Stereochemical and conformational consequences of the oxidation of 1,4-thiazane-3,5-dicarboxylates

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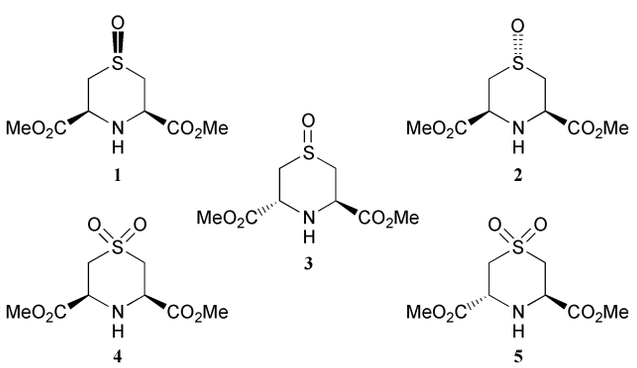
Received (in Cambridge, UK) 4th March 2002, Accepted 15th April 2002
First published as an Advance Article on the web 26th April 2002

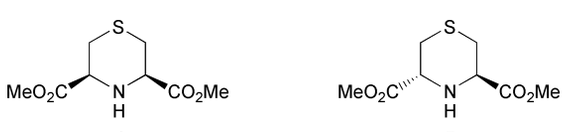
The stereoselectivity of the oxidation of 1,4-thiazane-3,5-dicarboxylate derivatives to the corresponding sulfoxides and sulfones was found to be dependent on the type of oxidant used and the conformational preference of the substrate. Direct oxidants, such as sodium periodate, peroxides and peracids, preferentially react with the axial sulfur lone-pair, providing the axial *S*-oxide. Oxidation with bromine–water yielded the epimeric equatorial *S*-oxide, presumably as a result of initial attack of the axial sulfur lone pair providing the axial bromosulfonium ion, with subsequent displacement of bromide by water leading to the equatorial *S*-oxide.

Introduction

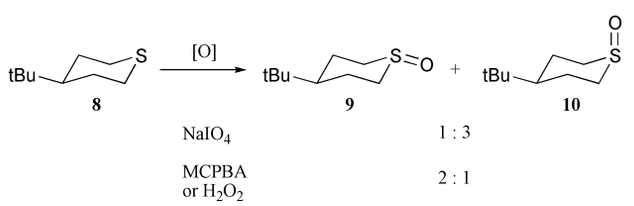
During the course of our investigations into the structure-based design of inhibitors of dihydrodipicolinate synthase (DHDPS)—the first committed enzyme in lysine biosynthesis—we required a stereoselective preparation of the 1,4-thiazane-1-oxide (1,4-thiazinane *S*-oxide, thiamorpholine *S*-oxide) derivatives **1**–**5**. Herein we report the results of our studies of the preparation of these sulfoxides **1**–**3** and related sulfones **4** and **5** by oxidation of the corresponding 1,4-thiazane (thiamorpholine) derivatives **6** and **7**.



The inherent symmetry of these substituted thiazanes, be it planar (**6**) or axial (**7**), renders asymmetric oxidant systems such as those of Kagan[1] and Uemura[2] of little use in their stereoselective oxidation. However, it was realised that adoption of a specific chair conformation would render the sulfur lone-pairs non-equivalent, such that preferential reactivity of either the axial or equatorial sulfur lone-pair would be a feasible approach to stereoselective oxidation.

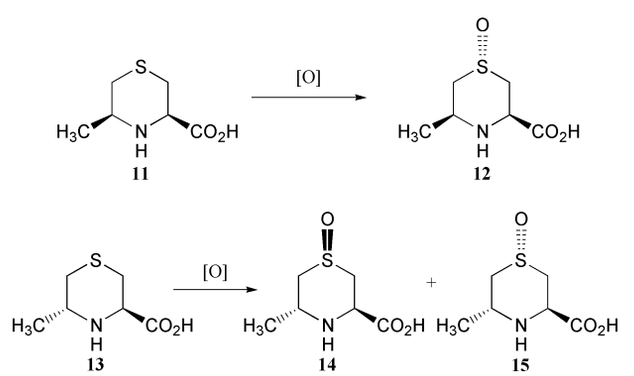


Numerous reports have described the stereoselective oxidation of 1,4-thiazane and thiane ring-systems. Johnson and McCants[3] have reported that selective oxidation of 4-substituted thianes can be achieved through use of an appropriate oxidant. Treatment of 4-*tert*-butylthiane **8** with sodium periodate gave predominantly the *cis*-sulfoxide **10** with the oxygen in the axial position (1 : 3 ratio of **9** : **10**), whereas treatment with MCPBA gave the equatorial sulfoxide **9** as the major product (2 : 1 ratio of **9** : **10**, Scheme 1). Studies of the



Scheme 1

more closely related cycloalliin systems by Carson *et al.*[4] showed that oxidation of the *cis*-substituted thiazane **11** gave cycloalliin **12** (*S*-oxygen occupying axial position) as the only product, regardless of the oxidant. In contrast, oxidation of the *trans*-substituted thiazane **13** proceeded with no selectivity to give a mixture of the sulfoxides **14** and **15**, with either periodate or hydrogen peroxide (Scheme 2). These results suggest that



Scheme 2

there are several subtle factors which control the stereoselectivity of oxidation of thiane and thiazane systems, not all of which are fully understood.

