Optically active 1,5-benzothiazepin-4-ones by ring transformation of 5-ylidene-1,3-dioxan-4-ones with 2-aminothiophenol

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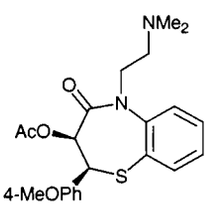
Received (in Cambridge, UK) 9th March 2000, Accepted 18th April 2000
Published on the Web 1st June 2000

Optically active *cis*- and *trans*-3-(1-hydroxyethyl)-1,5-benzothiazepin-4-ones **4** and **5** have been synthesised by ring transformation of (*E*)- and (*Z*)-5-ylidene-1,3-dioxan-4-ones **1** with 2-aminothiophenol. Stereoselective conjugate addition of the –SH group of 2-aminothiophenol to the Michael system of the chiral 5-ylidene-1,3-dioxan-4-one **1**, catalysed by BuLi, gave adducts **2** and **3**. The stereochemical mode of attack can be rationalised by hydrogen bonding of the attacking 2-aminothiophenolate with the oxygen atoms of the dioxanone ring. Treatment of the adducts **2** and **3** with ethylmagnesium bromide afforded ring transformation by attack of the amino group at the carbonyl carbon atom cleaving the dioxanone ring. The resulting 3-(1-hydroxyethyl)-1,5-benzothiazepin-4-ones **4** and **5** represent structural analogues of Diltiazem®, a widely used drug in the treatment of hypertension.

Diltiazem® is a widely used Ca-channel blocker for the treatment of hypertension.[1,2] This compound consists of a (2*S*,3*R*)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one



Diltiazem

moiety. Several asymmetric syntheses for Diltiazem® are known, including the application of optically active glycidic acid derivatives as precursors for the benzothiazepine ring,[3–6] asymmetric reduction of benzothiazepine-3,4-diones[7] and the conjugate addition of 2-aminothiophenol to α,β-unsaturated carboxylic acids using auxiliary techniques.[8,9] Thus 2-aminothiophenolate could stereoselectively be added to cinnamoyl substituents attached to Evans's chiral oxazolidinones.[8,9] The great success of Diltiazem® has stimulated much activity in related chemical syntheses aimed at new asymmetric approaches as well as structural analogues. We have recently developed a synthesis of new optically active 3-(2-hydroxyethyl)- and 3-(3-hydroxypropyl)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-ones by reaction of chiral α-alkylidenelactones with 2-aminothiophenol *via* Michael-like addition and ring transformation of the resulting α-[1-(2-aminophenylthio)alkyl]lactones by attack of the amino group on the carbonyl carbon atom. As compared with the Diltiazem® structure these products bear the hydroxy group in the ω-position of a 3-alkyl side chain rather than at the benzothiazepinone ring.[10]

We now report the synthesis of enantiomerically pure 2,3-dihydro-3-(1-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-ones **4** and **5** using 5-ylidene-1,3-dioxan-4-ones **(*E*)-1** and **(*Z*)-1** as starting materials. These dioxanones can be synthesised using the procedure developed by Seebach *et al.*, starting from (*R*)-3-hydroxybutyric acid, the monomer of naturally occurring poly(hydroxybutyrate) (PHB), by acetalisation with pivalaldehyde and a two step aldol reaction.[11–13] These ylidenedioxanones present a chiral Michael system which can undergo asymmetric 1,4-additions of cuprates,[13] silanes[14] and nitromethane.[15] These additions as well as the epoxidation of the double bond occurred from the *Re*-face. On the other hand, diazomethane approaches the C–C-double bond of 5-ylidene-dioxan-4-ones from the *Si*-face.[16] This difference in face selectivity is not yet well understood.

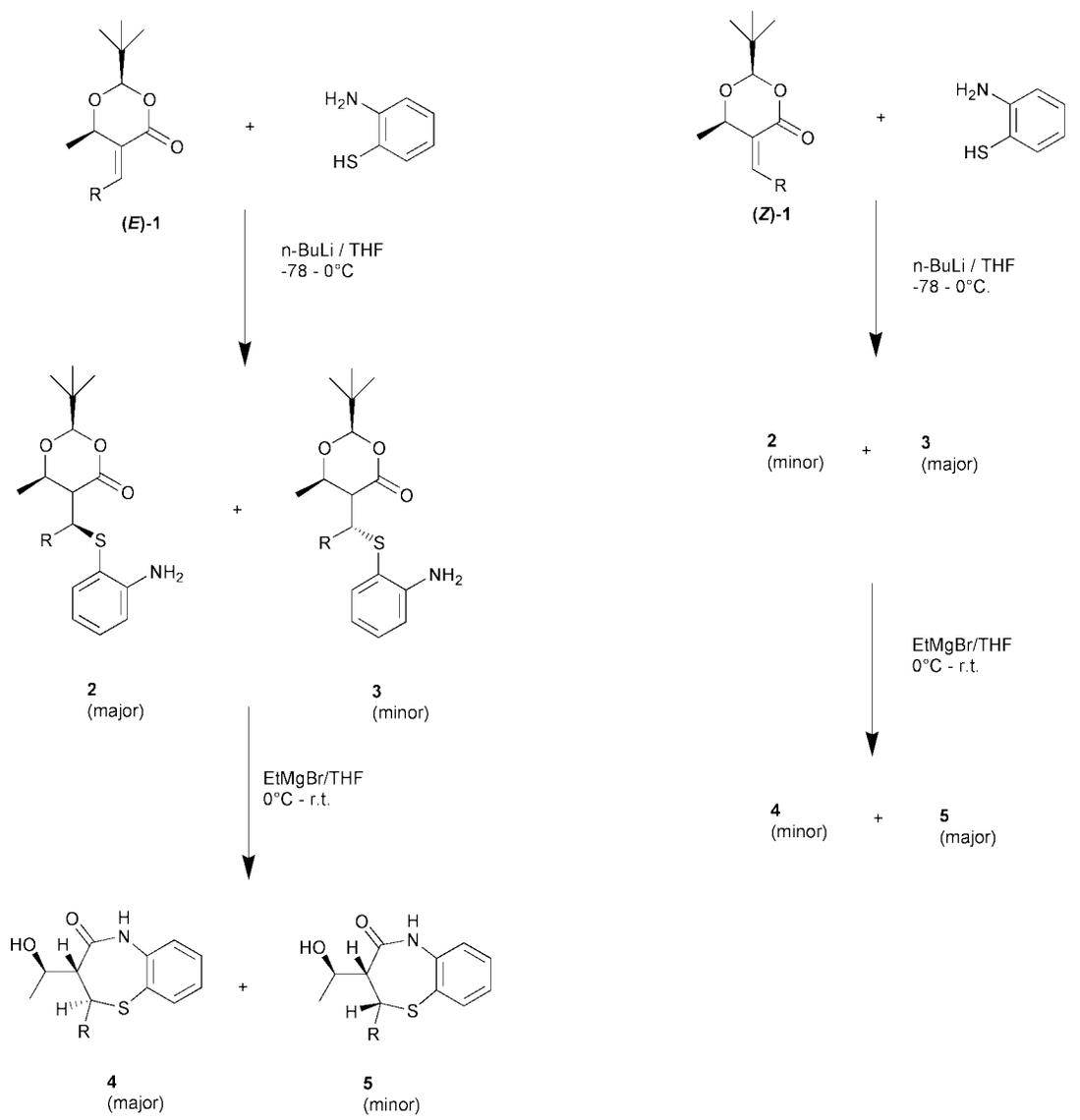
Table 1 1,4-Adducts **2** and **3** and 2,3-dihydro-1,5-benzothiazepin-4-ones **4** and **5**

