# The thio-adduct facilitated, enzymatic kinetic resolution of 4-hydroxycyclopentenone and 4-hydroxycyclohexenone†

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The addition of 3,4-dimethoxybenzyl thiol **8**, as a benzyl thiol surrogate, to racemic 4-hydroxycyclopent-2-enone **2** and 4-hydroxycyclohex-2-enone **15** gave the corresponding *cis*-adducts (±)-3-(3,4-dimethoxybenzylthio)-4-hydroxycyclopentanone **4b** and (±)-3-(3,4-dimethoxybenzylthio)-4-hydroxycyclohexanone **16** with good diastereocontrol. In both cases, subsequent treatment with vinyl acetate, in the presence of a lipase enabled enantiomer resolution. Thus, (+)-**16** and the acetate of its enantiomer, (–)-(1*R*,2*S*)-2-(3,4-dimethoxybenzylthio)-4-oxocyclohexyl acetate, (–)-**17** were isolated in 98% enantiomeric excess. Based on the 1,4-dioxygenation pattern, (–)-**17** can be used to prepare both enantiomers of 4-(*tert*-butyldimethylsilyloxy)cyclohex-2-enone **19**. Firstly, saponification, with a sub-stoichiometric amount of NaOMe, followed by a one-pot silyl ether formation–sulfide elimination sequence gave (+)-**19**. Then using the same starting material a 6-step sequence, featuring a diastereoselective $NaBH_4$ reduction and a Cope-type sulfoxide elimination, gave (–)-**19**.

## Introduction

Cyclic molecules bearing stereogenic hydroxyl groups represent a commonly occurring structural motif in natural products. Additionally, they are useful building blocks for the synthesis of species containing functionalised carbocyclic rings more generally. In relation to this class of compound, in which the carbon atoms flanking the single stereogenic centre are of similar size but differ due to their level of hybridisation, it has been reported that standard enzymatic kinetic resolution (EKR) is typically not successful.[1] For example, studies performed by us,[2] and others,[3] indicate that both enantiomers of 4-hydroxycyclopentenone **1**‡ and 4-hydroxycyclohexenone **15** are recognised with poor selectivity, presumably as a consequence of the similarity in steric requirement of the groups adjacent to the secondary alcohol centre. We reasoned that for this type of cyclic alkenol, in which the alkene was conjugated to a ketone, the steric environment in close proximity to the stereogenic centre might be adjusted by conjugate addition to the alkenyl moiety and in doing so might facilitate a more efficient enantiodiscrimination by the enzyme.[2] An important consideration was that the $sp^2$ to $sp^3$ functionalisation process was potentially reversible in order that, following the resolution, the steric buttress could be removed.[2b] Therefore, based on these two criteria it was felt that the conjugate addition of an organosulfur group[5] represented an ideal candidate, since under appropriate conditions, this conjugate addition may be reversed.[6]

It should be noted that this type of temporary alteration of the steric environment around a reactive centre has been used to good effect in the resolution of both cyclic[1,7] and acyclic[8] secondary alcohols. In the former case a 2-bromo substituent was employed and in the latter bulky protecting groups were used for the primary alcohol component of a 1,2-diol. More recently, Figueredo and co-workers have reported a similar *S*-conjugate addition tactic to us in order to facilitate the EKR of a cyclohexenol.[9]

## Results and discussion

As Scheme 1 illustrates this general concept has been partially realised in the case of the 5-membered ring containing series. Thus, conjugate addition of benzyl mercaptan to **1** in dichloromethane with a sub-stoichiometric amount of triethylamine gave good yields of the corresponding adduct **4a**. The *cis*-diastereoselective outcome for this process was not anticipated and a possible explanation is discussed below (Scheme 2). Unlike enone **1**, only one enantiomer of **4a** proved to be a good substrate for several commercially available lipase enzymes in particular Novozym 435. Using this solid supported lipase from *Candida antarctica*, under standard conditions for this type of procedure, resolution was encountered and proton NMR spectroscopy of the crude mixture indicated that approximately 50% conversion had occurred after 24 h. Attempts to purify the mixture of **5a** and unreacted **4a**, however, proved problematic. Under a variety of chromatographic conditions **5a** proved to be unstable and partially afforded enone **6a**. Furthermore, **5a** and **6a** proved to have similar retention times on silica. Consequently, prior to purification we treated the crude mixture with triethylamine, in order to fully effect elimination, whereupon (–)-**4a** and (–)-**6a** were separated and characterised.

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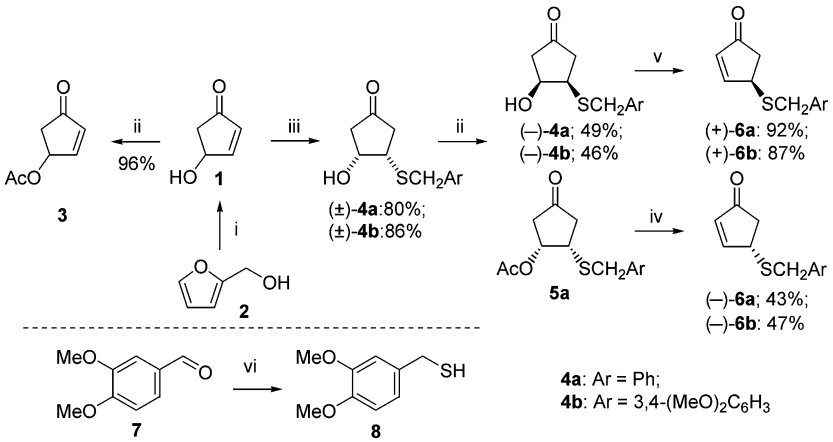
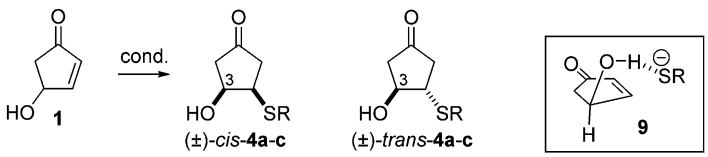
‡ 4-Hydroxycyclopentenone, **1**, synthesised from fufuryl alcohol **2** according to a literature procedure,[4] undergoes rapid non-selective acylation under the influence of a variety of commercially available enzymes. This method, in fact, represents a synthetically useful means to prepare **3** since under standard conditions low yields are typically obtained (for example: $Ac_2O$, pyridine, rt, 40%).