 DOI: 10.1039/b202231a

Table 1 Oxidation of (*R*,*R*)-thiazane **7**

Oxidant	% yield of **3**
$NaIO_4$	82
MCPBA	77
H_2O_2	78

Results and discussion

The *meso*- and (*R*,*R*)-thiazanes (**6** and **7**, respectively) were prepared according to the method of Paradisi *et al.*,[5] by treatment of L-cysteine methyl ester hydrochloride with 2,3-dibromopropionate in the presence of triethylamine. Separation of the diastereomers was accomplished efficiently by flash column chromatography, providing each of the diastereomers in 36% yield.

Oxidation of the (*R*,*R*)-thiazane 7

Initial investigations of the oxidation of the thiazanes **6** and **7** were conducted with the (*R*,*R*)-thiazane isomer **7**, as the C_2 axis of symmetry renders the sulfur centre non-chirotopic. Hence, only one sulfoxide stereoisomer is produced upon oxidation of **7**. Various oxidants were trialed, all of which provided the corresponding sulfoxide **3** in good yield (Table 1). Sodium periodate proved the oxidant of choice, giving the product **3** in 82% yield.

Although oxidation of thiazane **7** can yield only one sulfoxide stereoisomer, two non-equivalent chair conformations of **3** are possible (not accounting for configurational isomers at nitrogen, interconversion of which is very rapid and not observable on the NMR timescale). By adopting a chair conformation the molecule loses its symmetry, with one of the methoxycarbonyl substituents occupying an axial position and the other an equatorial position. The ring protons are therefore all in chemically distinct environments, as are the two *O*-methyl groups. The chair conformations differ in that one conformation has the sulfoxide oxygen in an axial position (**3a**), whereas the other conformation has the sulfoxide oxygen in an equatorial position (**3b**) (Fig. 1).

Fig. 1 Chair conformations of (*R*,*R*)-thiazane *S*-oxide **3**.

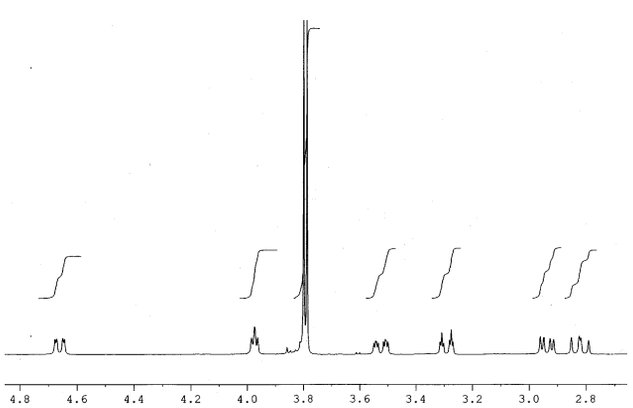


Fig. 2 ^{1}H NMR spectrum of (*R*,*R*)-thiazane *S*-oxide **3**.

The ^{1}H NMR spectrum of **3** (Fig. 2) does indeed exhibit six distinct resonances attributed to the ring protons, and the coupling constants are consistent with the adoption of a chair conformation. The doublet of doublets resonance at δ 2.82 exhibits large coupling constants (10.8 and 13.2 Hz), consistent with *trans*-diaxial and geminal couplings, whereas the nearby doublet of doublets resonance at δ 2.94 exhibits medium (5.2 Hz) and large (13.8 Hz) coupling constants, consistent with vicinal gauche and geminal couplings. The resonances at δ 3.29 and δ 3.53 both exhibit large (geminal) and medium (vicinal gauche) couplings, and interestingly also exhibit 4-bond coupling to each other, consistent with being in a relative "W"-orientation. These resonances are therefore attributed to the H_{2e} and H_{6e} protons.[6] The resonance at δ 3.98 exhibits small–medium couplings, consistent with the equatorial $H_{3/5}$ proton, and the resonance at δ 4.66 exhibits a *trans*-diaxial coupling of 10.8 Hz, consistent with the axial $H_{5/3}$ proton. These coupling constants suggest that only one of the chair conformations is adopted to any significant extent. If equilibration between the two conformers was occurring, averaging of the *trans*-diaxial and vicinal gauche couplings would be observed.