R	Configuration of **1**	**2** + **3** (yield %)	dr **2**:**3**	**4** + **5** (yield %)
CH_3	*E*	**a** (97)	80:20	**a** (88)
C_2H_5	*E*	**b** (92)	83:17	**b** (88)
C_2H_5	*Z*	**b** (92)	30:70	**b** (90)
Iso-C_3H_7	*E*	**c** (92)	90:10	**c** (86)
$(CH_2)_2Ph$	*E*	**d** (96)	93:07	**d** (90)
$(CH_2)_2Ph$	*Z*	**d** (94)	20:80	**d** (91)
Ph	*E*	**e** (90)	95:05	**e** (85)
Cyclohexyl	*E*	**f** (89)	70:30	**f** (88)

Results and discussion

Our present investigations revealed that 2-aminothiophenol as a heteronucleophile adds to ylidenedioxanones **(*E*)-1** and **(*Z*)-1** after deprotonation with n-BuLi in a ratio of 50:1 (2-aminothiophenol–n-BuLi) at −78 °C affording inseparable mixtures of 1,4-adducts **2** and **3** with diastereomeric ratios between 70:30 and 95:5 in excellent yields (Table 1, Scheme 1). The application of a 100:1 ratio of 2-aminothiophenol–n-BuLi as reported in literature[8] gave lower yields while a 10:1 ratio considerably lowered the diastereoselectivity. The preferred stereochemical mode of attack by 2-aminothiophenol occurred from the *Si*-face unlike other 1,4-additions such as cuprates, silanes or nitromethane as mentioned above, *i.e.* epimers **2** were the major products derived from **(*E*)-1**, while **(*Z*)-1** preferably afforded epimers **3**.

DOI: 10.1039/b001928n



Scheme 1

The mixtures of epimers **2** and **3** were further treated with EtMgBr at 0 °C in order to reinforce nucleophilicity of the amino function by deprotonation, enabling nucleophilic attack at the carbonyl function of the dioxanone ring. The anticipated ring transformation occurred in high yields while the pivalaldehyde moiety was split off, affording mixtures of 2,3-dihydro-3-(1-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-ones **4** and **5**. The application of trimethylaluminium as reported for the analogous ring transformations of cinnamic acid derivatives[8] gave lower yields as compared to EtMgBr. The products 2,3-dihydro-3-(1-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-ones **4** and **5** could easily be separated by flash chromatography, affording stereochemically pure products. All the products from 1,4-addition, *i.e.* **2** and **3**, as well as those from ring transformation, *i.e.* **4** and **5**, are new. The structures of **4e** and **5b** were confirmed by X-ray crystal analysis (Figs. 1 and 2). Consistent geminal coupling constants were found for the two H-atoms on the thiazepinone ring in the *trans* **4** (11.3–12.4 Hz) and in the *cis* series **5** (8.2–8.3) as well as similar CD-spectra for the two series (Figs. 3 and 4). The opposite stereochemical mode of addition of 2-aminothiophenol to 5-ylidenedioxan-4-ones as compared with C-nucleophiles could originally be caused by an interaction of the amino group with the lone pairs of the ring oxygen atoms by hydrogen bonding as shown in Fig. 5.

In summary, we have found a straightforward route to new 2,3-dihydro-3-(1-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-ones starting from the chiral pool starting material PHB or (*R*)-3-hydroxybutyric acid which allows synthesis of *cis*- and *trans*-substituted compounds in a regio- and stereoselective manner.

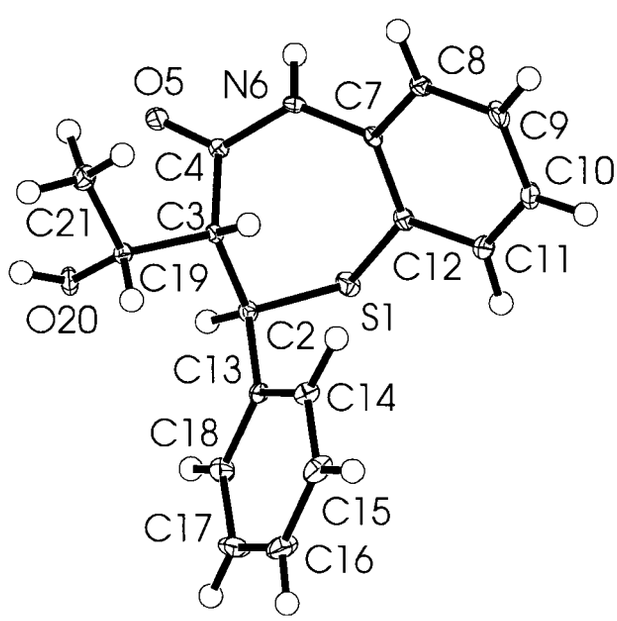


Fig. 1 X-ray structural analysis of **4e**.

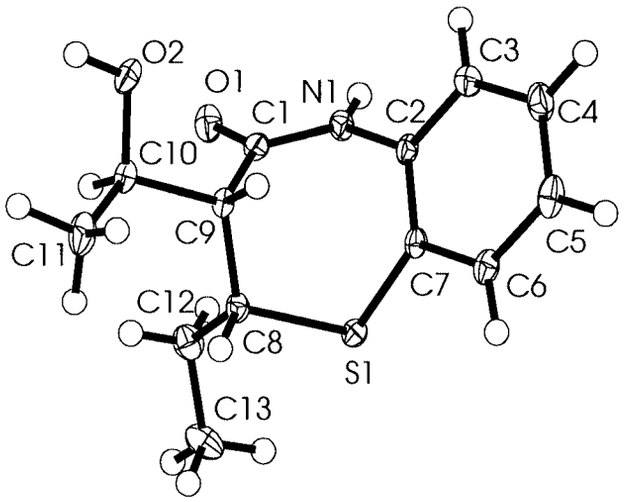


Fig. 2 X-ray structural analysis of **5b**.