i, $KH_2PO_4$ (*p*H 4), $H_2O$, 100 ºC, 30-50%; ii, Novozym 435, *or* CAL-B, vinyl acetate, *i*-$Pr_2O$, rt; iii, $ArCH_2SH$, $Et_3N$ (0.1 equiv), $CH_2Cl_2$, rt, d.e. >95%; iv, $Et_3N$, 0 ºC to rt; v, $Ac_2O$, pyridine, $CH_2Cl_2$, 0 ºC to rt; vi, (a) $NaBH_4$, MeOH, 0 ºC, 95%; (b) $SOCl_2$, pyridine, $CH_2Cl_2$, rt, 97%; (c), KSAc, DMF, rt, 95%; (d) $NaBH_4$, EtOH, rt, 78%.

**Scheme 1** Enzymatic kinetic resolution (EKR) of 4-hydroxycyclopentenone facilitated *S*-derivatisation.




| Entry | cond.[a] | Adduct | R | *cis*:*trans*[b] | yield[c] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$, $Et_3N$ (0.1 equiv.) | **4a** | Bn | >19:1 | 80% |
| 2 | $CH_2Cl_2$ | **4a** | Bn | 9:1 | 86% |
| 3 | DMSO, $Et_3N$ (0.1 equiv.) | **4a** | Bn | 1:2 | *cis*: 24%; *trans*: 59% |
| 4 | EtOH, $Et_3N$ (0.1 equiv.) | **4a** | Bn | 1:2.3 | *cis*: 19%; *trans*: 51% |
| 5 | $CH_2Cl_2$, $Et_3N$ (0.1 equiv.) | **4b** | 3,4-$(MeO)_2C_6H_3CH_2$ | >19:1 | 86% |
| 6 | $CH_2Cl_2$, $Et_3N$ (0.1 equiv.) | **4c** | 2-Naphthyl | 1:1 | - |

[a]Reactions performed at room temperature, under nitrogen for 3 to 24 hours; [b]Determined by $^1H$ NMR spectroscopy; [c]Yield obtained following purification by flash column chromatography

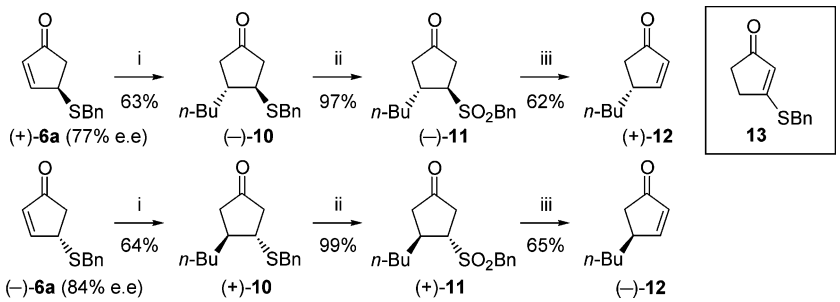
**Scheme 2** Diastereoselective *S*-conjugate addition to 4-hydroxycyclopentenone (±)-**1**.

The absolute stereochemistry of (–)-**4a** was uncovered by a series of studies detailed previously[2] and is consistent with the Kazlauskas model of lipase enzyme selectivity.[7] An acylation–elimination procedure afforded enantiomeric sulfide (+)-**6a** in good yield. Chiral HPLC analysis of the enantiomeric allylic sulfides obtained using Novozym 435§ indicated enantiomeric excess values of >98% for both enantiomers thus obtained. However, using the commercially available lipase immobilised on an acrylic resin similar analysis indicated that these results were not reproducible and lower levels of enantiodiscrimination (77–85% e.e.) were observed. Currently we do not have an explanation for the lower levels of enantioselectivity obtained for the lipases from different sources.[10]

Although this general sequence represents a useful method enabling access to both enantiomerically enriched series of 4-substituted cyclopent-2-enones one considerable issue with the applicability of this chemistry is the lingering stench associated with the use of benzyl mercaptan. In relation to this problem Node and co-workers have indicated that introduction of substituents into the aromatic ring can serve to reduce the smell of the thiol without diminishing its nucleophilicity.[11] Therefore, we investigated whether the enzymatic kinetic resolution would proceed in a similar fashion with the alternative sulfide substituent. Compound **8** was selected in this respect and a four step sequence was developed for its multi-gram preparation starting from 3,4-dimethoxybenzaldehyde **7**. This thiol **8** did indeed possess a significantly reduced odour compared to benzyl mercaptan and, as indicated in Scheme 2, it underwent efficient, diastereoselective conjugate addition with racemic **1**. As hoped, resolution of adduct **4b** proceeded similarly to the adduct containing the benzyl sulfide substituent **4a** and a mixture of (–)-**4b** and (–)-**6b** were isolated in 46% and 47% yield respectively. The former proved crystalline and X-ray crystallography[12] served to reinforce both the assignment of the *cis*-stereochemistry obtained on conjugate addition and of the sense of enantioselectivity derived from the lipase (Fig. 1). Chiral HPLC analysis of the enantiomeric allylic sulfides indicated e.e.