Analysis of the coupling constants, however, does not allow determination of which conformer exists in solution, as the geometry of the ring protons is essentially identical in each case. In order to confirm the conformational preference of the sulfoxide, we further analysed the ^{1}H NMR spectrum. It has been shown that the signal for the axial H_3-proton of thiane *S*-oxides bearing an axial sulfoxide oxygen occurs significantly downfield with respect to the corresponding signal of thiane *S*-oxides bearing an equatorial sulfoxide oxygen.[6,7] The significant downfield shift of the axial $H_{5/3}$ proton signal relative to that of the equatorial $H_{3/5}$ proton signal in the ^{1}H NMR spectrum of sulfoxide **3** ($\Delta\delta$ = 0.68 ppm) therefore suggests that **3** adopts the axial *S*-oxygen conformation (**3a**) in solution. The solid-state conformation of **3** was unambiguously determined by X-ray crystallography, which did indeed show that **3** exists in the axial *S*-oxygen conformation (Fig. 3).[8]

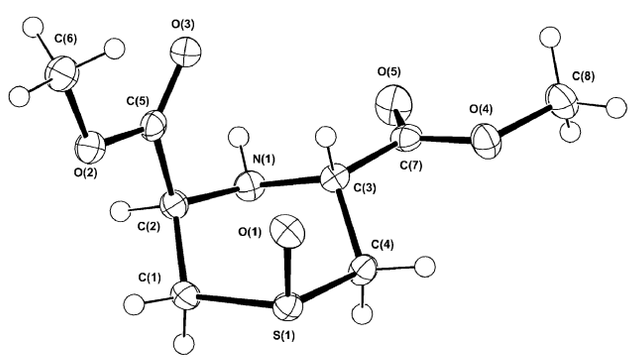


Fig. 3 X-ray structure of **3**.

This confirmation seemed unusual at first glance, and certainly goes against the accepted tenet of avoiding 1,3-diaxial interactions in six-membered ring-systems. While it has been well established that thiane *S*-oxides and related ring-systems containing an axial *S*-oxygen are generally more stable than the corresponding species with an equatorial *S*-oxygen,[9–12] studies by Lambert[12,13] and Webber[14] show that this preference is reversed when 3-axial substituents are present. For example, whereas 4,4-dimethylthiane-1-oxide exists predominantly as the axial *S*-oxide conformer, 3,3-dimethylthiane-1-oxide exists nearly exclusively as the equatorial *S*-oxide isomer.[13] The greater stability of axial *S*-oxides when no 3-axial substituent is present has been attributed to a combination of attractive van der Waals interactions between the oxygen and axial 3- and 5-protons and electrostatic/dipole interactions,[10,11] whereas the reversal of stability in the presence of 3-axial substituents is attributed to repulsive 1,3-diaxial interactions.

In order to ascertain a rationale for the apparent stability of the axial *S*-oxide conformation of **3** we performed computer modelling studies on the chair conformers of sulfoxide **3** using density functional theory (DFT) calculations utilising the Gaussian98 programs.[15] The equilibrium geometries and zero

Table 2 Relative equilibrium energies of conformers of **3**

Isomer	Relative energies[a]	Relative energies[b]
3a(NH_{eq})	0.0	0.0
3b(NH_{eq})	9.7	7.9
3a(NH_{ax})	13.5	12.7
3b(NH_{ax})	16.5	14.5

[a] Geometries and energies determined at B3LYP/6-31G(d) level of theory. [b] Geometries determined at B3LYP/6-31G(d), energies at B3LYP/cc-pVTZ level of theory.

point vibrational energies of the two conformers (which are equivalent in cyclohexane) were computed using the B3LYP hybrid functional in conjunction with the the 6-31G(d) basis set. The relative energies were recomputed at the B3LYP/cc-pVTZ level of theory (at the B3LYP/6-31G(d) geometries). The energetics are summarised in Table 2. In the gas phase the computations predict **3a**(NH_{eq}), with S–O axial and N–H equatorial, to be the most stable isomer, with its conformer **3b**(NH_{ax}) being the least stable. The best estimate for the energy difference is 14.5 kJ mol^{-1}. The stabilities of the other two possible isomers, with S–O and N–H either both axial or both equatorial, are predicted to be bracketed by those of **3a**(NH_{eq}) and **3b**(NH_{ax}).

