHz; $CDCl_3$) 49.5, 56.9, 68.0, 114.7, 121.4, 129.5, 158.5; *m/z* (CI+) 256 (M^+, 100%), 181 (29), 183 (29), 185 (23), 173 (67); HRMS (CI+) found 257.1169; $C_{16}H_{17}O_3$ (MH^+) requires 257.1178.

Sulfide **8h** was prepared from 2,2-di(phenoxymethyl)-oxirane by general procedure A; white solid (mp 68–70 °C); ν_{max}/cm^{-1} (KBr) 3377, 2951, 2924, 2932, 1599, 1590, 1497; δ_H (400 MHz; $CDCl_3$) 1.33 (9H, s), 3.04 (2H, s), 4.11 (4H, s), 6.94–6.98 (6H, m), 7.26–7.31 (4H, m); δ_C (75 MHz; $CDCl_3$) 30.9, 33.3, 42.6, 70.0, 72.8, 114.7, 121.2, 129.5, 158.5; *m/z* (EI) 346 (M^+, 13%), 235 (100), 179 (46), 131 (65), 107 (84), 94 (58); HRMS (EI) found 346.1610; $C_{20}H_{26}O_3S$ (M^+) requires 346.1603.

4.3. Conversion of sulfides to 1,3-oxathiolanes

4.3.1. Methyl (5*S*)-2-*tert*-butyl-1,3-oxathiolane-5-carboxylate (2) (general procedure B). To a solution of methyl (2*S*)-3-*tert*-butylsulfanyl-2-hydroxypropanoate (**6**, 0.38 g, 2 mmol) in dry dichloromethane (5 mL) were added successively pivalaldehyde (0.22 mL, 2 mmol), thioanisole (0.24 mL, 2 mmol) and boron trifluoride diethyl etherate (0.50 mL, 4 mmol). The mixture was stirred at room temperature for 3 h then quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with dichloromethane (3×10 mL), and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. ^1H NMR analysis showed the ratio of products to be 2:1 in favour of the trans isomer. Purification of the residue by flash chromatography (silica, hexane/ethyl acetate 90:10) afforded **2** (0.22 g, 55%) as a colourless oil, as a 2:1 trans:cis diastereomeric mixture: ν_{max}/cm^{-1} (film) 2962, 1743, 1365, 1209, 1107; δ_H (500 MHz; $CDCl_3$); *(2R,5S)-trans-isomer* **2-t**. 0.98 (9H, s), 3.12 (1H, dd, J=10.8, 6.6 Hz), 3.26 (1H, dd, J=10.8, 2.5 Hz), 3.77 (3H, s), 4.97 (1H, dd, J=6.5, 2.5 Hz), 5.22 (1H, s). *(2S,5S)-cis-isomer* **2-c**. 1.02 (9H, s), 3.00 (1H, dd, J=10.4, 9.1 Hz), 3.23 (1H, dd, J=10.4, 5.8 Hz), 3.78 (3H, s), 4.49 (1H, dd, J=9.1, 5.8 Hz), 4.99 (1H, s); δ_C (125 MHz; $CDCl_3$); *(2R,5S)-trans-isomer* **2-t**. 25.6, 34.3, 35.7, 52.3, 80.6, 95.9, 171.3; *(2S,5S)-cis-isomer* **2-c**. 25.8, 34.6, 35.3, 52.4, 80.8, 96.3, 169.6; *m/z* (electrospray) 227 (M+Na, 100%), 217 (30); HRMS (electrospray) found: 227.0714; $C_9H_{16}O_3SNa$ (M+Na) requires 227.0712.