§ Novozym 435 was a kind donation from Novozymes (Denmark). CAL-B (lipase B from *Candida antarctica* immobilised on an acrylic resin) was obtained from Sigma (L4777).




**Scheme 3** Synthesis of (+)- and (–)-**12** *via* a conjugate addition–elimination sequence.¶

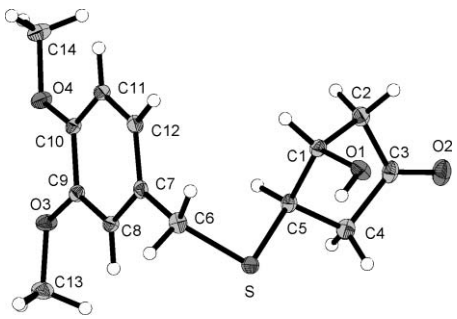



**Fig. 1** X-Ray crystal structure of (–)-**4b** (diamond representation, thermal ellipsoids at 15%).

of 85%. The enantiomeric excess of the (–)-**4b** may be improved following recrystallisation from dichloromethane–pentane (95% e.e.). Attempts to optimise this reaction by halting the process before 50% conversion was reached [(**4b** : **5b**; 1 : 0.3) gave (–)-**6b**: 84% e.e. and (+)-**6b**: 30% e.e.] and using a quarter of the standard amount of the enzyme, in order to slow the reaction down [(–)-**6b**: 87% e.e. and (+)-**6b**: 65% e.e. after 5 days], did not enhance the e.e. obtained. We speculate that under the reaction conditions some reversibility of the acylation process is taking place.

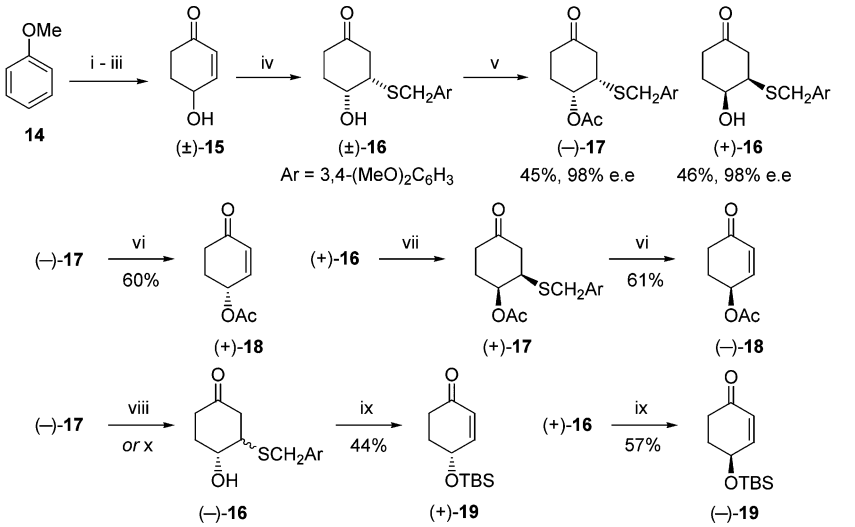
In relation to the *cis*-diastereoselectivity of the conjugate addition reaction, **1** to *cis*-**4a**, it seems plausible that a situation in which a hydrogen bond-ion interaction is present (Scheme 2). Such an interaction, we propose, leads to a diastereotopic delivery of the nucleophile to the planar cyclopentenone (*i.e.* **9**).[13] In terms of support for this postulate it was found that in the absence of the base slightly more of the *trans*-diastereoisomer was observed (Entry 2) and then using dimethyl sulfoxide and ethanol (Entries 3 and 4), which are likely to disrupt the type of delivery proposed (**9**), a separable mixture of the diastereoisomers formed which favoured the *trans*-adduct **4a**. NMR spectroscopic studies concerned with the stability, or otherwise, of the *cis*-adduct **4a** demonstrated that in deuterated DMSO at room temperature no conversion of *cis*-**4a** into *trans*-**4a** occurred. Similarly, it was also found that under acidic (cat. TsOH, $CDCl_3$) and basic (cat. $Et_3N$, $CDCl_3$) conditions no diastereoisomer interconversion occurred. It was also notable that *trans*-**4a** was not a good substrate for the enzyme and negligible conversion was observed with the lipase under identical conditions described for the resolution of its diastereoisomer (Scheme 1).[14]

Unsurprisingly, when thiol **8**, possessing similar electronic and steric effects to BnSH, was used with $CH_2Cl_2$ as the solvent (Entry 5) only formation of *cis*-**4b** was detected. However, the identity of the nucleophile was crucial since when 2-naphthalenethiol was employed, under identical conditions to those that proved highly diastereoselective with benzyl mercaptan and **8**, an equal mixture of diastereoisomers formed (Entry 6). It seems reasonable to speculate that the cause for this latter observation reflects the altered nucleophilicity and p$K_a$ of the alternative thiols. A diagnostic spectroscopic signal that may be used to distinguish between the *cis*- and *trans*-diastereoisomers are the respective signals for C-3 in their carbon NMR spectra (*cis*-C-3: 68–69 ppm; *trans*-C-3: 73–74 ppm).[2b]

With regards to the utility of the enantioenriched allylic sulfides **6a** obtained, their further functionalisation was briefly investigated as outlined in Scheme 3. Thus, conjugate addition of both enones (+)- and (–)-**6a** with *n*-BuMgCl and catalytic CuI gave the adducts (+)- and (–)-**10** as a single undetermined diastereoisomer (>95% d.e.). Subsequently, an oxidation–elimination sequence was developed in order to prepare the enantiomeric 4-butylcyclopentenones **12** and their signs of optical rotation proved to be equal and opposite. Furthermore, by comparison with a literature figure[15] the *trans*-stereochemistry of the conjugate addition reaction can be extrapolated. Based on the enantiomeric excesses of the substrates, (±)-**6a**, these 4-alkyl cyclopentenones are formed in 77% and 84% e.e. respectively. In relation to this sequence substrates featuring a Lewis basic sulfide moiety have only occasionally been reported to undergo reactions with organometallic reagents of this type.[16]