A reasonable explanation for the difference in stabilities between conformers **3a**(NH_{eq}) and **3b**(NH_{ax}) is that attractive intra-molecular dipolar interactions may be expected to exist between the axial S–O and C–CO_2Me groups. This hypothesis was tested by computing the electrostatic interactions between the atomic charges of the S–O and C–CO_2Me moieties. The atomic charges were obtained by the Merz–Kollman method,[16] with calculations predicting an (attractive) interaction energy of −12.0 kJ mol^{-1} in **3a**(NH_{eq}), to be compared with a repulsion of 1.0 kJ mol^{-1} in **3b**(NH_{ax}). The total calculated energy difference is thus 13.0 kJ mol^{-1}, consistent with the quantum chemical values in Table 2. Accounting for facile inversion of configuration at nitrogen, the low-energy axial S–O isomer is still predicted to be 7.9 kJ mol^{-1} more stable than the low-energy equatorial S–O isomer.

The computed equilibrium geometry for **3a**(NH_{eq}) is in close agreement with the X-ray data. The difference between theory and experiment for the heavy atom distances is generally within ~0.002 Å, the largest difference being for the S–C distances where the computed bond lengths are ~0.05 Å longer than the X-ray values. The largest discrepancies in the bond angles are ~2°, which occur around the heavy atoms of the ring.

Further evidence for the attractive dipolar interaction between the *S*-oxygen and carbonyl carbon is provided by analysis of the solid-state structure of **3**, which indicates that the carbonyl carbon atom of the axial C–CO_2Me group deviates from the plane of its three attached substituents by 0.032 Å towards the transannular axial sulfoxide oxygen. The distance between the axial oxygen and the carbonyl carbon is 3.068 Å, which is slightly shorter than the sum of the van der Waals radii for O and C (3.15–3.2 Å).[17] Dipole–dipole or donor–acceptor interactions of this type have been observed by Dunitz *et al.*,[18] together with a corresponding deviation of the carbonyl carbon from a planar arrangement, and are believed to represent the initial stages of the reaction pathway of an attack at the carbonyl group by the nearby nucleophile.

Oxidation of the *meso*-thiazane 6

Having prepared the sulfoxide **3** from (*R*,*R*)-thiazane **7** in good yield, attention was turned to the oxidation of the *meso*-thiazane **6** to the corresponding sulfoxides **1** and **2**. In contrast to the oxidation of (*R*,*R*)-thiazane **7**, oxidation of *meso*-thiazane **6** leads to two diastereomeric sulfoxide products. The sulfur of the *meso*-thiazane **6** is a non-chirotopic centre, as it lies on a plane of symmetry. However, the *syn*- and *anti*-sulfoxides **1** and **2** generated from the *meso*-thiazane **6** are clearly diastereomeric, indicating the sulfur atoms of **1** and **2** are *pseudo-asymmetric* centres.[19]

Table 3 Oxidation of *meso*-thiazane **6**

Oxidant	Temperature/°C	Ratio **1** : **2**	Yield (**1** + **2**)
H_2O_2	25	1 : 2	88
MCPBA	25	1 : 2	98
MCPBA	−15	1 : 3	99
$NaIO_4$	25	1 : 5	80
Br_2–H_2O	25	10 : 1	61

Oxidation of *meso*-thiazane **6** was conducted with various oxidants as shown in Table 3. Treatment of **6** with MCPBA at ambient temperature gave the *syn*- and *anti*-sulfoxides **1** and **2** in a 1 : 2 ratio in 98% overall yield. Repeating the reaction at −15 °C improved the selectivity to 1 : 3. Oxidation of **6** using sodium periodate produced a 1 : 5 mixture of the *syn*- and *anti*-sulfoxides **1** and **2** in 80% yield. Diastereomeric ratios were determined by integration of the signals corresponding to the $H_{2/6}$ protons in the ^{1}H NMR spectrum of the crude product (Fig. 4).

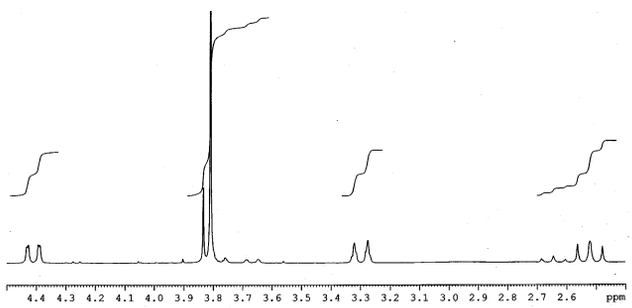


Fig. 4 ^{1}H NMR spectrum of mixture of sulfoxides **1** and **2**.