4.3.2. Ethyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate (9a). Prepared as a 2.2:1 trans:cis mixture (crude) from **8a** by general procedure B and isolated in 67% yield as a 2.4:1 trans:cis mixture; colourless oil; ν_{max}/cm^{-1} (film) 2957, 2868, 1744, 1364, 1186, 1144; δ_H (500 MHz; $CDCl_3$); *(2RS, 5SR)-trans-isomer*. 0.99 (9H, s), 1.23–1.31 (3H, m), 3.12 (1H, dd, J=10.7, 6.6 Hz), 3.24–3.28 (1H, m), 4.18–4.28 (2H, m), 4.94 (1H, dd, J=6.6, 2.5 Hz), 5.23 (1H, s); *(2RS, 5RS)-cis-isomer*. δ 1.02 (9H, s), 1.23–1.31 (3H, m), 2.99 (1H, app. dd, J=10.4, 9.0 Hz), 3.22–3.25 (1H, m), 4.18–4.28 (2H, m), 4.47 (1H, dd, J=9.0, 5.8 Hz), 4.99 (1H, s); δ_C (75 MHz; $CDCl_3$); *(2RS, 5SR)-trans-isomer*. 14.2, 25.7, 34.3, 35.7, 61.5, 80.6, 95.9, 170.9; *(2RS, 5RS)-cis-isomer*. 14.2, 25.9, 34.7, 35.4, 61.5, 80.9, 96.4, 169.2; *m/z* (CI+) 219 (MH^+, 16%), 161 (81), 149 (24), 133 (100), 101 (41); HRMS (CI+) found 219.1056; $C_{10}H_{19}O_3S$ (MH^+) requires: 219.1055.

4.3.3. 2-*tert*-Butyl 5-propyl-1,3-oxathiolane (9b). Prepared as a 2.5:1 cis:trans mixture from **8b** by general procedure B; from this mixture a pure sample of the cis-diastereomer could be isolated in 15% yield by flash chromatography. Colourless oil; ν_{max}/cm^{-1} (film) 2957, 2930, 2864, 1479, 1464, 1362; δ_H (500 MHz; $CDCl_3$) 0.92 (3H, broad t, $J=7.4$ Hz), 0.95 (9H, s), 1.33–1.50 (2H, m), 1.53–1.60 (1H, m), 1.68–1.75 (1H, m), 2.47 (1H, app. t, $J=9.9$ Hz), 2.94 (1H, dd, $J=9.8$, 4.7 Hz), 3.83–3.88 (1H, m), 4.90 (1H, s); δ_C (75 MHz; $CDCl_3$) 14.2, 19.6, 25.8, 35.1, 35.9, 36.9, 84.0, 95.4; *m/z* (EI) 188 (M^+, 23%), 131 (100), 103 (31); HRMS (EI) found 188.1235; $C_{10}H_{20}OS$ (M^+) requires 188.1235.

4.3.4. 5-Benzyl-2-*tert*-butyl-1,3-oxathiolane (9c). Prepared as a 3.8:1 cis:trans mixture (crude) from **8c** by general procedure B and isolated in 47% yield as a 3.8:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2930, 2864, 1497, 1479, 1454, 1362, 1182, 1076; δ_H (500 MHz; $CDCl_3$); *(2RS, 5RS)-cis isomer*. 0.96 (9H, s), 2.56 (1H, app. t, $J=9.9$ Hz), 2.85–2.89 (2H, m), 3.11 (1H, dd, $J=13.8$, 6.2 Hz), 4.06–4.11 (1H, m), 4.92 (1H, s), 7.19–7.24 (3H, m), 7.26–7.30 (2H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.77–2.83 (2H, m), 2.85–2.89 (1H, m), 2.99 (1H, dd, $J=13.5$, 6.1 Hz), 4.57–4.59 (1H, m), 5.04 (1H, s), 7.19–7.24 (3H, m), 7.26–7.30 (2H, m); δ_C (75 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 25.8, 35.9, 36.6, 40.1, 84.4, 95.4, 126.5, 128.4, 129.4, 137.9; *(2RS, 5SR)-trans-isomer*. 25.9, 35.2, 36.6, 39.2, 84.3, 94.6, 126.5, 128.5, 129.3, 138.1; *m/z* (CI+) 237 (MH^+, 7%), 151 (55), 117 (100), 91 (50); HRMS (CI+) found 237.1314; $C_{14}H_{21}OS$ (MH^+) requires 237.1313.