During the initial studies we also demonstrated that this resolution could successfully be performed on the corresponding cyclohexenone series.[2,17] Therefore, as above, we set out to investigate whether the chemistry could be transferred to the less odorous thiol **8** (Scheme 4). As before (Scheme 2) the conjugate addition of **8** to racemic **15**, prepared according to a literature procedure,[18] gave the *cis*-**16** in high d.e. Pleasingly, the resolution of racemic **16** also proceeded smoothly, albeit taking longer to reach completion than the corresponding cyclopentanone **4b**. Thus, after 36 h approximately equal quantities of (–)-**17** and (+)-**16** were isolated following flash column chromatography, since, in this case, elimination of acetate was not an issue. Notably, under the same conditions (±)-**15** was converted with no selectivity into racemic

¶ One issue encountered concerning the use of these enantioenriched allylic sulfides in organic synthesis is the apparent proclivity for these compounds to undergo an isomerisation into the vinylogous thioester **13**, which was observed following prolonged exposure of **6a** to basic, or acidic conditions.




i, Li, $NH_3$, *t*-BuOH, THF, -78 °C; ii, $HClO_4$, $CHCl_3$-$H_2O$ (1:2), rt; iii, (a) *m*-CPBA, $CH_2Cl_2$, rt; (b) $Al_2O_3$ (basic), $CH_2Cl_2$, rt, 50%; iv, **8**, $Et_3N$ (0.1 equiv.), $CH_2Cl_2$, rt, 82% (d.e. >95%); v, CAL-B, vinyl acetate, *i*-$Pr_2O$, rt; vi, (a) *m*-CPBA, $CH_2Cl_2$, rt; (b) $Et_3N$, $CH_2Cl_2$, rt; vii, (a) $Ac_2O$, pyridine, rt, 83%; viii, $K_2CO_3$, MeOH, rt; ix, TBSCl, DBU, $CH_2Cl_2$, rt; x, cat. NaOMe, MeOH, rt, 97%.

**Scheme 4** Enzymatic kinetic resolution (EKR) of 4-hydroxycyclohexenone facilitated by temporary *S*-derivatisation.

**18** (not shown). Compound (–)-**17** proved crystalline and X-ray crystallography,[19] once again, confirmed both the stereochemical outcome of the initial conjugate addition and selectivity of acylation mediated by the lipase (Fig. 2). Unchanged (+)-**16** was converted into (+)-**17** and chiral HPLC analysis indicated that both compounds possessed e.e. of 98%. In contrast to the corresponding studies with the cyclopentyl systems (see Scheme 1) this selectivity proved reliably reproducible using the commercially sourced CAL-B.

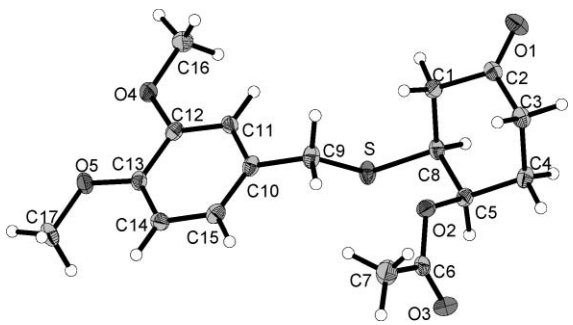


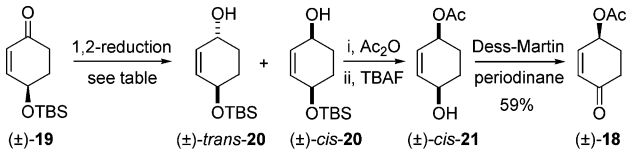

**Fig. 2** X-Ray crystal structure of (–)-**17** (diamond representation, thermal ellipsoids at 50%).

Yields for the DBU promoted elimination process in this acetoxy series proved moderate. However, using the new oxidation–elimination protocol improved yields of either isomeric form of **18** were observed. Although the values of optical rotation recorded for (–)-**18** and (+)-**18** were found to differ from literature[7,20] analysis by chiral HPLC proved that no reduction of percentage e.e. had taken place during this process. These cyclohexyl enantioenriched building blocks were also converted into the corresponding silyl ethers (+)- and (–)-**19** following the one-pot DBU based silylation–elimination protocol. As above analysis of chiral HPLC for these compounds indicated 98% e.e. One noteworthy point in relation to this sequence concerns the conversion of (–)-**17** into (–)-**16**. Under standard basic conditions ($K_2CO_3$, MeOH), used in order to liberate the secondary alcohol, a mixture of compounds were formed corresponding to epimerisation at C-3.[21] Since this stereogenic centre is lost on subsequent elimination this is not crucial, however, hydrolysis without C-3 epimerisation can be achieved using sub-stoichiometric amounts of NaOMe in MeOH.