Assignment of the signals corresponding to each of the diastereomers was based on the report of Lambert *et al.*,[12] which showed that the $H_{2/6}$ proton signals from thiane *S*-oxide isomers bearing an equatorial oxygen always have a lower field centrepoint and a larger chemical shift difference than the corresponding signals of the isomers bearing an axial oxygen. The major sulfoxide isomer exhibits resonances at δ 3.30 and δ 2.52 attributed to H_{2e} and H_{2a}, respectively (ave. = δ 2.91, $\Delta\delta$ = 0.78), whereas the minor isomer exhibits the corresponding resonances at δ 3.78 and 2.65 (ave. = 3.22, $\Delta\delta$ = 1.13). The minor isomer therefore exhibits the lower field centrepoint and larger chemical shift difference for the C2 protons, indicating it is the *syn*-isomer with an equatorial *S*-oxygen. Further evidence is provided through the observation that the H_3 signal for the major isomer (δ 4.41) is significantly downfield of that of the minor isomer (δ 3.67), indicative of the major isomer possessing an axial *S*-oxygen, as described earlier. Note that assignment of the signals at δ 3.78 and 3.67, corresponding to the $H_{2/6e}$ and $H_{3/5}$ protons of **1**, was based on the observed coupling of the upfield resonance to the NH resonance in the spectrum of the purified sulfoxide.

Both peracid and periodate oxidants therefore produce the *anti*-sulfoxide **2** (with an axial *S*-oxygen) selectively, in general agreement with the results observed by Carson *et al.*[4] in the selective oxidation of **11** to **12** (Scheme 2). The greater selectivity for the axial sulfoxide observed upon oxidation with periodate, with respect to the use of MCPBA as the oxidant, is also in general agreement with the observations of Johnson and McCants[3] shown in Scheme 1.

Recrystallisation of the sulfoxide mixture provided a pure sample of the *anti*-sulfoxide **2**, which was analysed by X-ray crystallography to confirm its stereochemistry (Fig. 5).[20]

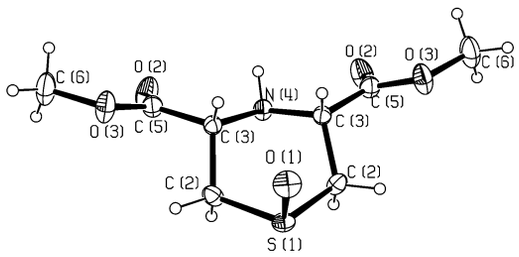
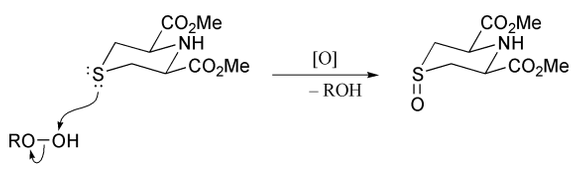


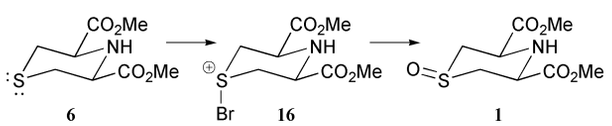
Fig. 5 X-ray structure of *anti*-sulfoxide **2**.

The use of hydrogen peroxide also gave a predominance of the *anti*-sulfoxide isomer (Table 3). It seemed plausible, given that these oxidants operate through a direct mechanism in which the sulfur attacks the electrophilic oxygen,[21] that the selectivity of these reactions is governed by a preferential attack of the axial sulfur lone pair (Scheme 3). If this is indeed the case,



Scheme 3 One-step oxidation of **6** to give axial sulfoxide **2**.

we surmised that a stepwise mechanism, in which initial attack of the sulfur onto an appropriate electrophile, followed by attack (with inversion) at the sulfur by an oxygen nucleophile (Scheme 4), would reverse the observed stereoselectivity and allow for preparation of the *syn*-sulfoxide **1**.



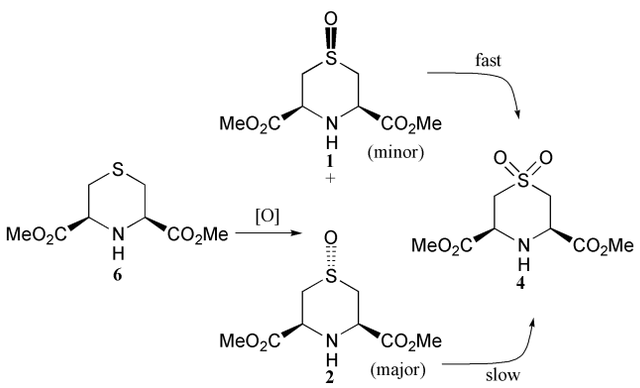
Scheme 4 Proposed aqueous bromine oxidation of **6** to give **1**.

The oxidation of sulfides to sulfoxides with *tert*-butyl hypochlorite or wet bromine has been investigated, and evidence suggests these reactions proceed *via* a stepwise process through the corresponding halosulfonium intermediates,[22] although Klein and Stollar[23] have proposed that the oxidation with wet bromine may occur by a one-step mechanism through attack of the sulfur at the oxygen atom of hypobromous acid.