4.3.5. 2-*tert*-Butyl-5-phenoxymethyl-1,3-oxathiolane (9d). Prepared as a 3.1:1 cis:trans mixture (crude) from **8d** by general procedure B and isolated in 74% yield as a 2.2:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} ($CDCl_3$ cast) 2957, 2870, 1599, 1497, 1244, 1049, 908; δ_H (500 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 2.79 (1H, app. t, $J=9.6$ Hz), 3.11 (1H, dd, $J=10.3$, 5.2 Hz), 4.05 (1H, dd, $J=9.8$, 5.6 Hz), 4.19 (1H, dd, $J=9.8$, 5.3 Hz), 4.29–4.34 (1H, m), 5.00 (1H, s), 6.89–6.96 (3H, m), 7.25–7.29 (2H, m); *(2RS, 5SR)-trans-isomer*. 0.97 (9H, s), 3.03 (1H, dd, $J=10.8$, 4.3 Hz), 3.05–3.11 (1H, m), 3.99 (1H, dd, $J=9.4$, 6.8 Hz), 4.03–4.08 (1H, m), 4.72–4.77 (1H, m), 5.00 (1H, s), 6.89–6.96 (3H, m), 7.25–7.29 (2H, m); δ_C (75 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.4, 35.2, 68.6, 81.7, 96.1, 114.7, 121.1, 129.5, 158.6; *(2RS, 5SR)-trans-isomer*. 25.9, 34.2, 36.1, 67.6, 81.2, 95.4, 114.7, 121.1, 129.5, 158.6; *m/z* (FAB+) 252 (M^+, 30%), 195 (100), 154 (56) 137 (33); HRMS (FAB+) found 253.1254; $C_{14}H_{21}O_2S$ (MH^+) requires 253.1262.

4.3.6. 5-Benzyloxymethyl-2-*tert*-butyl-1,3-oxathiolane (9e). Prepared as a 3.0:1 cis:trans mixture (crude) from **8e** by general procedure B and isolated in 82% yield as a 2.7:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2864, 1479, 1454, 1364, 1090; δ_H (500 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 2.65 (1H, app. t, $J=9.8$ Hz), 2.99 (1H, dd, $J=10.1$, 5.2 Hz), 3.60 (1H, dd, $J=10.4$, 4.7 Hz), 3.67 (1H, dd, $J=10.4$ 5.7 Hz), 4.12–4.17 (1H, m), 4.55–4.62 (2H, m), 4.97 (1H, s), 7.31–7.37 (5H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.90 (1H, dd, $J=10.7$, 4.6 Hz), 2.99 (1H, dd, $J=10.7$, 5.9 Hz), 3.49 (1H, dd, $J=9.8$, 6.2 Hz), 3.55 (1H, dd, $J=9.8$, 5.8 Hz), 4.55–4.62 (3H, m), 4.93 (1H, s), 7.31–7.37 (5H, m); δ_C (75 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.3, 35.1, 70.9, 73.5, 82.9, 96.0, 127.7, 128.4, 138.1; *(2RS, 5SR)-trans-isomer*. 25.9, 34.1, 36.0, 70.0, 73.4, 82.0, 95.3, 127.7, 128.4, 138.1; *m/z* (CI+) 267 (MH^+, 15%), 271 (61), 209 (100), 181 (43); HRMS (CI+) found 267.1410; $C_{15}H_{23}O_2S$ (MH^+) requires 267.1419.

4.3.7. 5-Allyloxymethyl-2-*tert*-butyl-1,3-oxathiolane (9f). Prepared as a 2.9:1 cis:trans mixture (crude) from **8f** by general procedure B and isolated in 36% yield as a 2.8:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2951, 2926, 1724, 1641, 1479, 1464; δ_H (500 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 0.96 (9H, s), 2.63 (1H, app. t, $J=9.8$ Hz), 2.98 (1H, dd, $J=10.1$, 5.2 Hz), 3.56 (1H, dd, $J=10.5$, 4.8 Hz), 3.64 (1H, dd, $J=10.5$, 5.7 Hz), 4.02–4.05 (2H, m), 4.08–4.13 (1H, m), 4.95 (1H, s), 5.16–5.29 (2H, m), 5.84–5.92 (1H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.89 (1H, dd, $J=10.7$, 4.7 Hz), 2.98 (1H, dd, $J=10.7$, 5.9 Hz), 3.46 (1H, dd, $J=9.9$, 6.3 Hz), 3.51 (1H, dd, $J=9.9$, 5.7 Hz), 4.00–4.02 (2H, m), 4.51–4.55 (1H, m), 4.94 (1H, s), 5.16–5.29 (2H, m), 5.84–5.92 (1H, m); δ_C (75 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.4, 35.1, 70.9, 72.5, 82.9, 96.0, 117.2, 134.6; *(2RS, 5SR)-trans-isomer*. 25.9, 34.1, 36.0, 70.1, 72.4, 82.0, 95.3, 117.2, 134.6; *m/z* (DCI): 235 (18%), 217 (MH^+, 9), 159 (100), 131 (19), 97 (57).

