Chemoenzymatic methods in the asymmetric synthesis of α-diazosulfoxides

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Dedicated to Professor M. Anthony McKervey on his 65th birthday

(received 18 Feb 03; accepted 22 Apr 03; published on the web 01 May 03)

Abstract

Asymmetric synthesis of the sulfide lactones **12** and **13** in excellent enantiopurity is achieved by reduction of cyclohexanone derivative **10** using baker's yeast, followed by acid catalysed cyclisation. The outcome of the yeast reduction is very sensitive to the reaction conditions employed. Transformation of **12** to the α-diazosulfoxide **4** (≥98%ee) and rhodium acetate catalysed decomposition of this are also described.

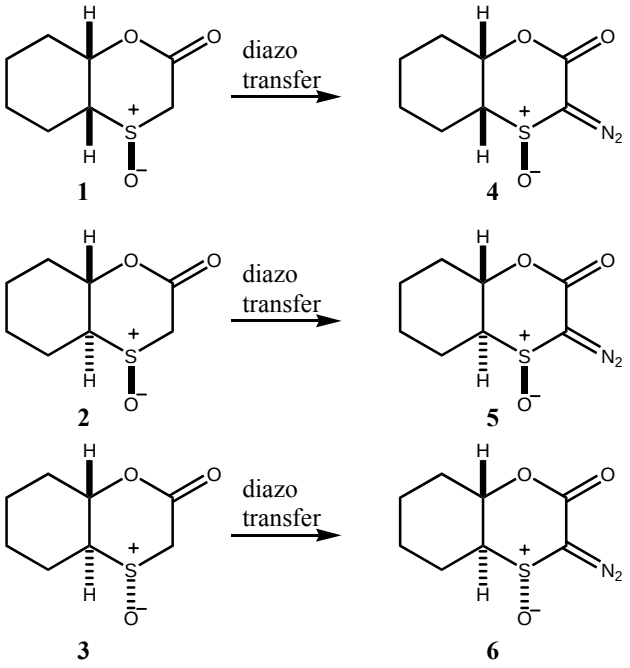
Keywords: Baker's yeast, dynamic kinetic resolution, α-diazosulfoxides

Introduction

While diazo groups are readily introduced to active methylene positions in β-dicarbonyl compounds, β-keto sulfones, β-keto phosphonates *etc.*,[1] introduction of a diazo group adjacent to a sulfoxide is generally unsuccessful due to the inherent instability of the α-diazosulfoxide moiety.[2] As α-diazosulfoxides are envisaged to have significant potential in stereoselective synthesis, we decided to investigate the reason for this instability with the objective of designing and synthesising stable α-diazosulfoxide derivatives. We found that by constraining the conformational mobility of the sulfoxide precursors for example in the bicyclic lactones **1-3**, diazo transfer to form stable isolable α-diazosulfoxides **4-6** is possible (Scheme 1).[3]

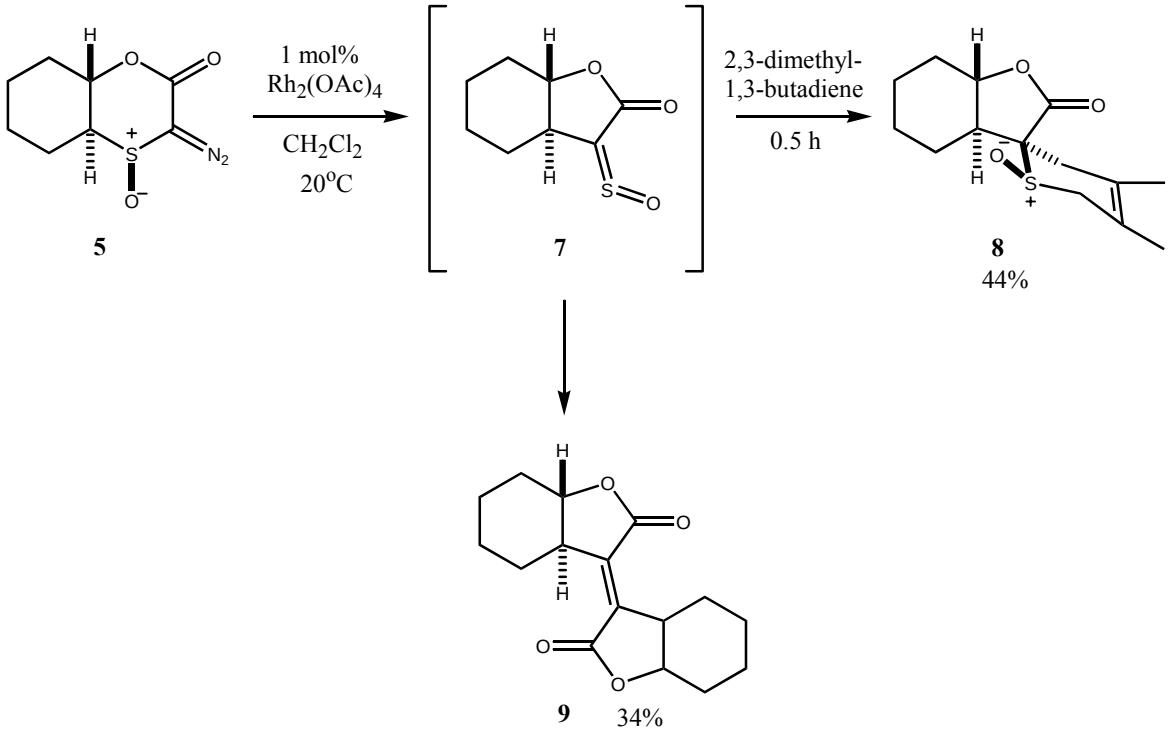
Furthermore, rhodium catalysed decomposition of these derivatives offers a novel synthetic route to α-oxo sulfine intermediates which undergo dimerisation to form sterically hindered alkenes, or can be trapped as cycloadducts with dienes as illustrated in Scheme 2 for α-diazosulfoxide **5**.[4] Direct evidence for the formation of the key α-oxo sulfine intermediate was secured by photolysis in an argon matrix.[5] This novel route to α-oxo sulfines and the resulting sterically hindered dimeric alkenes or the cycloadducts offers considerable synthetic potential;