Based on the 1,4-dioxgenation pattern present we wished to be able to access a single enantiomeric product (*i.e.* **18**/**19**) from both (+)-**16** and (–)-**17**, in order to increase the usability and efficiency of this EKR-based method. With this in mind (±)-**16** was converted into (±)-**19** using the DBU silylation–elimination route discussed above and its 1,2-reduction was investigated (Scheme 5). Recently, it has been shown that treatment of **19** with Dibal resulted in a moderately selective reduction favouring the *trans*-diol **20**, which proved separable from its diastereoisomer, *cis*-**20** (Entry 1).[9] Based on this report several reducing agents were screened in the hope that improved selectivity for the minor diastereoisomer could be achieved. Optimal conditions proved to be $LiAlH_4$ which yielded a 0.85 : 1.0 mixture of *trans* : *cis* isomers in favour of our desired product. K-selectride and superhydride were also investigated, however, they did not prove selective for the carbonyl group over the double bond and a complicated mixture of products was obtained. With (±)-*cis*-**20** in hand we proceeded to acetylate the secondary alcohol and to deprotect the silyl ether to give (±)-*cis*-**21**. Oxidation of (±)-*cis*-**21** with Dess–Martin periodinane gave (±)-**18**, in which the stereogenic centre has been transposed in relation to the starting compound (±)-**19**.

Due to the low stereoselectivity seen for the reduction of (±)-**19** an alternative method was developed to achieve the same goal (Scheme 6). Reduction of (–)-**17** with $NaBH_4$ gave only one diastereoisomer which nOe studies suggested was (–)-**22**. Sulfoxide **23** was subsequently synthesised from (–)-**22** in three steps; the hydroxyl group was initially protected as a silyl ether and then the acetate group was removed. Finally, the sulfide




| Entry | Reagent | *trans*:*cis*[a] | yields[b] *trans* | *cis* | (combined) |
|---|---|---|---|---|---|
| 1 | Dibal[c] | - | 72% | 26% | (98%) |
| 2 | $NaBH_4$, $CeCl_3{\cdot}7H_2O$ | 1.0:0.75 | 33% | 26% | (59%) |
| 3 | $CaCl_2$, $NaBH_4$ | 1.0:0.70 | 49% | 33% | (82%) |
| 4 | $LiAlH_4$ | 0.85:1.0 | 39% | 41% | (80%) |
| 5 | $Zn(BH_4)_2$ | 1.0:0.75 | 30% | 21% | (51%) |

[a]Ratio determined by $^1$H NMR spectroscopy; [b]Isolated yields following flash column chromatography; [c]Taken from ref. 9: *J. Org. Chem.*, 2008, **73**, 3486.

**Scheme 5** 1,2-Reduction of (±)-**19**.

was chemoselectively oxidised to the sulfoxide using sodium periodate. This oxidation resulted in the formation of **23** as a 3 : 2 mixture of diastereomers at the sulfoxide position. Compound **23** was then studied as a substrate for Cope-type elimination. This proved problematic and after a series of attempts based on modified literature conditions[22] (–)-**20** was eventually isolated in low yield (14%) using mesitylene in the presence of a base in a sealed tube at 165 °C. Spectral data and optical rotation of (–)-**20** matched that reported in the literature, thereby proving the relative stereochemistry expected for compound (–)-**22**. Following the Cope elimination starting material **23** was recovered (71%) and interestingly this material proved a single diastereoisomer of **23**. Based on this observation we speculate that the minor sulfoxide diastereoisomer undergoes the Cope elimination whereas the major sulfoxide diastereoisomer does not. This major diastereoisomer may be stabilised by an intermolecular H-bond in which the benzyl substituent occupies an equatorial orientation (see **25**) and temperatures of 165 °C may not be high enough for this compound to undergo Cope elimination. It has, however, also been shown that benzyl substituted sulfoxides epimerise at temperatures of 165 °C explaining how it is possible to recover over 66% of the major sulfoxide.[23] After this desulfuration step (–)-**20** was then oxidised with Dess–Martin periodinane to give (–)-**19**. This sequence demonstrates that both enantiomers of **19** may be accessed from a common precursor, *i.e.* (–)-**17**. In the hope of increasing the yield of the Cope elimination we oxidised **23** to (–)-**24** using the Dess–Martin periodinane. Pleasingly, possibly due in part to the removal of H-bond stabilization, Cope-type elimination proceeded in good yield (75%) under less forcing conditions to give (–)-**19**.

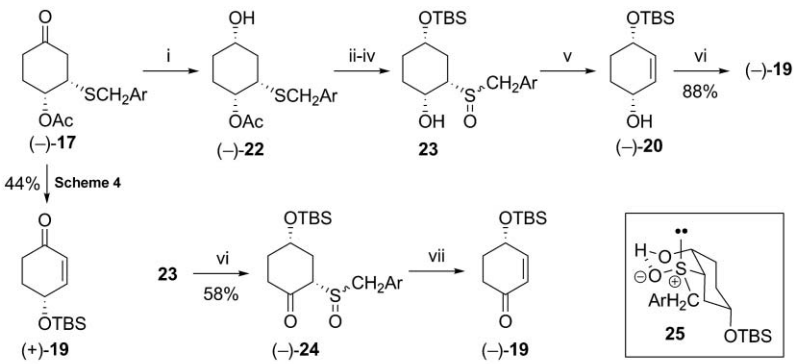
In summary, we have demonstrated that an alternative thiol exhibiting diminished odour may be effectively employed as an alternative to benzyl mercaptan in our enzymatic kinetic resolution reaction of 4-hydroxycyclopentenone and 4-hydroxycyclohexenone. We have also developed an alternative method for the removal of the sulfide motif post resolution that involves an oxidation–elimination process. Finally, it proved possible to access a single enantiomeric 4-hydroxycyclohexenone derivative [(–)-**19**] from both the products [(+)-**16** and (–)-**17**] of EKR in the 6-membered series.[24]

## Experimental directions

For details concerning the syntheses of (±)-4-hydroxycyclopent-2-enone **1**, the synthesis of (+)- and (–)-**6a**/**6b**, 3,4-dimethoxybenzyl thiol **8**, 4-butylcyclopenten-2-one **12** and 4-hydroxycyclohex-2-enone **15**, the reduction of (±)-4-(*tert*-butyldimethylsilyloxy)cyclohex-2-enone **19** and the Cope-type sulfoxide elimination for conversion of (–)-**17** to (–)-**19** see the accompanying ESI section.