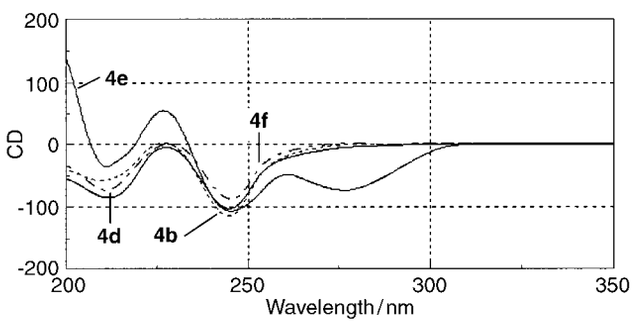


Fig. 3 CD-spectra of **4b**, **4d**, **4e** and **4f** in CH_3CN.

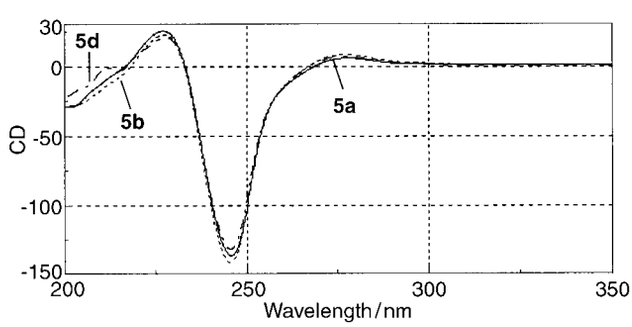


Fig. 4 CD-spectra of **5a**, **5b** and **5d** in CH_3CN.

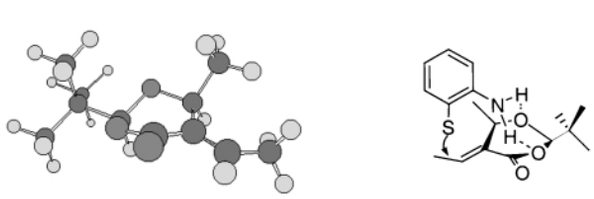


Fig. 5 MOPAC-geometry-optimised structure (***E***)**-1a** and proposed mode of attack by 2-aminothiophenolate.

The products represent structural analogues of the heterocyclic moiety of Diltiazem®.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. Optical rotations were determined with a Perkin-Elmer polarimeter 241 ($c = 1$, $CHCl_3$, $d = 2$ mm). Circular dichroism in terms of ellipticity theta (in deg) was measured on a JASCO J710 spectrometer (minimum wavelength 190 nm). For preparative column chromatography silica (0.04–0.063 mm, Merck) was used. Starting materials **1a**–**1f** were obtained following or adapting literature procedures.[11–13] Starting materials (***E***)**-1d**, (***Z***)**-1d** and (***E***)**-1f** are new.

(2*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-[(*E*)-3-phenylpropylidene]-1,3-dioxan-4-one (*E*)-1d

Colourless oil; R_f 0.40 (hexane–ether, 5:1); $[a]_D^{20}$ +106.2 ($c = 1$, $CHCl_3$) (Found: C, 74.81; H, 8.30. Calc. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%); δ_H 0.86 [9 H, s, C(CH_3)$_3$], 1.19 (3 H, d, *J* 6.4, CH_3CHO), 2.31–2.39 (2 H, m, CH_2CH_2Ph), 2.58–2.78 (2 H, m, CH_2CH_2Ph), 4.40 (1 H, s, OC*H*O), 4.52 (1 H, q, *J* 6.4, CHO), 6.64 (1 H, dd, *J* 2.2, 7.5, C=C*H*), 7.07–7.14 (3 H, m, ArH), 7.16–7.23 (2 H, m, ArH); δ_C 21.14 (CH_3CHO), 23.97 [C(CH_3)$_3$], 30.45 (CH_2CH_2Ph), 34.42 [*C*(CH_3)$_3$], 34.57 (CH_2CH_2Ph), 71.62 (CHO), 105.05 (O*C*HO), 126.44, 128.52 (×2), 128.56 (×2) (CH, Ar), 131.58 (*C*=CH), 140.38 (C, Ar), 141.91 (C=*C*H), 166.93 (C=O).

(2*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-[(*Z*)-3-phenylpropylidene]-1,3-dioxan-4-one (*Z*)-1d

Colourless crystals; mp 33–34 °C (hexane); R_f 0.62 (hexane–ether, 5:1); $[a]_D^{20}$ +89.6 ($c = 1$, $CHCl_3$) (Found: C, 74.74; H, 8.32. Calc. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%); δ_H 0.88 [9 H, s, C(CH_3)$_3$], 1.26 (3 H, d, *J* 6.4, CH_3CHO), 2.60–2.92 (4 H, m, CH_2CH_2Ph), 4.46 (1 H, q, *J* 6.4, CHO), 4.59 (1 H, s, OC*H*O), 5.93 (1 H, dd, *J* 1.5, 7.1, C=C*H*), 7.09–7.13 (3 H, m, ArH), 7.18–7.22 (2 H, m, ArH); δ_C 22.18 (CH_3CHO), 23.99 [C(CH_3)$_3$], 30.63 (CH_2CH_2Ph), 34.60 [*C*(CH_3)$_3$], 35.04 (CH_2CH_2Ph), 74.76 (CHO), 105.88 (O*C*HO), 126.09, 128.40 (×2), 128.53 (×2) (CH, Ar), 130.31 (*C*=CH), 140.86 (C, Ar), 143.44 (C=*C*H), 164.14 (C=O).

(2*R*,6*R*)-2-(*tert*-Butyl)-6-methyl-5-[(*E*)-cyclohexylmethylene]-1,3-dioxan-4-one (*E*)-1f

Colourless crystals; mp 79–80 °C (hexane); R_f 0.65 (hexane–ether, 5:1); $[a]_D^{20}$ +89.7 ($c = 1$, $CHCl_3$) (Found: C, 71.87; H, 9.72. Calc. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%); δ_H 0.91 [9 H, s, C(CH_3)$_3$], 1.05–1.23 (5 H, m, cyclohexyl), 1.31 (3 H, d, *J* 6.4, CH_3CHO), 1.52–1.75 (6 H, m, cyclohexyl), 4.67 (1 H, s, OC*H*O), 4.81 (1 H, q, *J* 6.4, CHO), 6.50 (1 H, d, *J* 11.3, C=C*H*); δ_C 22.30 (CH_3CHO), 23.98 [C(CH_3)$_3$], 25.22, 25.25, 25.58, 31.35, 31.95 (CH_2, cyclohexyl), 34.51 [*C*(CH_3)$_3$], 37.80 (CH, cyclohexyl), 71.55 (CHO), 105.12 (O*C*HO), 128.47 (*C*=CH), 148.37 (C=*C*H), 167.40 (C=O).

General procedure for the synthesis of 5-[1′-(2-aminophenyl)-sulfanylalkyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-ones 2 and 3

A solution of 2-aminothiophenol (1.25 g, 10 mmol) in 10 ml dry THF was added to an ice-cold solution of BuLi (1.6 M solution) (0.12 ml, 0.2 mmol) in 5 ml dry THF under an argon atmosphere with stirring. After 45 min the solution was cooled to −78 °C. A solution of 5-alkylidenedioxanone **1** (1 mmol) in 5 ml dry THF was added dropwise over 20 min. After stirring overnight, the reaction mixture was allowed to warm to 0 °C and was quenched with 20 ml of aqueous 2 M NaOH solution. The organic phase was extracted with CH_2Cl_2 (3 × 30 ml), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow residue, which was purified by flash chromatography using EtOAc–hexane (1:5).