accordingly we wished to extend this work to the enantiomerically enriched series of α−diazosulfoxides to allow access to the products of rhodium catalysed decomposition in enantioenriched form.



1 4 2 5 3 6

Scheme 1

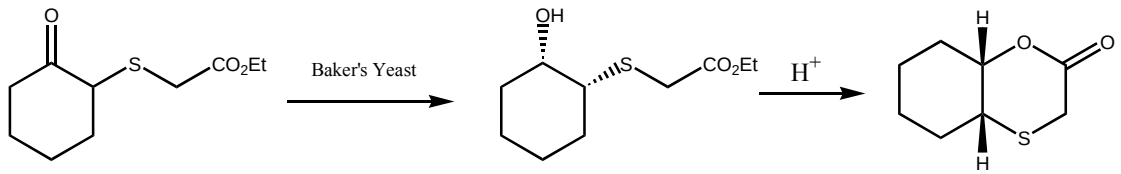


5 7 8 44%

9 34%

Scheme 2

Based on our experience in baker's yeast[6] (*Saccharomyces cerevisiae*) mediated reduction of cycloalkanones bearing sulfur substituents at the α-position,[7] we envisaged that this methodology could be employed for the asymmetric synthesis of the lactone precursors. We have recently demonstrated that efficient dynamic kinetic resolution of 2-benzenesulfonylcyclopentanones and -cyclohexanones can be achieved using baker's yeast,[8] while Fujisawa and co-workers have reported that analogous 2-phenylthiocycloalkanones also undergo dynamic kinetic resolution on treatment with baker's yeast.[9] Therefore, we envisaged that yeast mediated reduction of the α-thio cyclohexanone **10**, followed by ring closure of the resulting hydroxy ester **11** should lead to the lactone **12** (Scheme 3). Prior to this work, Vankar and co-workers had reported that baker's yeast mediated reduction of **10** leads to the *trans*-fused lactone **13** in low yield (~16%),[10] but did not furnish details of the enantiopurity or the absolute stereochemistry of the isolated lactone. Based on our experience, we envisaged the *cis*-fused product should predominate and therefore found this report rather surprising. In this paper we report the asymmetric synthesis of the lactones **12** and **13** using this approach and transformation of **12** to the diazosulfoxide **4** in excellent enantiomeric purity.