### Synthesis of enantioenriched cyclohex-2-enones (+)- and (–)-18 and (+)- and (–)-19

***cis*-3-(3,4-Dimethoxybenzylthio)-4-hydroxycyclohexanone 16.** To a solution of the 4-hydroxycyclohex-2-enone **15** (0.46 g, 4.10 mmol, 1 equiv.) and the mercaptan **8** (0.76 g, 4.10 mmol, 1 equiv.) in dry $CH_2Cl_2$ (12 mL), TEA was added (60 µL, 0.41 mmol, 0.1 equiv.). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue purified by flash column chromatography ($CH_2Cl_2$–MeOH; 98 : 2) which gave the product **16** (1.00 g, 82%) as a colourless oil. $R_f$ 0.1 (cyclohexane–EtOAc; 2 : 1); $\nu_{max}$ (neat/cm$^{-1}$) 3495, 2935, 2835, 1707, 1591, 1262; $\delta_H$ (600 MHz, $CDCl_3$) 1.70–1.77 (1H, m, $CH_2$), 2.22 (1H, dddd, $J$ = 2.0, 3.0, 5.0, 14.5 Hz, $CH_2$), 2.30 (1H, dddd, $J$ = 3.0, 4.0, 6.5, 14.5 Hz, $CH_2$), 2.40 (1H, ddd, $J$ = 1.5, 5.0, 14.5 Hz, $CH_2$), 2.59 (1H, app. t,




i, $NaBH_4$, EtOH, rt, 96%; ii, TBSCl, DBU, $CH_2Cl_2$, rt, 90%; iii, $K_2CO_3$, MeOH, rt, 95%; iv, $NaIO_4$, THF-$H_2O$ (1:1), rt, 78%; v, mesitylene, $CaCO_3$, 165 ºC (sealed tube), 14% (71% **23** recovered); vi, Dess-Martin periodinane, $CH_2Cl_2$, rt; vii, PhMe, $CaCO_3$, 110 ºC (sealed tube), 75%

**Scheme 6** Cope-type elimination for the conversion of (–)-**17** into (–)-**19**.

$J$ = 13.5 Hz, $CH_2$), 2.63–2.74 (2H, m, $CH_2$, OH), 3.04 (1H, ddd, $J$ = 2.0, 5.0, 12.5 Hz, CH), 3.72 (1H, d, $J$ = 13.5 Hz, $CH_2$), 3.77 (1H, d, $J$ = 13.5 Hz, $CH_2$), 3.86 (3H, s, $CH_3$), 3.88 (3H, s, $CH_3$), 3.98–4.01 (1H, m, CH), 6.77–6.82 (2H, m, ArH), 6.87 (1H, d, $J$ = 2.0 Hz, ArH); $\delta_C$ (150 MHz, $CDCl_3$) 30.1 ($CH_2$), 35.0 ($CH_2$), 35.3 ($CH_2$), 44.2 ($CH_2$), 48.3 (CH), 55.9 ($CH_3$), 56.0 ($CH_3$), 64.9 (CH), 111.1 (CH), 111.7 (CH), 120.9 (CH), 129.6 (C), 148.6 (C), 149.4 (C), 208.1 (CO); HRMS ($ES^+$) cald. for $C_{15}H_{20}O_4SNa$ ($MNa^+$) requires 319.0980; found 319.0971; HPLC analysis (IA) isocratic heptane–EtOH; 80 : 20, (1.0 mL $min^{-1}$): $t_r$(3*R*,4*S*): 26.6 min, $t_r$(3*S*,4*R*): 28.5 min.

**(3*R*,4*S*)-3-(3,4-Dimethoxybenzylthio)-4-hydroxycyclohexanone (+)-16 and (1*R*,2*S*)-2-(3,4-dimethoxybenzylthio)-4-oxocyclohexyl acetate (–)-17.** (±)-**16** (8.00 g, 27.0 mmol, 1 equiv.) was dissolved in diisopropyl ether (400 mL)‖ before vinyl acetate (12.4 mL, 135.0 mmol, 5 equiv.) and Cal-B (8.00 g) were added to the mixture. At room temperature (*ca.* 20 °C) the reaction was shaken at 300 rpm for 25 h. The mixture was filtered and the enzyme washed with diisopropyl ether (4 × 50 mL). Solvent removal under reduced pressure furnished the crude product mixture that was purified by column chromatography (EtOAc–pentane; 1 : 3) to yield (–)-**17** (4.09 g, 45%) as a white solid, M.p. = 75–76 °C (MeOH). $R_f$ 0.2 (cyclohexane–EtOAc; 2 : 1); $\nu_{max}$ (neat/$cm^{-1}$) 3062, 2963, 1737, 1716, 1514, 1238; $\delta_H$ (600 MHz, $CDCl_3$) 1.81 (1H, ddd, $J$ = 4.5, 7.0, 17.0 Hz, $CH_2$), 2.16 (3H, s, $CH_3$) 2.26–2.32 (2H, m, $CH_2$), 2.49–2.56 (2H, m, $CH_2$), 2.64 (1H, dd, $J$ = 12.5, 14.5 Hz, $CH_2$), 2.99 (1H, ddd, $J$ = 3.0, 5.0, 12.5 Hz, CH), 3.70 (1H, d, $J$ = 13.5 Hz, $CH_2$), 3.77 (1H, d, $J$ = 13.5 Hz, $CH_2$), 3.86 (3H, s, $CH_3$), 3.88 (3H, s, $CH_3$), 5.34–5.37 (1H, m, CH), 6.78 (1H, d, $J$ = 8.5 Hz, ArH), 6.81 (1H, dd, $J$ = 2.0, 8.5 Hz, ArH), 6.87 (1H, d, $J$ = 2.0 Hz, ArH); $\delta_C$ (150 MHz, $CDCl_3$) 20.9 ($CH_3$) 28.6 ($CH_2$), 35.3 ($CH_2$), 35.8 ($CH_2$), 43.4 ($CH_2$), 44.7 (CH), 55.8 ($CH_3$), 55.9 ($CH_3$), 68.3 (CH), 111.0 (CH), 111.8 (CH), 120.9 (CH), 129.6 (C), 148.4 (C), 149.2 (C), 170.2 (CO), 207.1 (CO); HRMS ($ES^+$) cald. for $C_{17}H_{22}O_5SNa$ ($MNa^+$) requires 361.1086; found 361.1076; $[\alpha]_D^{20}$ = –24.0 ($c$ = 0.2, $CHCl_3$); HPLC analysis (ASH) isocratic heptane–EtOH; 90 : 10, (1 mL $min^{-1}$): $t_r$ (1*R*,2*S*): 21.9 min; 98% e.e. An X-ray crystal structure was obtained from crystals obtained by recrystallisation in MeOH.