(1′*S*,2*R*,5*R*,6*R*)-5-[1′-(2-Aminophenyl)sulfanylethyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2a and (1′*R*,2*R*,5*R*,6*R*)-5-[1′-(2-aminophenyl)sulfanylethyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 3a. Starting material (***E***)**-1a**; yield: 97%; colourless oil; R_f 0.52 (n-hexane–EtOAc, 4:1); mixture of **2a** and **3a**; dr 80:20; major isomer **2a**: δ_H 0.90 [9 H, s, C(CH_3)$_3$], 1.27 (3 H, d, *J* 7.1, CH_3CHS), 1.28 (3 H, d, *J* 6.0, CH_3CHO), 2.61 (1 H, dd, *J* 3.0,

9.4, C*H*C=O), 3.54 (1 H, dq, *J* 3.0, 7.1, CHS), 3.96 (1 H, dq, *J* 6.0, 9.4, CHO), 4.30 (2 H, br s, NH_2), 4.92 (1 H, s, OC*H*O), 6.54–6.66 (2 H, m, ArH), 7.05 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.28 (1 H, dd, *J* 1.5, 7.9, ArH); δ_C 20.15 (*C*H_3CHS), 21.98 (*C*H_3CHO), 23.87 [C(*C*H_3)$_3$], 35.07 [*C*(CH$_3$)$_3$], 43.36 (*C*HC=O), 53.43 (CHS), 72.81 (CHO), 107.62 (O*C*HO), 115.11 (CH, Ar), 115.30 (C, Ar), 118.09, 130.75, 137.36 (CH, Ar), 149.15 (C, Ar), 170.07 (C=O); minor isomer **3a**: δ_C 20.66 (*C*H_3CHS), 21.09 (*C*H_3CHO), 23.92 [C(*C*H_3)$_3$], 35.12 [*C*(CH$_3$)$_3$], 43.22 (*C*HC=O), 53.93 (CHS), 73.12 (CHO), 107.89 (O*C*HO), 115.17 (CH, Ar), 116.51 (C, Ar), 118.56, 130.38, 136.50 (CH, Ar), 148.72 (C, Ar), 168.85 (C=O).

(1′*S*,2*R*,5*R*,6*R*)-5-[1′-(2-Aminophenyl)sulfanylpropyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2b and (1′*R*,2*R*,5*R*,6*R*)-5-[1′-(2-aminophenyl)sufanylpropyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 3b. Starting material **(*E*)-1b**; yield: 92%; colourless oil; R_f 0.52 (n-hexane–EtOAc, 4:1); mixture of **2b** and **3b**; dr 83:17; major isomer **2b**: δ_H 0.89 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 0.90 [9 H, s, C(CH$_3$)$_3$], 1.26 (3 H, d, *J* 6.0, CH$_3$CH), 1.58 and 1.71 (2 × H, each m, CH$_2$), 2.74 (1 H, dd, *J* 3.0, 9.4, C*H*C=O), 3.40 (1 H, ddd, *J* 3.0, 6.8, 9.0, CHS), 4.01 (1 H, dq, *J* 6.0, 9.4, CHO), 4.29 (2 H, br s, NH_2), 4.95 (1 H, s, OC*H*O), 6.54–6.65 (2 H, m, ArH), 7.04 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.28 (1 H, dd, *J* 1.5, 7.9, ArH); δ_C 12.33 (*C*H$_3$CH$_2$), 21.84 (*C*H$_3$CHO), 23.88 [C(*C*H$_3$)$_3$], 27.32 (CH$_2$), 35.12 [*C*(CH$_3$)$_3$], 50.61 (CHS), 50.73 (*C*HC=O), 72.64 (CHO), 107.51 (O*C*HO), 115.14 (CH, Ar), 115.35 (C, Ar), 118.13, 130.55, 137.18 (CH, Ar), 148.96 (C, Ar), 170.78 (C=O).

Starting material **(*Z*)-1b**; yield: 92%; colourless oil; R_f 0.52 (n-hexane–EtOAc, 4:1); mixture of **2b** and **3b**; dr 30:70; major isomer **3b**: δ_H 0.88 [9 H, s, C(C*H*$_3$)$_3$], 0.90 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.26 (3 H, d, *J* 6.0, C*H*$_3$CHO), 1.87 and 1.96 (2 × H, each m, CH$_2$), 2.61 (1 H, dd, *J* 1.9, 10.1, C*H*C=O), 3.0 (1 H, dt, *J* 1.9, 7.5, CHS), 3.92 (1 H, dq, *J* 6.0, 10.1, CHO), 4.29 (2 H, br s, NH_2), 4.90 (1 H, s, OC*H*O), 6.61–6.66 (2 H, m, ArH), 7.04 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.28 (1 H, dd, *J* 1.5, 7.9, ArH); δ_C 12.66 (*C*H$_3$CH$_2$), 20.45 (*C*H$_3$CHO), 23.90 [C(*C*H$_3$)$_3$], 27.94 (CH$_2$), 35.12 [*C*(CH$_3$)$_3$], 50.73 (CHS), 51.85 (*C*HC=O), 73.39 (CHO), 107.93 (O*C*HO), 115.21 (CH, Ar), 117.26 (C, Ar), 118.70, 130.07, 136.04 (CH, Ar), 148.39 (C, Ar), 168.70 (C=O).

(1′*S*,2*R*,5*R*,6*R*)-5-[1′-(2-Aminophenyl)sulfanyl-2′-methylpropyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2c. Starting material **(*E*)-1c**; yield: 92%; colourless oil; R_f 0.45 (n-hexane–EtOAc, 4:1); mixtures of **2c** and **3c**; dr 90:10; major isomer **2c**: δ_H 0.86 [9 H, s, C(C*H*$_3$)$_3$], 1.02 and 1.14 [2 × 3 H, each d, *J* 6.8, CH(C*H*$_3$)$_2$], 1.15 (3 H, d, *J* 6.0, CH$_3$), 2.33 [1 H, m, C*H*(CH$_3$)$_2$], 2.75 (2 × H, m, C*H*C=O and CHS), 3.81 (1 H, dq, *J* 6.0, 9.4, CHO), 4.22 (2 H, br s, NH_2), 4.88 (1 H, s, OC*H*O), 6.59–6.64 (2 H, m, ArH), 6.99 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.23 (1 H, dd, *J* 1.5, 7.9, ArH); δ_C 19.83 and 21.53 [CH(*C*H$_3$)$_2$], 22.13 (CH$_3$), 23.92 [C(*C*H$_3$)$_3$], 32.59 [*C*H(CH$_3$)$_2$], 35.09 [*C*(CH$_3$)$_3$], 52.03 (*C*HC=O), 57.0 (CHS), 73.65 (CHO), 107.85 (O*C*HO), 115.25 (CH, Ar), 115.52 (C, Ar), 118.91, 129.26, 134.54 (CH, Ar), 147.35 (C, Ar), 168.59 (C=O).