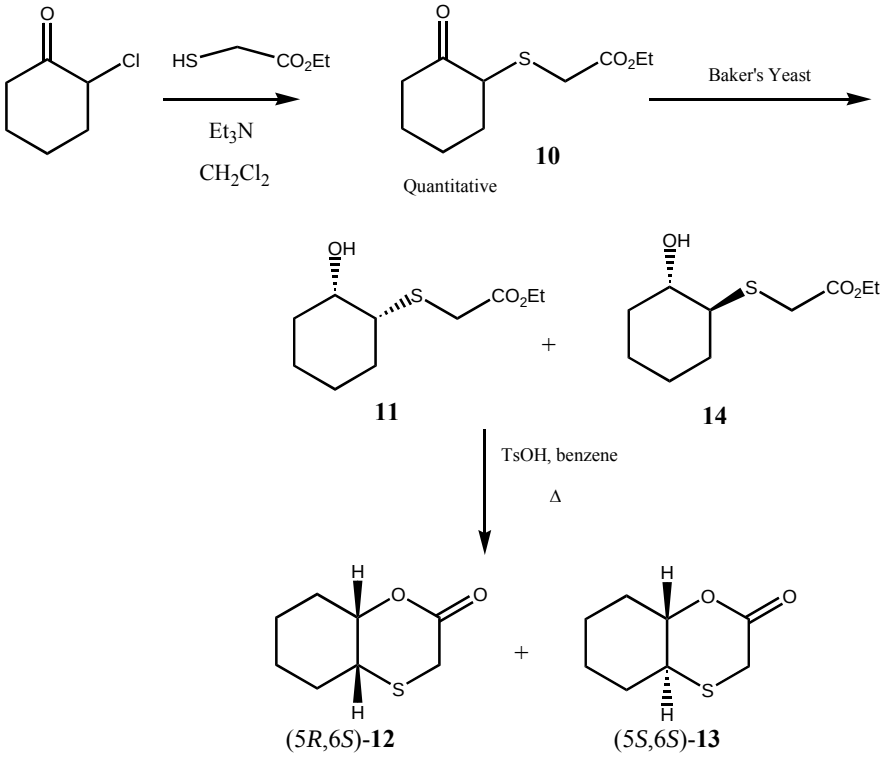
10 **11** **12**

Scheme 3

Results and Discussion

The α-thio cyclohexanone **10** required for investigation of the baker's yeast reduction was readily synthesised from commercially available 2-chlorocyclohexanone as outlined in Scheme 4. Investigation of the reduction of this compound with baker's yeast was explored under a variety of conditions as illustrated in Table 1. As we have observed in our earlier work[7,8] the outcome of the reduction, in terms of efficiency and stereoselectivity, is very sensitive to variation of the reduction conditions.[11] On a small scale, analysis of the hydroxy esters **11** and **14** is complicated by spontaneous partial cyclisation; therefore it is convenient to cyclise these directly by warming in the presence of *p*-toluenesulfonic acid (tosic acid). For larger scale reactions cyclisation *in situ* proves not to be reproducible; extensive work showed that the cyclisation is best carried out precisely as described by Vankar.[10] Heating with tosic acid for longer than 15 minutes leads to extensive decomposition of the lactones **12** and **13**.

Determination of the efficiency of the reduction, the diastereoselectivity, and the enantiomeric purity of each of **12** and **13** is very straightforward using NMR and HPLC analysis. Assignment of the diastereomers by ^{1}H NMR is straightforward, while the absolute stereochemistry of (5*R*, 6*S*)-**12** and (5*S*, 6*S*)-**13** is assigned on the basis of the well established literature precedent for the enantioselectivity of baker's yeast in the reduction of sulfur substituted ketones.[6-8]



Scheme 4

As can be seen from Table 1 mixtures of the *cis* and *trans* fused lactones **12** and **13** were isolated from each of the yeast reductions, indicating that both hydroxy esters **11** and **14** were formed in the reactions.[12] However, the ratio of the products varied considerably indicating that the diastereoselectivity of the yeast reduction is very sensitive to the reaction conditions. Apparently, different yeast alcohol dehydrogenases catalyse the reduction of 2*R*-**10** to form **11** and 2*S*-**10** to form **14** and the relative activity of these enzymes is readily influenced by the reaction conditions. Significantly, in our earlier work[8] on the yeast mediated reduction of 2-benzenesulfonylcyclohexanone only the *cis* isomer of 2-benzenesulfonylcyclohexanol was isolated with excellent enantiopurity. In this work the dynamic kinetic resolution is less efficient, leading to both the *cis* and *trans* substituted products **11** and **14**. Similarly, Fujisawa[9] reported a ~9:1 ratio of *cis* and *trans* isomers of 2-phenylthiocyclohexanol from the yeast mediated reduction of 2-phenylthiocyclohexanone. Thus, while dynamic kinetic resolution of 2-thiocycloalkanones is possible, it is less diastereoselective than the process with

2-sulfonylcycloalkanones. This may be due to the decreased acidity of the α-hydrogen in the sulfide derivatives compared to the sulfonyl substituted cyclohexanone, which could result in less efficient interconversion of the enantiomers, or it may reflect decreased steric demands of the sulfide substituent relative to the sulfone.

Table 1. Baker's yeast reduction of **10**

Entry	Conditions[a]	Conversion	Isolated yield[b]	Composition of product %**12** (ee)	%**13** (ee)
1	procedure A	100%	26%	78% (≥ 98%)	22% (≥ 98%)
2	procedure B	100%	57%	59% (≥ 98%)	41% (66%)
3	procedure C	0	—		
4	procedure D	0	—		
5	procedure A, inhibited with allyl alcohol	100%	19%	77% (97%)	23% (≥98%)
6	procedure A, inhibited with methyl vinyl ketone	100%	multiple products		
7	procedure A, inhibited with ethyl chloroacetate	100%	multiple products		
8	procedure A, inhibited with ethyl bromoacetate	100%	multiple products		
9	procedure B, inhibited with allyl alcohol	0%	—		
10	procedure A, higher substrate concentration, 24 h	20%	n.d.	87% (≥98%)	13% (≥98%)
11	procedure A, full scale-up	100%	12%	78% (≥ 98%)	22% (≥ 98%)
12	procedure B scale-up	100%	25%	47% (≥98%) 4%[c] (≥98%)	53% (76%)
13	procedure B with modified workup	100%	45%[d]	32%[e] (≥98%)	10%[f] (≥98%)

[a] see experimental for details of procedures.

[b] isolated yield as a mixture of diastereomers. Composition of product and ee's determined by HPLC; where ≥ 98% ee is quoted only one enantiomer was detected.

[c] isolated yield of pure **12.**

[d] isolated yield of pure hydroxy esters **11** and **14.**

[e] isolated yield of pure **12** based on the hydroxy esters.