4.3.8. 2-*tert*-Butyl-5-(oct-7-enyl)-1,3-oxathiolane (9g). Prepared as a 3.7:1 cis:trans mixture (crude) from **8g** by general procedure B and isolated in 12% yield as a 14:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2928, 2856, 1641, 1479, 1362, 1072; δ_H (400 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 1.25–1.79 (10H, m), 2.02–2.07 (2H, m), 2.49 (1H, app. t, $J=9.9$ Hz), 2.96 (1H, dd, $J=9.8$, 4.7 Hz), 3.83–3.90 (1H, m), 4.92 (1H, s), 4.94–5.02 (2H, m), 5.81 (1H, ddt, $J=17.0$, 10.3, 6.7 Hz); δ_C (75 MHz; $CDCl_3$); *(2RS, 5RS)-cis-isomer*. 25.8, 26.2, 28.8, 29.0, 29.5, 33.7, 33.8, 35.1, 36.9, 84.2, 95.4, 114.2, 139.1; *m/z* (CI+) 257 (MH^+, 15%), 199 (80), 171 (100), 137 (31); HRMS (CI+) found 257.1934; $C_{15}H_{29}OS$ (MH^+) requires 257.1939.

4.3.9. 2-*tert*-Butyl-5,5-di(phenoxymethyl)-1,3-oxathiolane (9h). Prepared in 91% yield from **8h** by general procedure B; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2932, 1599, 1587, 1497, 1244; δ_H (400 MHz; $CDCl_3$) 0.99 (9H, s), 3.13 (1H, d, $J=11.4$ Hz), 3.27 (1H, d, $J=11.4$ Hz), 4.13 (1H, d, $J=9.4$ Hz), 4.19 (1H, d, $J=9.4$ Hz), 4.21 (2H, s), 5.08 (1H, s), 6.92–6.80 (6H, m), 7.26–7.30 (4H, m); δ_C (75 MHz; $CDCl_3$) 26.0, 35.2, 35.4, 67.6, 69.0, 87.8, 96.1, 114.8, 114.9, 121.1, 129.5, 158.7, 158.8; *m/z* (EI) 358 (M^+, 50%), 301 (100), 145 (98), 107 (53), 94 (30); HRMS (EI) found 358.1592; $C_{21}H_{26}O_3S$ (M^+) requires 358.1603.

Acknowledgements

We thank Pfizer for the award of a summer scholarship (to A.K.S.) and the Engineering and Physical Sciences Research Council for PhD studentships (to F.S. and A.K.S.).

References and notes

1. Ioannou, M.; Porter, M. J.; Saez, F. *Tetrahedron* **2005**, *61*, 43–50.
2. (a) Mitchell, R. E.; Durbin, R. D. *Physiol. Plant Pathol.* **1981**, *18*, 157–168. (b) Mitchell, R. E.; Coddington, J. M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501–504.
3. For a review of related reactions, see: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708–2748.
4. Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291–2298.
5. Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131–2138.
6. (a) Petit, Y.; Larchevêque, M.; *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. 10, pp 401–404. (b) Cavelier, F.; Yim, A.-M. *Org. Prep. Proced. Int.* **1998**, *30*, 103–106.
7. For deprotection conditions, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999; pp 470–471. (b) Nishimura, O.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576–1585. (c) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441–5444. (d) Akaji, K.; Yoshida, M.; Tatsumi, T.; Kimura, T.; Fujiwara, Y.; Kiso, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 288–290. (e) Kolovos, M. G.; Moutevelis-Minakakis, P. *Tetrahedron Lett.* **1984**, *25*, 4153–4156.
8. Keskinen, R.; Nikkilä, A.; Pihlaja, K. *Tetrahedron* **1972**, *28*, 3943–3955.
9. Luly, J. R.; Yi, N.; Soderquist, J.; Stein, H.; Cohen, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1987**, *30*, 1609–1616.
10. Teodori, E.; Gualtieri, F.; Angeli, P.; Brasili, L.; Giannella, M.; Pigini, M. *J. Med. Chem.* **1986**, *29*, 1610–1615.
11. For typical reaction conditions, see: (a) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677–10678. (b) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315–3318. (c) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403–5409; see also Ref. 3.
12. Wielechowska, M.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3203–3210.
13. Kraynack, E. A.; Pedersen, S. F. *J. Org. Chem.* **1993**, *58*, 6114–6117.
14. Weiss, F.; Isard, A. *Bull. Soc. Chim. Fr.* **1967**, *6*, 2033–2038.