(1′*S*,2*R*,5*R*,6*R*)-5-{1′-[(2-Aminophenyl)sulfanyl]-3′-phenylpropyl}-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2d and (1′*R*,2*R*,5*R*,6*R*)-5-{1′[(2-aminophenyl)sulfanyl]-3′-phenylpropyl}-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 3d. Starting material **(*E*)-1d**; yield: 96%; colourless oil; R_f 0.50 (n-hexane–EtOAc, 4:1); mixture of **2d** and **3d**; dr 93:7; major isomer **2d**: δ_H 0.88 [9 H, s, C(C*H*$_3$)$_3$], 1.18 (3 H, d, *J* 6.0, CH$_3$), 1.86 and 2.03 (2 × H, each m, C*H*$_2$CH$_2$Ph), 2.58 and 2.70 (2 × H, each m, CH$_2$C*H*$_2$Ph), 2.72 (1 H, dd, *J* 2.6, 9.4, C*H*C=O), 3.47 (1 H, ddd, *J* 2.6, 6.8, 7.9, CHS), 3.90 (1 H, dq, *J* 6.0, 9.4, CHO), 4.32 (2 H, br s, NH_2), 4.90 (1 H, s, OC*H*O), 6.54–6.65 (2 H, m, ArH), 6.95–7.22 (6 H, m, ArH), 7.29–7.32 (1 H, m, ArH); δ_C 21.52 (CH$_3$), 23.89 [C(*C*H$_3$)$_3$], 33.72 [*C*(CH$_3$)$_3$], 35.10 (CH$_2$*C*H$_2$Ph), 36.17 (*C*H$_2$CH$_2$Ph), 48.22 (CHS), 51.74 (*C*HC=O), 72.80 (CHO), 107.65 (O*C*HO), 115.18 (CH, Ar), 115.60 (C, Ar), 118.36, 126.18, 128.30 (×2), 128.53 (×2), 130.58, 137.02 (CH, Ar), 140.77, 148.96 (C, Ar), 170.13 (C=O).

Starting material **(*Z*)-1d**; yield: 94%; colourless oil; R_f 0.50 (n-hexane–EtOAc, 4:1); mixture of **2d** and **3d**; dr 20:80; major isomer **3d**: δ_H 0.87 [9 H, s, C(C*H*$_3$)$_3$], 1.12 (3 H, d, *J* 6.0, CH$_3$), 2.13–2.37 (2 H, m, C*H*$_2$CH$_2$Ph), 2.60 (1 H, dd, *J* 1.9, 9.8, C*H*C=O), 2.68–2.73 (2 H, m, CH$_2$C*H*$_2$Ph), 3.08 (1 H, dt, *J* 1.9, 7.5, CHS), 3.86 (1 H, dq, *J* 6.0, 9.8, CHO), 4.21 (2 H, br s, NH_2), 4.86 (1 H, s, OC*H*O), 6.56–6.63 (2 H, m, ArH), 6.97–7.21 (6 H, m, ArH), 7.28 (1 H, dd, *J* 1.5, 7.5, ArH); δ_C 22.5 (CH$_3$), 23.92 [C(*C*H$_3$)$_3$], 33.37 (CH$_2$*C*H$_2$Ph), 35.14 [s, *C*(CH$_3$)$_3$], 36.12 (*C*H$_2$CH$_2$Ph), 47.86 (CHS), 52.47 (*C*HC=O), 73.44 (CHO), 108.0 (O*C*HO), 115.23 (CH, Ar), 116.95 (C, Ar), 118.75, 126.11, 128.43 (×2), 128.47 (×2), 130.09, 135.92 (CH, Ar), 140.67, 148.36 (C, Ar), 168.59 (C=O).

(1′*R*,2*R*,5*R*,6*R*)-5-[α-(2-Aminophenyl)sulfanylbenzyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2e. Starting material **(*E*)-1e**; yield: 90%; colourless oil; R_f 0.45 (n-hexane–EtOAc, 4:1); mixture of **2e** and **3e**; dr 95:5; major isomer **2e**: δ_H 0.73 (3 H, d, *J* 6.0, CH$_3$), 0.86 [9 H, s, C(C*H*$_3$)$_3$], 2.88 (1 H, dd, *J* 3.8, 9.4, C*H*C=O), 3.92 (1 H, dq, *J* 6.0, 9.4, CHO), 4.35 (2 H, br s, NH_2), 4.64 (1 H, d, *J* 3.8, CHS), 4.75 (1 H, s, OC*H*O), 6.41 (1 H, ddd, *J* 1.5, 7.5, 8.6, ArH), 6.56 (1 H, dd, *J* 1.1, 7.9, ArH), 6.95 (1 H, ddd, *J* 1.5, 7.5, 8.6, ArH), 7.11–7.24 (4 H, m, ArH), 7.38–7.41 (2 H, m, ArH); δ_C 21.17 (CH$_3$), 23.71 [C(*C*H$_3$)$_3$], 34.98 [*C*(CH$_3$)$_3$], 52.88 (CHS), 55.02 (*C*HC=O), 72.94 (CHO), 107.52 (O*C*HO), 115.18 (CH, Ar), 115.28 (C, Ar), 118.02, 127.85, 128.52 (×2), 128.70 (×2), 130.65, 136.77 (CH, Ar), 138.79, 149.06 (C, Ar), 169.84 (C=O).

(1′*S*,2*R*,5*R*,6*R*)-5-[1′-(2-Aminophenyl)sulfanyl(cyclohexyl)-methyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 2f and (1′*R*,2*R*,5*R*,6*R*-5-[1′-(2-aminophenyl)sulfanyl(cyclohexyl)methyl]-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one 3f. Starting material **(*E*)-1f**; yield: 89%; colourless oil; R_f 0.53 (n-hexane–EtOAc); mixture of **2f** and **3f**; dr 70:30; major isomer **2f**: δ_H 0.80–1.05 (2 H, m, cyclohexyl), 0.86 [9 H, s, C(C*H*$_3$)$_3$], 1.08–1.27 (3 H, m, cyclohexyl), 1.13 (3 H, d, *J* 6.0, CH$_3$), 1.43–1.72 (4 H, m, cyclohexyl), 1.89–1.96 (2 H, m, cyclohexyl), 2.76–2.82 (2 × H, m, C*H*C=O and CHS), 3.80 (1 H, dq, *J* 6.0, 9.4, C*H*O), 4.23 (2 H, br s, NH_2), 4.87 (1 H, s, OC*H*O), 6.57-6.64 (2 H, m, ArH), 7.0 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.22 (1 H, dd, *J* 1.5, 7.9, ArH); δ_C 19.82 (CH$_3$), 23.93 [C(*C*H$_3$)$_3$], 26.23 (×2), 31.45, 31.79, 32.31 (CH$_2$, cyclohexyl), 35.09 [*C*(CH$_3$)$_3$], 41.32 (CH, cyclohexyl), 51.37 (*C*HC=O), 55.78 (CHS), 73.57 (CHO), 107.84 (O*C*HO), 115.20, 118.90 (CH, Ar), 119.16 (C, Ar), 129.15, 134.49 (CH, Ar), 147.25 (C, Ar), 168.63 (C=O); minor isomer **3f**: δ_C 21.48 (CH$_3$), 23.87 [C(*C*H$_3$)$_3$], 25.97, 26.05, 31.58, 31.88, 32.41 (CH$_2$, cyclohexyl), 34.99 [*C*(CH$_3$)$_3$], 41.97 (CH, cyclohexyl), 50.37 (*C*HC=O), 56.19 (CHS), 73.13 (CHO), 107.14 (O*C*HO), 115.13 (CH, Ar), 117.54 (C, Ar), 118.71, 129.54, 135.34 (CH, Ar), 147.59 (C, Ar), 170.94 (C=O).