[f] isolated yield of pure **13** based on the hydroxy esters.

Our first experiment followed a modification of a procedure described by Ridley and co-workers[13] using a very high concentration of yeast (Table 1, procedure A, entry 1). While total

consumption of the starting material **10** was observed, isolation of the products from this yeast medium is difficult, resulting in low yields of the hydroxy esters **11** and **14** and the resulting lactones **12** and **13**. Both lactones displayed excellent enantiomeric purity with only a single enantiomer of each detected by chiral HPLC. As we expected, the *cis* fused lactone **12** predominates (78%). Due to the difficulties in isolation of the products from the concentrated yeast medium, reduction under more dilute conditions following a modification of the procedure described by Seebach[14] was next attempted (Table 1, entry 2, procedure B). Isolation of the products is easier from the less concentrated medium, resulting in higher yields. However, the diastereoselectivity decreased (59:41 ratio of **12** and **13**) and, while **12** is still isolated in enantiopure form, the enantiopurity of the *trans* fused lactone **13** is significantly reduced. Use of immobilised baker's yeast in hexane[11,15] and free baker's yeast in ether[16] (Table 1, entries 3 and 4, procedures C and D respectively) were also explored as both of these conditions result in facile product isolation. However, in these reactions only unreacted starting material was recovered.

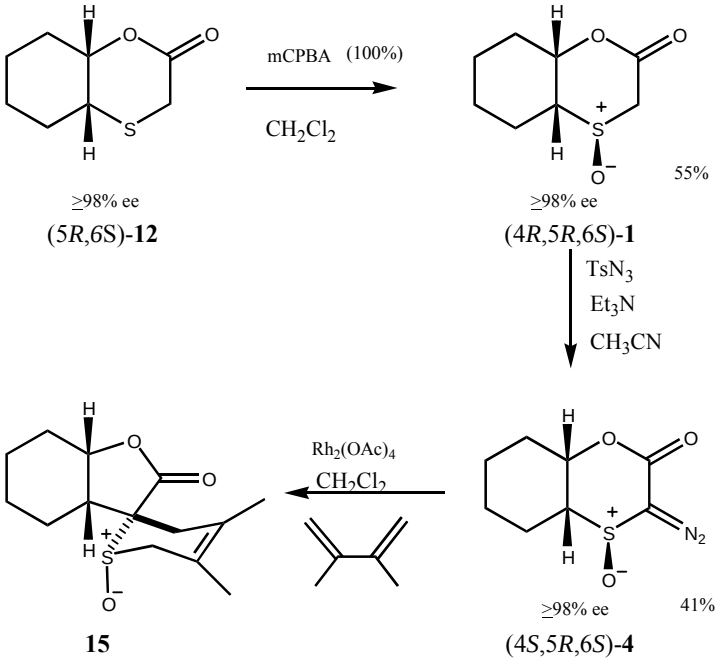
In order to investigate if the diastereoselectivity of the yeast reduction could be improved, use of inhibitors such as allyl alcohol, methyl vinyl ketone, ethyl chloroacetate and ethyl bromoacetate with procedure A was explored (Table 1, entries 5-8).[11] The reactions in the presence of methyl vinyl ketone, ethyl chloroacetate and ethyl bromoacetate result in complex mixtures of unidentifiable products, while use of allyl alcohol has little effect on the outcome of the reaction with the stereoselection essentially unchanged. The decrease in yield from 26% to 19% is not significant as isolation from the concentrated yeast medium is very difficult. Use of allyl alcohol as an inhibitor under the more dilute conditions (Table 1, entry 9) was also investigated but in this case no reduction is observed.

At this stage it was clear that isolation of the *cis* fused lactone **12** in excellent enantiopurity is best achieved using the more dilute conditions of Procedure B. However, to obtain the *trans* fused lactone **13** with high enantiopurity it seemed necessary to use the more concentrated conditions associated with Procedure A, although this has the disadvantage of difficult product isolation from the biomass. Later experiments (Table 1, entry 13) have indicated that Procedure B can lead to **13** with ≥98 %ee (after purification) when conducted on a larger scale as discussed below. In an attempt to improve the efficiency of Procedure A this biotransformation was repeated using a higher substrate concentration (Table 1, entry 10, 500 mg of **10** compared to 100 mg in entry 1). After 24h of reaction just 20 % conversion was observed. However, the diastereoselectivity of the reduction had improved significantly, presumably associated with the low conversion. Critically the enantioselectivity was unchanged.