Further elution gave (+)-**16** (3.66 g, 46%) as a colourless viscous oil with spectroscopic data as above. $[\alpha]_D^{20}$ = +6.3 ($c$ = 1.0, $CHCl_3$); HPLC analysis (IA) isocratic heptane–EtOH; 80 : 20, (1.0 mL $min^{-1}$): $t_r$ (3*R*,4*S*): 26.6 min; 98% e.e.

**(3*S*,4*R*)-3-(3,4-Dimethoxybenzylthio)-4-hydroxycyclohexanone (–)-16.** The acetoxy adduct (–)-**17** (82 mg, 0.24 mmol, 1 equiv.) was dissolved in dry methanol (5 mL) under nitrogen, then 0.1 M sodium methoxide (1.2 mL, 0.12 mmol, 0.5 equiv.) was added and the reaction was stirred for 45 min. After this time most of the methanol was removed under reduced pressure and dichloromethane (10 mL) and brine (10 mL) were added. The layers were separated and the resulting aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 1 : 1) afforded (–)-**16** (70 mg, 97%) as a clear, viscous oil. $[\alpha]_D^{20}$ = –15.3 ($c$ = 0.2, $CHCl_3$) with additional data as above; HPLC analysis (IA) isocratic heptane–EtOH; 80 : 20, (1.0 mL $min^{-1}$): $t_r$ (1*S*,2*R*): 28.5 min; 98% e.e.

**(1*S*,2*R*)-2-(3,4-Dimethoxybenzylthio)-4-oxocyclohexyl acetate (+)-17.** The hydroxyl adduct (+)-**16** (176 mg, 0.59 mmol, 1 equiv.) was dissolved in acetic anhydride (3 mL) at room temperature, then pyridine (50 µL, 0.65 mmol, 1.1 equiv.) was added dropwise and stirred for an hour. The reaction was then diluted with water (2 mL) and extracted with EtOAc (3 × 5 mL), washed with $NaHCO_3$ (3 × 5 mL), brine (5 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded the crude material which was purified by flash column chromatography affording (+)-**17** (165 mg, 83%) as a white solid with spectroscopic data as above. $[\alpha]_D^{20}$ = +24.5 ($c$ = 0.2, $CHCl_3$); HPLC analysis (ASH) isocratic heptane–EtOH; 90 : 10, (1 mL $min^{-1}$): $t_r$ (1*S*,2*R*): 19.0 min.

**(*S*)-4-Acetoxy-2-cyclohexen-1-one (–)-18.** The acetoxy adduct (+)-**17** (30 mg, 0.09 mmol, 1 eq.) was dissolved in dry $CH_2Cl_2$ (2 mL), then cooled to 0 °C before 77% w/w *m*-CPBA (42 mg, 0.19 mmol, 2.1 equiv.) was added. The mixture was stirred overnight at room temperature. 1 M sodium thiosulfate solution (4 mL) was added and stirring was maintained for 20 min. The aqueous layer was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* afforded the crude sulfone (57 mg). This was then dissolved in dichloromethane (3 mL), cooled to 0 °C and triethylamine (22 µL, 0.16 mmol, 1.8 equiv.) was added dropwise. Stirring was continued for 1 h after which time the solvent was removed *in vacuo* and the crude acetate was purified by column chromatography (pentane–EtOAc; 3 : 1) to yield (–)-**18** (8 mg, 61%) as a yellow oil. $R_f$ 0.35 (pentane–EtOAc; 3 : 1); $\nu_{max}$ (neat/$cm^{-1}$) 1741, 1686, 1372, 1236, 1037; $\delta_H$ (400 MHz, $CDCl_3$) 1.99–2.20 (1H, m, $CH_2$), 2.12 (3H, s, $CH_3$), 2.28–2.70 (3H, m, $CH_2$), 5.55–5.58 (1H, m, CH), 6.06 (1H, ddd, $J$ = 1.0, 1.5, 10.0 Hz, CH), 6.84 (1H, ddd, $J$ = 1.5, 2.5, 10.0 Hz, CH); $\delta_C$ (100 MHz, $CDCl_3$) 21.0 ($CH_3$), 28.7 ($CH_2$), 35.0 ($CH_2$), 67.7 (CH), 130.8 (CH), 147.6 (CH), 170.3 (CO); HRMS (CI) cald. for $C_8H_{14}O_3N$ ($MNH_4^+$) requires 173.08459; found 173.08510; $[\alpha]_D^{20}$ = –50 ($c$ = 0.7, $CHCl_3$); {lit. $[\alpha]_D$ = –71 ($c$ = 0.9, $CHCl_3$)};[17] HPLC analysis (OJH) isocratic heptane–EtOH; 90 : 10, (1.0 mL $min^{-1}$): $t_r$(*S*): 13.2 min; 98% e.e.