General procedure for the synthesis of 2,3-dihydro-3-(1′-hydroxyethyl)-2-alkyl-1,5-benzothiazepin-4(5*H*)-ones 4 and 5 by ring transformation with EtMgBr

EtMgBr (1 M solution in THF) (1.6 ml, 1.6 mmol) was slowly added to the solution of diastereomeric mixtures of adducts **2** and **3** (1 mmol) in 20 ml of THF at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 3–4 hours after which it was quenched with 10 ml of saturated aqueous NH_4Cl solution. The organic phase was extracted with CH_2Cl_2 (3 × 30 ml), combined organic extracts were evaporated under reduced pressure to give pale yellow viscous oils. The products were separated by flash chromatography on silica with EtOAc–hexane (1:1).

***trans*-(−)-(1′*R*,2*S*,3*R*)-2,3-Dihydro-3-(1′-hydroxyethyl)-2-methyl-1,5-benzothiazepin-4(5*H*)-one 4a and *cis*-(−)-(1′*R*,2*R*,3*R*)-2,3-dihydro-2-methyl-3-(1′-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-one 5a.** Starting material **2a**–**3a** (80:20); yield: 88% (**4a** + **5a**); R_f 0.42 (**4a**) and 0.30 (**5a**) (5% MeOH–CH_2Cl_2); major isomer **4a**: colourless crystals; mp 109–110 °C (from $CHCl_3$); $[\alpha]_D^{20}$ −467.2 (c = 1, $CHCl_3$) (Found: C, 60.81; H, 6.40; N, 5.91; S, 13.25. Calc. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51%); δ_H 1.23 (3 H, d, *J* 6.8, C*H*$_3$CHS), 1.32 (3 H, d, *J* 6.4, C*H*$_3$CHO), 2.04 (1 H, dd, *J* 2.2, 11.3, C*H*C=O), 3.70 (1 H, dq, *J* 2.2, 6.4, CHO), 3.84 (1 H, dq, *J* 6.8, 11.3, CHS), 4.23 (1 H, br s, OH), 7.07–7.15 (2 H, m, ArH), 7.23 (1 H, ddd, *J* 1.5, 7.9, 9.4, ArH), 7.54 (1 H, dd, *J* 1.5, 7.9, ArH), 8.72 (1 H, s, NHC=O); δ_C 22.31 (*C*H$_3$CHO), 22.71 (*C*H$_3$CHS), 46.99 (*C*HC=O), 53.53 (CHS), 66.62 (CHO), 123.35 (CH, Ar), 126.45 (C, Ar), 126.66, 130.25, 136.52 (CH, Ar), 140.97 (C, Ar), 177.28 (C=O); minor isomer **5a**: colourless crystals; mp 229–230 °C (from $CHCl_3$), $[\alpha]_D^{20}$ −231.4 (c = 1, $CHCl_3$); δ_H 1.08 (3 H, d, *J* 6.4, C*H*$_3$CHO), 1.33 (3 H, d, *J* 6.8, C*H*$_3$CHS), 2.58 (H, dd, *J* 2.6, 8.2, C*H*C=O), 3.02 (H, dq, *J* 6.8, 8.2, CHS), 3.27 (1 H, br s, OH), 3.87 (1 H, dq, *J* 2.6, 6.4, CHO), 7.01 (1 H, dd, *J* 1.5, 7.9, ArH), 7.11 (1 H, ddd, *J* 1.5, 7.9, 9.0, ArH), 7.29 (1 H, ddd, *J* 1.5, 7.9, 9.0, ArH), 7.51 (1 H, dd, *J* 1.5, 7.9, ArH), 7.69 (1 H, s, NHC=O); δ_C 16.33 (*C*H$_3$CHS), 19.80 (*C*H$_3$CHO), 46.21 (*C*HC=O), 52.94 (CHS), 66.02 (CHO), 123.12, 126.65 (CH, Ar), 127.69 (C, Ar), 129.94, 134.83 (CH, Ar), 140.91 (C, Ar), 174.51 (C=O).

***trans*-(−)-(1′*R*,2*S*,3*R*)-2,3-Dihydro-2-ethyl-3-(1′-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-one 4b.** Starting material **2b**–**3b** (83:17); yield: 88% (**4b** + **5b**); major isomer **4b**: R_f 0.53 (5% MeOH–CH_2Cl_2); colourless crystals; mp 128–130 °C (from CH_2Cl_2); $[\alpha]_D^{20}$ −488.5 (c = 1, $CHCl_3$) (Found: C, 62.08; H, 7.02; N, 5.49; S, 13.02. Calc. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76%); δ_H 0.99 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.24 (3 H, d, *J* 6.4, C*H*$_3$CHO), 1.30–1.45 (1 H, m, CH$_2$), 1.71–1.84 (1 H, m, CH$_2$), 2.17 (1 H, dd, *J* 1.9, 11.3, C*H*C=O), 3.68 (1 H, ddd, *J* 2.6, 9.4, 11.3, CHS), 3.76 (1 H, dq, *J* 1.9, 6.4, CHO), 4.57 (1 H, br s, OH), 7.06–7.14 (2 H, m, ArH), 7.32 (1 H, ddd, *J* 1.5, 7.5, 9.0, ArH), 7.55 (1 H, dd, *J* 1.5, 7.5, ArH), 8.33 (1 H, s, NHC=O); δ_C 10.56 (*C*H$_3$CH$_2$), 22.71 (*C*H$_3$CHO), 27.11 (CH$_2$), 51.60 (*C*HC=O), 54.18 (CHS), 66.45 (CHO), 123.25, 126.75 (CH, Ar), 127.13 (C, Ar), 130.14, 136.54 (CH, Ar), 141.08 (C, Ar), 177.26 (C=O).