Scale-up to synthetically useful reactions was next undertaken. When Procedure A was scaled up to 1g of **10**, the stereochemical outcome of the reaction was identical to the small scale reaction (Table 1, entry 11 cf. entry 1) but the recovery decreased due to practical difficulties with product isolation from the biomass. When the more dilute procedure B was scaled up to 1g of **10** (Table 1, entry 12, this was conducted in 5 flasks each containing 200 mg and combined for work-up), recovery decreased to 25 % and interestingly the diastereoselectivity of the

reaction changed with the *trans* fused lactone **13** predominating in the product in this instance (Table 1, entry 12 cf. entry 2). However, the overall alteration in product ratio of **12:13** from 59:41 to 47:53 is relatively small, and is indicative of the sensitivity of the biotransformation to minor variation in the reaction conditions; the enantioselectivity of the process was essentially unaltered. While the diastereomeric lactones **12** and **13** behave very similarly on silica gel, repeated careful chromatography allowed isolation of a pure sample of the enantiomerically pure lactone **12** in 4% yield from **10**. The decreased product recovery from this scale-up prompted us to explore a modified isolation procedure (Table 1, entry 13) using ether in place of ethyl acetate, and decanting the reaction mixture and ether washings from the biomass, rather than filtering the mixture, provides a much simpler practical method for product isolation and leads to greatly increased recoveries. In this case the intermediate hydroxy esters **11** and **14** were purified and recovered in 45% yield from **10,** instead of carrying the crude material through to the lactonisation step, as had been conducted in the previous experiments. Following cyclisation and chromatographic separation of the lactones, the *cis* fused lactone **12** was isolated as a single diastereomer in 32 % from the hydroxy esters; only one enantiomer of **12** could be seen by chiral HPLC. Furthermore, the *trans*-fused lactone **13** was isolated from this scale-up of Procedure B following chromatography in 10% yield in enantiopure form. As HPLC analysis of the product of the earlier reactions, conducted on mixtures of **12** and **13** without extensive chromatographic purification (Table 1, entries 2 and 12) had indicated reduced enantiopurity of **13**, the scale-up was repeated to ensure reproducibility and again led to enantiopure **13** following chromatography to separate the lactones. One of the most important advantages associated with the use of the more dilute conditions associated with Procedure B is that TLC monitoring of the yeast reduction is possible. In entries 12 and 13 it was found that the reduction takes approximately 6 days for complete consumption of **10** with addition of fresh yeast and sugar every 2 days.

Therefore, the optimised procedure for the synthesis of the enantiomerically pure lactones **12** and **13** involves use of Procedure B with the ether work-up and chromatographic purification.



Scheme 5

Transformation of the *cis* fused lactone **12** (≥98 %ee) to the sulfoxide was conducted using *m*-CPBA which had been purified before use (Scheme 5).[17] Oxidation occurs from the exo face only providing the sulfoxide **1** as a single diastereomer. As the very polar sulfoxide **1** is difficult to purify on silica gel, recrystallisation must be employed for purification, and therefore, it is essential that none of the sulfone is formed. A very short reaction time (3 minutes) is necessary to prevent over-oxidation. For this reason, it is more satisfactory to use purified oxidant rather than the commercial product (60-70%). Chiral HPLC analysis confirms the enantiopurity of the sulfoxide **1** as ≥ 98 %ee. Transformation to the diazosulfoxide **4** was achieved using tosyl azide and triethylamine in acetonitrile and again chiral HPLC demonstrated that **4** was obtained in ≥ 98 %ee. Finally rhodium acetate catalysed decomposition of enantiopure **4** in the presence of 2,3-dimethylbutadiene formed the enantiopure cycloadduct **15** which was identical by TLC and NMR to the racemic material we had previously synthesised.[4]

In conclusion, baker's yeast mediated dynamic kinetic resolution of the cyclohexanone derivative **10**, followed by cyclisation, can be employed for the asymmetric synthesis of the lactones **12** and **13**. The outcome of the biotransformation is very sensitive to the reaction conditions employed and the conditions for isolation of enantiopure **12** and **13** have been optimised. Use of this methodology for the asymmetric synthesis of the α-diazosulfoxide **4** in enantiopure form has been demonstrated, and further studies are underway.

Experimental Section

General Procedures. The baker's yeast used was *Saccharomyces cerevisiae* Type II, Sigma product YSC-2, antifoam refers to Antifoam 289; Sigma product A-5551. The chemicals used as additives were commercial materials used without purification. All the procedures were carried out using tap water, and unless otherwise stated were conducted in a reciprocal shaker thermostatted at 28 °C. The immobilised baker's yeast was prepared according to an established procedure.[11,15] Commercial *m*-CPBA was purified following the procedure described in ref. 17. Proton and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively, chemical shifts are quoted in ppm relative to tetramethylsilane and coupling constants are given in Hz. The concentrations of optical rotation samples are quoted in g/100 mL.

2-(Carboethoxymethylthio)cyclohexanone (10).[10] A solution of ethyl mercaptoacetate (2.49 g, 2.3 mL 20.7 mmol), Et_3N (2.10 g, 2.90 mL, 20.7 mmol) and 2-chlorocyclohexanone (2.5 g, 18.9 mmol) in CH_2Cl_2 (25 mL) was stirred for 2 h at ambient temperature. The mixture was diluted with CH_2Cl_2, washed twice with 2 M HCl, twice with saturated $NaHCO_3$ and once with brine. The organic layer was dried over $MgSO_4$ and concentrated to afford **10** (4.02 g, quantitative yield) as a pale oil which was pure enough to use directly. δ_H ($CDCl_3$) 1.28 (t, J = 7.1, 3 H, CH_2CH_3), 1.70-2.05 (m, 5 H, cyclohexyl ring), 2.17-2.35 (m, 2 H, cyclohexyl ring), 2.82-2.95 (m, 1 H, cyclohexyl ring), 3.26 (apparent q, J = 15.4, 2 H, SCH_2), 3.56-3.61 (m, 1 H, CHS), 4.18 (q, J = 7.1, 2 H, CH_2CH_3); δ_C ($CDCl_3$) 14.1, 22.4, 26.9, 32.9, 33.1, 38.4, 52.4, 61.5, 170.0, 207.5.