**(*R*)-4-Acetoxy-2-cyclohexen-1-one (+)-18.** As described above, (–)-**17** (60 mg, 0.18 mmol, 1 equiv.) was dissolved in dry dichloromethane (4 mL) and treated with 77% w/w *m*-CPBA (83 mg, 0.37 mmol, 2.1 equiv.) at 0 °C to room temperature for 18 h. The crude sulfone (119 mg) was obtained following work up described above. This material was dissolved in dichloromethane (3 mL), cooled to 0 °C and triethylamine (45 µL, 0.32 mmol, 1.8 equiv.) added dropwise. Stirring was continued for 1 h after which time the solvent was removed *in vacuo*. The crude acetate was purified by column chromatography (pentane–EtOAc; 3 : 1) to yield (+)-**18** (16 mg, 60%) as a yellow oil with data as described above. $[\alpha]_D^{20}$ = +48.0 ($c$ = 0.2, $CHCl_3$); {lit. $[\alpha]_D^{20}$ = +67.0 ($c$ = 0.6, $CHCl_3$)};[20] HPLC analysis (OJH) isocratic heptane-EtOH; 90 : 10, (1.0 mL $min^{-1}$): $t_r$(*R*): 12.9 min; 98% e.e.

‖ Note: sonication and moderate heating were required to effect solubilisation of **16** in diisopropyl ether. This was critical in terms of reproducibility of the reaction.

**(*R*)-4-(*tert*-Butyldimethylsilyloxy)cyclohex-2-enone (+)-19.** The acetoxy adduct (–)-**17** (1.00 g, 2.95 mmol, 1 equiv.) was dissolved in MeOH (20 mL), $K_2CO_3$ was added (429 mg, 3.10 mmol, 1.05 equiv.) and stirred for 30 min. The reaction mixture was diluted with brine (10 mL) and extracted with $CHCl_3$ ($3 \times 10$ mL) and dried over $MgSO_4$, reduced *in vacuo* and further dried under reduced pressure for 12 h. The crude alcohol **16** (0.53 g, 1.79 mmol, 1 equiv.) was dissolved in dichloromethane (6 mL) and TBSCl (539 mg, 3.58 mmol, 2 equiv.) was added followed by DBU (0.67 mL, 4.48 mmol, 2.5 equiv.) in a dropwise fashion. The reaction was stirred overnight at room temperature. The reaction mixture was then diluted with ether (20 mL) washed with 0.1 M HCl ($2 \times 12$ mL), saturated $NaHCO_3$ (10 mL), then dried over $MgSO_4$. Filtration followed by solvent removal *in vacuo* and flash column chromatography ($CH_2Cl_2$) gave (+)-**19** (290 mg, 44%) as a colourless oil. $R_f$ 0.15 ($CH_2Cl_2$); $\nu_{max}$ (neat/cm$^{-1}$) 3020, 3000, 2942, 2840, 1675, 1377, 1245; $\delta_H$ (400 MHz, $CDCl_3$) 0.12 (3H, s, $CH_3$), 0.13 (3H, s, $CH_3$), 0.91 (9H, s, $CH_3$), 1.95–2.05 (1H, m, $CH_2$), 2.17–2.24 (1H, m, $CH_2$), 2.30–2.39 (1H, m, $CH_2$), 2.54–2.60 (1H, m, $CH_2$), 4.50–4.55 (1H, m, CH), 5.92 (1H, ddd, $J = 1.0$, 2.0, 10.0 Hz, CH), 6.83 (1H, ddd, $J = 1.5$, 2.5, 10.0 Hz, CH); $\delta_C$ (100 MHz, $CDCl_3$) –4.8 ($CH_3$), –4.6 ($CH_3$), 18.1 (C), 25.7 ($CH_3$), 32.9 ($CH_2$), 35.5 ($CH_2$), 67.0 (CH), 128.7 (CH), 153.9 (CH), 198.8 (CO); HRMS (CI) cald. for $C_{12}H_{26}O_2SiN$ ($MNH_4^+$) requires 244.17791; found 244.17786; $[\alpha]_D^{20} = +101.0$ ($c = 1.0$, $CHCl_3$); {lit. $[\alpha]_D^{20} = +107.1$ ($c = 1.3$, $CHCl_3$)}.[25]

**(*S*)-4-(*tert*-Butyldimethylsilyloxy)cyclohex-2-enone (–)-19.** The hydroxy adduct (+)-**16** (1.30 g, 4.39 mmol, 1 equiv.) was dissolved in dichloromethane (100 mL) and TBSCl (1.32 g, 8.77 mmol, 2 equiv.) was added. DBU (1.64 mL, 10.98 mmol, 2.5 equiv.) was then added dropwise and the mixture was stirred overnight at room temperature. The reaction mixture was then diluted with ether (60 mL) washed with 0.1 M HCl ($2 \times 20$ mL), saturated $NaHCO_3$ (20 mL), then dried over $MgSO_4$. Upon filtration and solvent removal *in vacuo* the crude product was purified by flash column chromatography ($CH_2Cl_2$) to afford (–)-**19** (0.57 g, 57%) as a colourless oil with data in accord with that reported. $[\alpha]_D^{20} = -102.0$ ($c = 2.0$, $CHCl_3$); {lit. $[\alpha]_D = -115.94$ ($c = 1.06$, $CHCl_3$)}.[24a]

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