Treatment of thiazane **6** in dichloromethane with water and a solution of bromine in CCl_4 provided the *syn*-sulfoxide **1** in moderate to high selectivity. This reaction was found to be somewhat capricious, with quite variable yields (20–61%) and slight variation in selectivity (5–10 : 1). In all cases, however, good selectivity for the *syn*-isomer **1** was observed. These results indicate that the bromine–water oxidation system operates through a different mechanism to the direct oxidants, suggesting that initial attack of the axial sulfur lone pair toward molecular bromine, generating the corresponding bromosulfonium intermediate **16** is then followed by displacement of the bromide with water to ultimately provide the *syn*-sulfoxide **1** (Scheme 4). Attempts to oxidise the sulfide with freshly distilled hypobromous acid according to the method of Klein and Stollar[23] were unsuccessful, with decomposition of the starting material being observed. Hence, conversion of **6** to **1** *via* direct oxidation with hypobromous acid cannot be rigorously excluded, though the evidence is in favour of a two-step oxidation *via* the corresponding bromosulfonium ion **16**. Although we have been unable to determine the reasons for the capricious nature of the bromine–water oxidation, we believe that decomposition of the bromosulfonium ion **16**[22] may lead to the complex mixtures occasionally observed.

Preparation of sulfones 4 and 5

Oxidation of the sulfides **6** and **7** to the corresponding sulfones **4** and **5** was also investigated. It was observed that treatment of the sulfides with excess periodate or MCPBA failed to provide good yields of the corresponding sulfones. Treatment of *meso*-compound **6** with excess sodium periodate for 48 hours gave only a small amount of the sulfone **4**, with the major product being the *anti*-sulfoxide **2** (60%). This result is explained by a kinetic resolution of the sulfoxides **1** and **2**; oxidation of the minor *syn*-sulfoxide **1** to the sulfone **4** occurs much faster than oxidation of the *anti*-sulfoxide **2**, providing a mixture consisting of a minor amount of sulfone **4** together with the *anti*-sulfoxide **2** as the major product (Scheme 5). The faster oxidation of **1** to



Scheme 5

4, compared to the oxidation of **2** to **4**, is consistent with the reasoning explained above for the stereoselective oxidation of **6**; the *syn*-sulfoxide **1** possesses an axial sulfur lone-pair, which is more reactive toward the oxidant than the equatorial lone-pair of the *anti*-sulfoxide **2**, such that the minor sulfoxide **1** is oxidised more quickly to the sulfone **4**. This observation actually allows for an expedient preparation of pure *anti*-sulfoxide **2**, as it is easily separated from the sulfone **4** by column chromatography.

While use of excess oxidant did not provide the sulfone **4** in good yield, an efficient preparation of the *meso*-sulfone **4** was found through the addition of a Lewis acid catalyst to the reaction mixture. Accordingly, treatment of the sulfide **6** with two equivalents of hydrogen peroxide and one equivalent of $Ti(OiPr)_4$ provided the sulfone **4** in excellent (92%) yield. Similarly, treatment of the (*R*,*R*)-thiazane **7** with hydrogen peroxide in the presence of $Ti(OiPr)_4$ provided the (*R*,*R*)-sulfone **5** in 92% yield.

Analysis of compounds **1**–**5** as inhibitors of dihydrodipicolinate synthase will be reported in due course.

Conclusion

We have achieved the stereoselective preparations of both the *syn*- and *anti*-thiazane *S*-oxides **1** and **2**, respectively, through the choice of an appropriate oxidant. We have demonstrated that, in this system at least, the axial sulfur lone-pair of thiazane derivatives **6** and **7** reacts with an oxidant preferentially, allowing for the selective formation of axial thiazane *S*-oxides with direct oxidants such as periodate, MCPBA or hydrogen peroxide. In contrast, oxidation with bromine–water provides the equatorial thiazane *S*-oxide isomer selectively, consistent with a two-step oxidation mechanism *via* the corresponding bromosulfonium ion intermediate.

We have shown that axial thiazane *S*-oxides with *syn*-3-carbonyl substituents are stabilised by electrostatic interactions between the *S*-oxygen and carbonyl-carbon atoms, and are therefore more stable than the corresponding equatorial *S*-oxide isomers.

In all cases, analysis of the products by ^{1}H NMR spectroscopy allows the unambiguous determination of the conformational and stereochemical properties of these molecules.