Baker's yeast reductions

Procedure A. High yeast concentration (Table 1, entry 1). The procedure is adapted from that of Ridley.[13] A mixture of baker's yeast (10 g), sucrose (10 g) and antifoam (2-3 drops) in water (60 mL) was incubated for 30 min, after which compound **10** (100 mg), dissolved in DMSO (1 mL) was added and shaking was continued. After 24 h, Celite® (*ca.* 5 g) was added and after 30 min, the mixture was filtered. The filter cake was washed with two portions of EtOAc (40 mL), the filtrate was separated and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated. The residue was taken up in $CHCl_3$ (10 mL), a flake of tosic acid was added and the resulting mixture heated at reflux temperature for 3 h. The solvent was removed, the residue filtered twice though a plug of SiO_2 and the residue examined by HPLC to reveal the presence of **12** (78%, ≥98% ee) and **13** (22%, ≥98% ee)

Procedure B. Low yeast concentration (Table 1, entry 2). The procedure is adapted from that of Seebach.[14] A mixture of baker's yeast (130 mg) and sugar (0.98 g) in water (40 mL) was incubated for 30 min, after which compound **10** (65 mg) in DMSO (1 mL) was added. After shaking for 60 h, second portions of yeast (130 mg) and sugar (650 mg) were added, followed 1 h later by a second portion of substrate (65 mg). After a further 48 h, Celite® (*ca.* 5 g) was added, and the reaction was worked up as described above in procedure A. The crude product was purified by dry flash chromatography (4:1 hexanes-EtOAc, working over to EtOAc with 5%

gradient) to afford 25 mg (24%) of a mixture of **12** and **13**. HPLC analysis revealed 59% **12** (≥ 98% ee) and 41% **13** (66% ee).

Procedure C. Immobilised baker's yeast (Table 1, entry 3). Beads of Immobilised baker's yeast (100 mL, *ca* 10 g yeast content) were placed in hexanes (100 mL) and MeOH (1 mL) was added. The mixture was incubated for 30 min, whereupon compound **10** (100 mg) was added. After five days of shaking, the mixture was filtered and the beads washed with hexanes (3 × 25 mL). After conventional aqueous workup, the isolated material (74 mg) was determined by TLC and ^{1}H NMR analysis to be unreacted starting material (74% recovery).

Procedure D. Free baker's yeast in ether (Table 1, entry 4). A mixture of yeast (10 g) and **10** (100 mg) in Et_2O (50 mL) in a covered flask was shaken for 48 h at 28 °C. Celite® (*ca*. 5 g) was added, the mixture was diluted with brine (50 mL) and filtered. The filtrate was separated, the organic layer dried over $MgSO_4$ and concentrated. TLC and ^{1}H NMR analysis revealed no reaction.

Reduction in the presence of allyl alcohol (Table 1, entry 5). The reaction was carried out according to the general procedure A with the exception that allyl alcohol (240 μL) was added before the incubation period. After 24 h of reaction, usual workup and cyclisation followed by dry flash chromatography afforded 17 mg (19%) of the mixed lactones, which was shown by HPLC analysis to be 77% *cis*- (97% ee) and 23% *trans*- (≥98% ee).

Reduction in the presence of methyl vinyl ketone (Table 1, entry 6). The reaction was carried out according to the general procedure A with the exception that methyl vinyl ketone (300 μL) was added before the incubation period, and the mixture was incubated for 60 minutes. After 24 h the reaction was worked up and subjected to the cyclisation conditions described above. Analysis by TLC and ^{1}H NMR revealed a complex mixture of products, none of the desired material was present.

Reduction in the presence of ethyl chloroacetate (Table 1, entry 7). The reaction was carried out according to the general procedure A with the exception that ethyl chloroacetate (385 μL) was added before the incubation period. After 24 h the reaction was worked up and subjected to the cyclisation conditions described above. Analysis by TLC and ^{1}H NMR revealed a complex mixture of products which did not contain any of the desired material.

Reduction in the presence of ethyl bromoacetate (Table 1, entry 8). The reaction was carried out according to the general procedure A with the exception that ethyl bromoacetate (400 μL) was added before the incubation period. After 24 h the reaction was worked up and subjected to the cyclisation conditions described above. Analysis by TLC and ^{1}H NMR revealed a complex mixture of products, none of the desired material was present.

Low-yeast reduction in the presence of allyl alcohol (Table 1, entry 9). The reaction was carried out according to the general procedure B with the exception that allyl alcohol (25 μL) was added before the incubation period. After 24 h the reaction was worked up as before. Analysis by TLC and ^{1}H NMR revealed only unreacted starting material.