***cis*-(−)-(1′*R*,2*R*,3*R*)-2,3-Dihydro-2-ethyl-3-(1′-hydroxyethyl)-1,5-benzothiazepin-4(5*H*)-one 5b.** Starting material **2b**–**3b** (30:70); yield: 90% (**4b** + **5b**); major isomer **5b**: R_f 0.42 (5% MeOH–CH_2Cl_2); colourless crystals; mp 179–180 °C (from CH_2Cl_2); $[\alpha]_D^{20}$ −167.2 (c = 1, $CHCl_3$) (Found: C, 61.78; H, 6.89; N, 5.30; S, 12.67. Calc. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76%); δ_H 0.97 (3 H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.07 (3 H, d, *J* 6.4, C*H*$_3$CHO), 1.67 and 1.91 (2 × H, each m, CH$_2$), 2.62 (1 H, dd, *J* 1.5, 8.3, C*H*C=O), 3.29 (1 H, br s, OH), 3.69 (1 H, ddd, *J* 3.4, 5.3, 8.3, CHS), 4.24 (1 H, dq, *J* 1.5, 6.4, CHO), 7.02 (1 H, dd, *J* 1.5, 7.5, ArH), 7.09 (1 H, ddd, *J* 1.5, 7.5, 9.0, ArH), 7.27 (1 H, ddd, *J* 1.5, 7.5, 9.0 Hz, ArH), 7.50 (1 H, dd, *J* 1.5, 7.5, ArH), 8.38 (1 H, s, NHC=O); δ_C 12.05 (*C*H$_3$CH$_2$), 19.97 (*C*H$_3$CHO), 24.60 (CH$_2$), 53.09 (CHC=O), 53.79 (CHS), 65.94 (CHO), 123.15, 126.39 (CH, Ar), 127.73 (C, Ar), 129.71, 134.95 (CH, Ar), 140.93 (C, Ar), 174.41 (C=O).

***trans*-(−)-(1′*R*,2*S*,3*R*)-2,3-Dihydro-3-(1′-hydroxyethyl)-2-isopropyl-1,5-benzothiazepin-4(5*H*)-one 4c.** Starting material **2c**–**3c** (90:10), yield: 86% (**4c** + **5c**); major isomer **4c**: R_f 0.58 (5% MeOH-CH_2Cl_2); thick colourless oil; $[\alpha]_D^{20}$ −401.5 (c = 1, $CHCl_3$) (Found: C, 63.21; H, 7.34; N, 5.23; S, 12.0. Calc. for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28; S, 12.08%); δ_H 0.67, 1.02 [2 × 3 H, each d, *J* 6.8, CH(C*H*$_3$)$_2$], 1.23 (3 H, d, *J* 6.4, C*H*$_3$CHO), 2.21 [1 H, m, C*H*(CH$_3$)$_2$], 2.45 (1 H, dd, *J* 1.5, 11.8, C*H*C=O), 3.81 (1 H, dq, *J* 1.5, 6.4, CHO), 3.84 (1 H, dd, *J* 2.2, 11.8, CHS), 4.54 (1 H, br s, OH), 7.03–7.10 (2 H, m, ArH), 7.27 (1 H, ddd, *J* 1.5, 7.5, 9.0, ArH), 7.57 (1 H, dd, *J* 1.5, 7.5, ArH), 9.07 (1 H, s, NHC=O); δ_C 14.76 and 21.26 [CH(*C*H$_3$)$_2$], 22.52 (*C*H$_3$CHO), 30.16 [*C*H(CH$_3$)$_2$], 48.72 (*C*HC=O), 59.30 (CHS), 65.95 (CHO), 122.85, 126.71 (CH, Ar), 128.19 (C, Ar), 129.70, 135.88 (CH, Ar), 141.21 (C, Ar), 177.89 (C=O).

***trans*-(−)-(1′*R*,2*S*,3*R*)-2,3-Dihydro-3-(1′-hydroxyethyl)-2-(2″-phenylethyl)-1,5-benzothiazepin-4(5*H*)-one 4d.** Starting material **2d**–**3d** 93:7; yield: 90% (**4d** + **5d**); major isomer **4d**: R_f 0.52 (5% MeOH–CH_2Cl_2); colourless crystals; mp 125–126 °C (from $CHCl_3$), $[\alpha]_D^{20}$ −381.1 (c = 1, $CHCl_3$) (Found: C, 69.60; H, 6.58; N, 4.21; S, 9.68. Calc. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.78%); δ_H 1.20 (3 H, d, *J* 6.4, CH$_3$), 1.54–1.67 (1 H, m, C*H*$_2$CH$_2$Ph), 1.96–2.07 (1 H, m, C*H*$_2$CH$_2$Ph), 2.15 (1 H, dd, *J* 1.5, 11.3, C*H*C=O), 2.66 (1 H, ddd, *J* 6.0, 10.5, 13.5, CH$_2$C*H*$_2$Ph), 2.95 (1 H, ddd, *J* 4.5, 10.5, 13.5, CH$_2$C*H*$_2$Ph), 3.70–3.80 (2 H, m, CHS and CHO), 4.55 (1 H, br s, OH), 7.06–7.21 (7 H, m, ArH), 7.31 (1 H, ddd, *J* 1.5, 7.5, 9.0, ArH), 7.58 (1 H, dd, *J* 1.5, 7.5, ArH), 8.63 (1 H, s, NHC=O); δ_C 22.72 (CH$_3$), 32.58 (CH$_2$*C*H$_2$Ph), 35.87 (*C*H$_2$CH$_2$Ph), 52.19 (*C*HC=O), 52.35 (CHS), 66.49 (CHO), 123.46, 126.02 (CH, Ar), 126.74 (C, Ar), 126.86, 128.43 (×2), 128.50 (×2), 130.39, 136.62 (CH, Ar), 141.28, 141.42 (C, Ar), 177.24 (C=O).

***cis*-(−)-(1′*R*,2*R*,3*R*)-2,3-Dihydro-3-(1′-hydroxyethyl)-2-(2″-phenylethyl)-1,5-benzothiazepin-4(5*H*)-one 5d.** Starting material **2d**–**3d** 20:80; yield: 91% (**4d** + **5d**), major isomer **5d**: R_f 0.44 (5% MeOH–CH_2Cl_2); colourless oil; $[\alpha]_D^{20}$ −109.1 (c = 1, $CHCl_3$) (Found: C, 69.53; H, 6.66; N, 4.24; S, 9.71. Calc. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79%); δ_H 0.88 (3 H, d, *J* 6.4, CH$_3$), 1.96–2.15 (2 H, m, C*H*$_2$CH$_2$Ph), 2.44–2.59 (2 × H, m, C*H*C=O and CH$_2$C*H*$_2$Ph), 2.79–2.88 (1 H, m, C*H*CH$_2$Ph), 3.36 (1 H, br s, OH), 3.64 (1 H, ddd, *J* 3.0, 4.9, 8.3, CHS), 4.17 (1 H, dq, *J* 1.8, 6.4, CHO), 6.97–7.22 (8 H, m, ArH), 7.49 (1 H, dd, *J* 1.5, 7.5, ArH), 8.74 (1 H, s, NHC=O); δ_C 19.74 (CH$_3$), 33.07 (CH$_2$*C*H$_2$Ph), 33.07 (*C*H$_2$CH$_2$Ph), 50.77 (*C*HC=O), 52.80 (CHS), 65.80 (CHO), 123.27, 126.19, 126.33 (CH, Ar), 127.47 (C, Ar), 128.47 (×2), 128.53 (×2), 129.80, 134.96, 140.08 (CH, Ar), 140.67 (C, Ar), 174.57 (C=O).