Experimental

Melting points were determined using a Reichert heating stage and are uncorrected. Infrared absorption spectra were obtained using a Perkin Elmer 1600 series FTIR spectrometer as a thin film between sodium chloride plates. ^{1}H Nuclear magnetic resonance spectra were recorded using a Bruker AC 200B, Bruker Avance DPX 300 or a Bruker AMX 400 spectrometer and are reported as parts per million (ppm) downfield shift from tetramethylsilane as internal reference. The ^{1}H NMR data are reported as chemical shift (δ_H), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, app = apparent), coupling constant (J Hz) and assignment. ^{13}C Nuclear magnetic resonance spectra were recorded using a Bruker AC 200B or Bruker AMX 400 spectrometer. The ^{13}C NMR data are expressed as parts per million downfield shift (δ_C) from tetramethylsilane as internal reference. Low resolution mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact ionisation mode at 40 or 70 eV. High resolution mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Single crystal X-ray diffraction data for **2** were collected using an Enraf Nonius CAD4 diffractometer, and a Bruker SMART 1000 CCD diffractometer equipped with an Oxford Cryosystems Cryostream was used for **3**.† Analytical thin layer chromatography was performed using precoated silica gel plates (Merck Kieselgel 60 F254). Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Solvent compositions are mixed v/v as specified. Preparative HPLC was carried out using a Waters 600 multisolvent delivery pump, Waters 712 WISP (Waters Intelligent Sample Processor), UV200 Spectra Physics absorbance monitor (λ 210 nm). The column used was a Beckmann/Altex Ultrasphere ODS 5μ (250 mm × 10 mm id). Solvents and reagents were purified according to the methods of Perrin and Armarego.[24]

c-3,*c*-5-Bis(methoxycarbonyl)-1,4-thiazane-*r*-1-oxide[25] 1

To a solution of *meso*-thiazane **6**[5] (31 mg, 0.141 mmol) in dichloromethane (1 ml) was added a solution of $NaHCO_3$ (12 mg, 0.141 mmol) in water (1 ml). Bromine in CCl_4 (0.28 M) (510 μl, 0.141 mmol) was added dropwise and the mixture stirred at room temperature for 30 min. The mixture was diluted with $NaHCO_3$ (10 ml) and extracted into CH_2Cl_2 (4 × 10 ml) and dried ($MgSO_4$). The combined organic layers were concentrated *in vacuo* to give a 10 : 1 mixture of the sulfoxides **1** and **2** as a yellow oil in 61% yield. The *syn*-sulfoxide **1** was purified by preparative HPLC using a C_{18} reverse-phase column (5μ, 250 × 10 mm id) eluting with 96 : 4 acetonitrile : water at a flow rate of 2 ml min^{-1}. Fractions containing the *syn*-sulfoxide **1** (retention time 24 min) were collected and freeze-dried to give a white solid, mp 70–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 3.84 (6H, s, OCH_3), 3.78 (2H, br d, J = 11.9 Hz, 2- and 6-H_{eq}), 3.67 (2H, br dd, J = 3.6, 12.1 Hz, 3- and 5-H), 2.75 (1H, br t, J = 3.6 Hz, NH), 2.65 (2H, app t, J = 12.0 Hz, 2- and 6-H_{ax}); ^{13}C NMR (50 MHz, $CDCl_3$) 169.9, 54.8, 53.7, 53.2; IR ν_{max} (NaCl)/cm^{-1} 2915, 1741, 1222, 1044.

t-3,*t*-5-Bis(methoxycarbonyl)-1,4-thiazane-*r*-1-oxide[25] 2

To a solution of *meso*-thiazane **6**[5] (203 mg, 0.926 mmol) in methanol (2 ml) was added a solution of sodium periodate (198 mg, 0.926 mmol) in water (1 ml). The resulting mixture was left to stir at room temperature overnight. The reaction mixture was diluted with water (10 ml) and the product extracted into CH_2Cl_2 (4 × 10 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a 1 : 5 mixture of the *syn*-sulfoxide **1** and *anti*-sulfoxide **2** as a yellow oil (174 mg, 80%). The *anti*-sulfoxide **2** was purified by preparative HPLC using a C_{18} reverse-phase column (5μ, 250 × 10 mm id) eluting with 96 : 4 acetonitrile : water at a flow rate of 2 ml min^{-1}. Fractions containing the *anti*-sulfoxide **2** (retention time 21 min) were collected and freeze-dried to give an off-white solid, mp 95–96 °C; Found C 41.2, H 5.6, N 5.9, $C_8H_{13}NO_5S$ requires C 40.8, H 5.6, N 6.0%; ^{1}H NMR (300 MHz, $CDCl_3$) 4.41 (2H, br d, J = 11.7 Hz, 3- and 5-H), 3.81 (6H, s, OCH_3), 3.30 (2H, d, J = 13.6 Hz, 2- and 6-H_{eq}), 2.95 (1H, br s, NH), 2.52 (2H, dd, J = 11.7, 13.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 171.9, 49.5, 48.9, 46.9; IR ν_{max} (NaCl)/cm^{-1} 3307, 1738, 1229, 1044; MS *m*/*z* (EI) 235 ($M^{+\bullet}$, 100%), 176 (M − CO_2Me, 62%).