Reduction with increased concentration of substrate (Table 1, entry 10). The reaction was carried out according to procedure A with the exception that 0.5 g of **10** was used. Proton NMR

analysis of the material obtained after workup and cyclisation revealed roughly 20% conversion. The crude material was twice passed through a plug of SiO_2 and examined by HPLC revealing 87% **12** (≥ 98% ee) and 13% **13** (≥ 98% ee).

Reduction with procedure A on increased scale (Table 1, entry 11). A 2 L conical flask was charged with baker's yeast (100 g), sugar (100 g), tap water (600 mL) and antifoam (10 drops), and placed in a glycerol bath pre-equilibrated and maintained at 29±1 °C by means of a contact thermometer. After 30 min. incubation with gentle stirring, the substrate **10** (1.0 g, 4.62 mmol) was added and stirring was continued over three nights. Celite® (*ca* 50 mL) was added and after 30 min. further stirring, the mixture was filtered. The filter cake was washed with EtOAc (3 × 200 mL) and once with Et_2O (200 mL), the filtrate was separated and the aqueous phase extracted three times with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over $MgSO_4$ and evaporated. The residue was taken up in $CHCl_3$ (*ca* 30 mL), three flakes of TsOH were added and the mixture was heated under reflux for 3 h. The solvent was removed and the residue purified by dry flash chromatography to afford 111 mg (12%) of product which was shown by HPLC analysis to be 78% **12** (≥ 98 %ee) and 22% **13** (≥ 98%ee).

Reduction using procedure B on preparative scale (Table 1, entry 12). The reaction was carried out following procedure B using 1 g of **10** which was split between five conical flasks containing yeast (200 mg), sugar (1.5 g) and water (80 mL) and which were incubated in the usual way. The reaction vessels were shaken gently for two days then treated with further portions of yeast and sugar. After a further two days, second portions of yeast (200 mg) and sugar (1.5 g) were added and shaking was continued two days more. The contents of the flasks were combined together and worked up and cyclised as before. The yield of product was 188 mg (25%), shown by HPLC to be 47% *cis*- (≥98% ee) and 53% *trans*- (76% ee). Further purification by repeated flash chromatography (4:1 hexanes/EtOAc) afforded 30 mg (4%) of pure **12** as a colourless solid. δ_H ($CDCl_3$) 1.20-1.39 (m, 1 H, cyclohexyl ring), 1.54-1.78 (m, 6 H, cyclohexyl ring), 2.16-2.20 (m, 1 H, cyclohexyl ring), 3.18 (A part of ABq, J = 14.5, 1 H, one of SCH_2), 3.17-3.21 (m, 1 H, SCH), 3.57 (B part of ABq, J = 14.5, 1 H, one of SCH_2), 4.56-4.59 (m, 1 H, OCH); δ_C ($CDCl_3$) 19.3, 25.0, 25.7, 30.8, 30.9, 39.7, 76.3, 168.5; m.p. 58-59 °C; $[\alpha]_D^{22}$ −102° (c = 1.02, $CHCl_3$).

Reduction using procedure B on preparative scale with modified workup (Table 1, entry 13). The reduction reaction was carried out as described above for entry 12. After reaction completion was determined by TLC the water was decanted from the yeast residue and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product as a colourless oil. This first extraction afforded 700 mg of the crude. Ether was then added to the remaining slurry in the conical flasks and this mixture was filtered to remove the yeast residue. The filtrate was separated and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a further 200 mg of crude product as a colourless oil. The combined crude products were purified by flash chromatography (4:1 hexanes/ethyl acetate) to give the mixed hydroxy esters **11** and **14** as a colourless oil (450 mg,

45%) δ_H ($CDCl_3$) 1.29 (t, J = 7, 3 H, CH_3), 1.34-2.67 (m, 9 H cyclohexyl ring and OH), 3.01-3.08 (m, 1 H, CHS), 3.19-3.38 (ABq, J = 15.3, 2 H, SCH_2), 3.84-3.87 (m, 1 H, CHO), 4.20 (q, J = 7, 2 H , C*H*$_2$CH$_3$).

Cyclisation of the hydroxy esters. Bicyclic sulfides *(5R,6S)-cis*-hexahydro-1,4-benzoxathiin-2(3H)-one 12 and *(5S,6S)-trans*-hexahydro-1,4-benzoxathiin-2(3*H*)-one (13). The procedure is essentially that described by Vankar.[10] The hydroxy ester (200 mg 0.92 mmol) was dissolved in benzene (5 mL) and TsOH (9 mg 0.047 mmol) was added. The reaction mixture was heated under reflux for 15 min using a Dean-Stark trap. The reaction mixture was cooled and washed with water (1 mL), the organic layer was separated, dried over $MgSO_4$ and concentrated to give a brown oil. Repeated purification by column chromatography (4:1 hexanes/ethyl acetate) gave **12** (60 mg, 32% ≥ 98% ee), and **13** (20 mg, 10% ≥ 98% ee) δ_H ($CDCl_3$) 1.27-2.28 (m, 8 H, cyclohexyl ring), 2.96-3.05 (m, 1 H, CHS), 3.23, 3.69 (ABq, J = 14.6, 2 H, SCH_2), 4.13-4.18 (m, 1 H, CHO); δ_C ($CDCl_3$) 23.7, 25 1, 26.8, 32.2, 32.63, 43.07, 81.6, 168.1; $[\alpha]_D^{19}$ − 189° (c = 0.95, $CHCl_3$); mp 87.5-88.5 (lit.[18] 88-89 °C).