***trans*-(−)-(1′*R*,2*R*,3*R*)-2,3-Dihydro-3-(1′-hydroxyethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 4e.** Starting material **2e**–**3e** 95:5; yield: 85% (**4e** + **5e**); major isomer **4e**: R_f 0.45 (5% MeOH–CH_2Cl_2); colourless crystals; mp 205–206 °C (from CH_2Cl_2); $[\alpha]_D^{20}$ −668.4 (c = 1, $CHCl_3$) (Found: C, 68.02, H, 5.74; N, 4.62; S, 10.61. Calc. for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71%); δ_H 1.12 (3 H, d, *J* 6.4, CH$_3$), 1.72 (1 H, br s, OH), 2.68 (1 H, dd, *J* 1.5, 12.0, C*H*C=O), 3.19 (1 H, dq, *J* 1.5, 6.4, CHO), 4.87 (1 H, d, *J* 12.0, CHS), 7.08–7.11 (2 H, m, ArH), 7.16–7.23 (5 H, m, ArH), 7.40 (1 H, ddd, *J* 1.5, 7.5, 9.0, ArH), 7.56 (1 H, dd, *J* 1.5, 9.0, ArH), 8.39 (1 H, s, NHC=O); δ_C 22.45 (CH$_3$), 52.78 (*C*HC=O), 55.37 (CHS), 66.75 (CHO), 123.59, 126.61 (×2), 127.24 (CH, Ar), 127.28 (C, Ar), 127.87, 128.84 (×2), 130.47, 136.24 (CH, Ar), 140.83, 142.92 (C, Ar), 176.20 (C=O).

***trans*-(−)-(1′*R*,2*S*,3*R*)-2,3-Dihydro-2-cyclohexyl-3-(1′-hydroxyethyl-1,5-benzothiazepin-4(5*H*)-one 4f.** Starting material **2f**–**3f** 70:30; yield: 88% (**4f** + **5f**); major isomer **4f**: R_f 0.48 (5% MeOH–CH_2Cl_2); colourless crystals, mp 149–150 °C (from hexane–ether), $[\alpha]_D^{20}$ −486.5 (c = 1, $CHCl_3$) (Found: C, 66.76; H, 7.75; N, 4.58; S, 10.69; Calc. for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59; S, 10.50%); δ_H 1.02–1.30 (4 H, m, cyclohexyl), 1.23 (3 H, d, *J* 6.4, CH$_3$), 1.39–1.43 (1 H, m, cyclohexyl), 1.60–1.72 (4 H, m, cyclohexyl), 1.81–1.88 (2 H, m, cyclohexyl), 2.52 (1 H,

dd, *J* 1.8, 12.4, C*H*C=O), 3.80 (2 H, m, CHS and CHO), 4.50 (1 H, br s, OH), 7.03–7.12 (2 H, m, ArH), 7.28 (1 H, ddd, *J* 1.5, 7.9, 9.0, ArH), 7.59 (1 H, dd, *J* 1.5, 7.9, ArH), 8.83 (1 H, s, NHC=O); δ_C 22.54 (CH_3), 25.31, 25.89, 26.21, 26.36, 31.31 (CH_2, cyclohexyl), 40.50 (CH, cyclohexyl), 47.82 (*C*HC=O), 58.70 (CHS), 65.96 (CHO), 122.83, 126.75 (CH, Ar), 128.32 (C, Ar), 129.7, 135.98 (CH, Ar), 141.18 (C, Ar), 177.92 (C=O).

Crystal structure determination of compound 4e[17]

A single crystal of **4e** with the dimensions 0.60 × 0.28 × 0.20 mm was measured on a STOE Ipds diffractometer using Mo-K_α radiation ($\lambda = 0.71073$ Å). Crystal data: $C_{17}H_{17}NO_2S$, $M = 299.38$, monoclinic space group $P2_1$, $a = 5.4491$ (11), $b = 8.7088$ (15), $c = 14.951$ (3) Å, $\alpha = 90$, $\beta = 94.31$ (3), $\gamma = 90°$, $V = 707.5$ (2) Å^3, $Z = 2$, $D_c = 1.405$ g cm^{-3}, $F(000) = 316$, μ(Mo-K_α) = 0.233 mm^{-1}. At 180 (2) K in the range of $2.71° < \theta < 25.24°$, 4743 reflections were measured, 2541 were unique ($R_{(int)} = 0.0382$). The final residuals were $wR_{2(all)} = 0.0804$, $R_{1(all)} = 0.0353$ and $R_{1(obs)} = 0.0328$. The maximum and minimum peaks in the final difference map were 0.277 and −0.300 e Å^{-3} respectively.

Crystal structure determination of compound 5b[17]

A single crystal of **5b** with the dimensions 0.40 × 0.36 × 0.09 mm was measured on a STOE Ipds diffractometer using Mo-K_α radiation ($\lambda = 0.71073$ Å). Crystal data: $C_{13}H_{17}NO_2S$, $M = 251.34$, orthorhombic space group $P2_12_12_1$, $a = 8.5736$ (15), $b = 12.007$ (3), $c = 12.669$ (2) Å, $\beta = 90°$, $V = 1304.2$ (4) Å^3, $Z = 4$, $D_c = 1.280$ g cm^{-3}, $F(000) = 536$, μ(Mo-K_α) = 0.238 mm^{-1}. At 180 (2) K in the range of $2.34° < \theta < 25.25°$, 8705 reflections were measured, 2360 were unique ($R_{(int)} = 0.0307$). The final residuals were $wR_{2(all)} = 0.0546$, $R_{1(all)} = 0.0270$ and $R_{1(obs)} = 0.0238$. The maximum and minimum peaks in the final difference map were 0.157 and −0.128 e Å^{-3}, respectively.

Acknowledgements

We gratefully acknowledge financial support from the Deutscher Akademischer Austauschdienst (DAAD) and the Fonds der Chemischen Industrie. We thank Dr Burkhard Ziemer, Institut für Chemie, Humboldt-Universität Berlin for the X-ray crystal analysis.

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17 Full details have been deposited at the Cambridge Crystallographic Data Centre, CCDC reference number 207/427. See http://www.-rsc.org/suppdata/p1/b0/b001928n/ for crystallographic files in .cif format.