(3*R*,5*R*)-3,5-Bis(methoxycarbonyl)-1,4-thiazane-1-oxide 3

To a solution of (*R*,*R*)-thiazane **7**[5] (46 mg, 210 μmol) in methanol (0.5 ml) was added a solution of sodium periodate (45 mg, 210 μmol) in water (0.5 ml), which resulted in an exothermic reaction and immediate precipitation of a white solid. The reaction was left to stand for 48 h. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (9 × 10 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the sulfoxide **3** as a white solid. Purification by column chromatography eluting with ethyl acetate afforded sulfoxide **3** as a white crystalline solid (40 mg, 82%), mp 149–151 °C; Found C 40.7, H 5.6, N 6.0, $C_8H_{13}NO_5S$ requires C 40.8, H 5.6, N 6.0%; ^{1}H NMR (400 MHz, $CDCl_3$) 4.66 (1H, dd, J = 2.4, 10.8 Hz, 5-H_{ax}), 3.98 (1H, dd, J = 3.8, 5.2 Hz, 3-H_{eq}), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.53 (1H, ddd, J = 2.4, 3.8, 13.8 Hz, 2-H_{eq}), 3.29 (1H, dt, J = 13.4, 2.4 Hz, 6-H_{eq}), 2.94 (1H, dd, J = 5.2, 13.8 Hz, 2-H_{ax}), 2.82 (1H, dd, J = 10.8, 13.4 Hz, 6-H_{ax}); ^{13}C NMR (100 MHz, $CDCl_3$) 172.4, 172.0, 53.5, 53.3, 50.8, 47.7, 46.1, 30.4; IR ν_{max} (NaCl)/cm^{-1} 3347, 1728, 1232, 1031; MS *m*/*z* (EI) 235 ($M^{+\bullet}$, 73%), 176 (M − CO_2Me, 100%).

meso-3,5-Bis(methoxycarbonyl)-1,4-thiazane-1,1-dioxide 4

To a stirred solution of *meso*-thiazane **6** (55 mg, 0.251 mmol) in dichloromethane (0.5 ml) was added titanium isopropoxide (74 μl, 0.251 mmol) and the mixture cooled to 0 °C. Hydrogen peroxide (69 μl, 0.502 mmol) was added and the resulting mixture was left to stand at −15 °C for 16 h. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (4 × 10 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the sulfone **4** (58 mg, 92%) as a white solid, mp 117–119 °C; Found C 38.4, H 5.3, N 5.6, $C_8H_{13}NO_6S$ requires C 38.2, H 5.2, N 5.6%; ^{1}H NMR (100 MHz, $CDCl_3$) 3.95 (2H, br d, J = 11.7 Hz, 3- and 5-H), 3.82 (6H, s, OCH_3), 3.55 (2H, br d, J = 13.3 Hz, 2- and 6-H_{eq}), 3.10 (1H, br s, NH), 2.97 (2H, app t, J = 12.5 Hz, 2- and 6-H_{ax}); ^{13}C NMR (200 MHz, $CDCl_3$) 169.3, 56.1, 54.1, 53.6; IR ν_{max} (NaCl)/cm^{-1} 3332, 1746, 1308, 1231, 1130; MS *m*/*z* (EI) 252 (M + H, 18%), 192 (M − CO_2Me, 100%), 132 (C_4H_6SNO, 86%).

(3*R*,5*R*)-3,5-Bis(methoxycarbonyl)-1,4-thiazane-1,1-dioxide 5

To a stirred solution of (*R*,*R*)-thiazane **7** (524 mg, 2.39 mmol) in dichloromethane (5 ml) was added titanium isopropoxide (705 μl, 2.39 mmol) and the mixture was cooled to 0 °C. Hydrogen peroxide (822 μl, 5.98 mmol) was added and the resulting mixture was left to stand at −15 °C overnight. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (4 × 10 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the sulfone **5** (444 mg, 92%) as a white solid, mp 104–105 °C; Found C 38.2,

† CCDC reference numbers 180846–180847. See http://www.rsc.org/suppdata/p2/b2/b202231a/ for crystallographic files in .cif or other electronic format.

H 5.2, N 5.4, $C_8H_{13}NO_6S$ requires C 38.2, H 5.2, N 5.6%; ^{1}H NMR (400 MHz, $CDCl_3$) 4.29 (2H, app t, J = 5.9, 3- and 5-H), 3.77 (6H, s, OCH_3), 3.34 (4H, d, J = 5.7 Hz, 2- and 6-H), 3.10 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) 169.9, 53.4, 52.8, 52.4; IR ν_{max} (NaCl)/cm^{-1} 3352, 1742, 1323, 1245, 1126; MS m/z (EI) 252 (M + H, 25%), 192 (M − CO_2Me, 100%), 132 (C_4H_6SNO, 84%).

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