***(4R,5R,6S)*-(−)-*cis*-Hexahydro-1,4-benzoxathiin-2(3*H*)-one-*S*-oxide (1).** A solution of *m*-CPBA (25 mg, 0.14 mmol) in dichloromethane (5 ml) was added to a stirring solution of **12** (25 mg, 0.14 mmol) in dichloromethane (15 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 3 min. The mixture was then filtered and the dichloromethane solution washed with cold with 10% $NaHCO_3$ (2 × 5 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product as a white solid. The white solid was recrystallised from dichloromethane/hexane slowly at room temperature to give the pure *cis*-sulfoxide **1** as a single diastereomer (15 mg, 55%). HPLC analysis revealed (≥ 98% ee). $[\alpha]_D^{21}$ −17 (c = 0.7, $CHCl_3$); υ_{max}(NaCl)/cm^{-1} 1732 (C=O), 1051 (S=O); δ_H ($CDCl_3$) 1.18-2.21 (8H, m, cyclohexyl ring), 2.83-2.89 (1H, m, C*H*S), 3.44-3.49, 3.98-4.04 (2H, ABq, J = 16, SOC*H*$_2$CO), 5.26-5.34 (1H, br s, C*H*O); δ_C ($CDCl_3$) 18.23, 21.52, 24.83, 30.45 (4 × *C*H$_2$, cyclohexyl ring), 49.29 (*C*H$_2$, SO*C*H$_2$CO) 59.26 (*C*H, *C*HS), 71.46 (*C*H, *C*HO), 163.58 (*C*=O).

***(4S,5R,6S)*-(+)-*cis*-Hexahydro-3-diazo-1,4-benzoxathiin-2(3*H*)-one-*S*-oxide (4).** Triethylamine (10 μL, 0.08 mmol) was added to a stirring solution of 1 (15 mg, 0.08 mmol) in acetonitrile (10 ml). Tosyl azide (15 mg, 0.08 mmol) was then added dropwise at 0 °C and the solution was stirred overnight while slowly returning to room temperature. The mixture was concentrated under reduced pressure to give the crude product as an orange oil. Purification by flash chromatography (3:2 hexanes/ethyl acetate) gave the pure *cis*-diazosulfoxide 4 as a yellow crystalline solid (7 mg, 41%); mp 112-114 °C (blackened 104-108 °C). HPLC analysis revealed ≥ 98% ee. $[\alpha]_D^{21}$ +40° (c = 0.6, $CHCl_3$); (Found: C, 44.81; H, 4.83; N, 13.15; S, 14.55; $C_8H_{10}N_2O_3S$ requires C, 44.85; H, 4.70; N, 13.08; S, 14.96%); υ_{max}(KBr)/cm^{-1} 2128 (C=N$_2$), 1681 (C=O); δ_H ($CDCl_3$) 1.25-1.76 (5H, m, cyclohexyl ring), 1.92-1.96 (2H, br d, C*H*$_2$ cyclohexyl ring), 2.29-2.41 (1H, br d, C*H*$_2$), 2.94-2.99(1H, ddd, J = 2, 3, 13, C*H*S), 5.35-5.41 (1H, br s, C*H*O); δ_C ($CDCl_3$) 19.07, 20.10, 24.57, 31.01 (4 × *C*H$_2$), 58.76 (*C*HS), 69.84 (*C*HO), 159.27 (*C*=O); m/z 214 (M^+).

Table 2. Chiral HPLC data

Compound	Column/Conditions[a]	Retention times/min
12	AS	15.1 [(5*R*,6*S*)-(−)-(*cis*-)]
	20 °C, 30% IPA in hexane	57.5 [(5-*S*,6-*R*)-(+)-(*cis*-)]
13	AS	22.9 [(5*S*,6*S*)-(−)-(*trans*-)]
	20 °C, 30% IPA in hexane	41.6 [(5*R*,6*R*)-(+)-(*trans*-)]
1	AD	6.1 [(4*S*,5*S*,6*R*)-(+)-(*cis*-)]
	Ambient, 60% IPA in hexane	14.4 [(4*R*,5*R*,6*S*)-(−)-(*cis*-)]
4	AD	11.1 [(4*R*,5*S*,6*R*)-(−)-(*cis*-)
	Ambient, 20% IPA in hexane	15.1 [4*S*,5*R*,6*S*)-(+)-(*cis*-)]

[a] Columns: Chiralpak AS 0.46 × 25 cm, Chiralpak AD. 0.46 × 25 cm; Flow rates 1.0 mL/min, detector wavelength 220 nm.

Acknowledgements

Financial support from Enterprise Ireland, Pfizer Ireland Pharmaceuticals, and BioResearch Ireland is gratefully acknowledged. We also wish to thank Johnson Matthey for a loan of rhodium acetate and B. O'Donovan (UCC) for provision of the immobilized baker's yeast used in this work.

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