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Novel preparation of (−)-4-hydroxycyclohex-2-enone: reaction of 4-hydroxycyclohex-2-enone and 4-hydroxycyclopent-2-enone with some thiols

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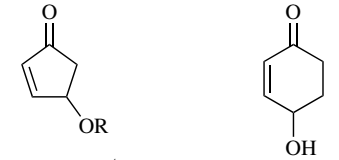
Abstract—A new route to (*R*)-4-hydroxycyclohex-2-enone from cyclohexanedione monoketal (27% yield) commences with reaction of the ketal with nitrosobenzene catalysed by L-proline. 4-Hydroxycyclohex-2-enone and 4-hydroxycyclopent-2-enone react with thiols to afford the corresponding *syn*-disubstituted cycloalkanones.

1. Introduction

For some time, we and others have been interested in the use of 4-substituted cycloalk-2-enones in synthetic organic chemistry.[1] Within this broad series of compounds, 4-*tert*-butyldimethylsilyloxycyclopent-2-enone **1** is the best known example, particularly in connection with Noyori's three component synthesis of prostaglandins.[2] More recently, silyl compound **1** has been shown to exhibit startling biological activity in its own right; for instance it shows significant inhibition of the important gene-signalling agent NF kappa B.[3]

Enone **1** undergoes a Michael-type 1,4-conjugate addition reactions with nucleophiles, such as cuprate reagents and thiols. The bulky silyloxy group directs the incoming nucleophile to the opposite face of the electrophilic enone unit. Herein we report the addition of thiols to the parent compound 4-hydroxycyclopent-2-enone **2**.

4-Hydroxycyclohex-2-enone **3** (and its derivatives) have also been utilised extensively as synthetic building blocks in organic chemistry.[4] In the latter section of this paper, we describe a new route to the optically active hydroxy ketone **3** (Fig. 1).



1 R = $SiMe_2{}^tBu$
2 R = H
3

Figure 1.

2. Results and discussion

Addition of benzylthiol to silyl compound **1** gave a single diastereomer of the adduct **4**[5] (Scheme 1) as expected and as described previously.[6]

Reduction of adduct **4** using sodium borohydride under Lüche conditions was not very selective, affording the diastereomers **5** and **6** in a ratio 4:3 (by ^{1}H NMR), separable by column chromatography. Deprotection of the major isomer **5** under standard conditions furnished diol **7**, the structure of which was confirmed by X-ray crystallography (Fig. 2).[7] Similarly, compound **6** was deprotected to give a sample of diol **8**.

Reaction of 4-hydroxycyclopent-2-enone **2** with benzyl thiol in dichloromethane containing a catalytic amount of triethylamine gave a single product.[6] However, conducting the same reaction in the absence of triethylamine

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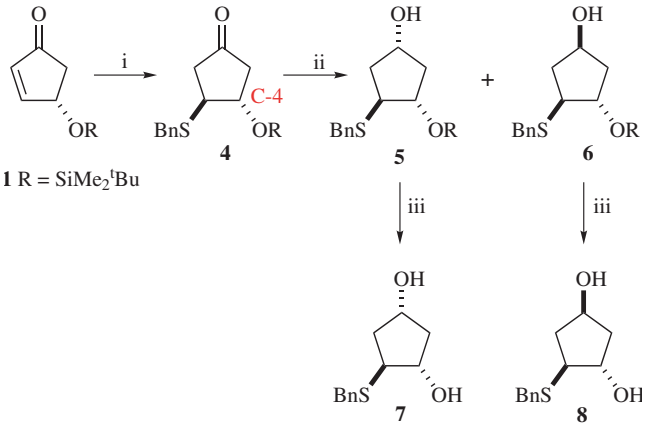


Scheme 1. Reagents and conditions: (i) BnSH (1 equiv), Et_3N (0.1 equiv), DCM, rt, 91%; (ii) $NaBH_4$ (1 equiv), $CeCl_3{\cdot}7H_2O$ (0.5 equiv), MeOH, 99%; (iii) TBAF (1 equiv), DCM, 98%.

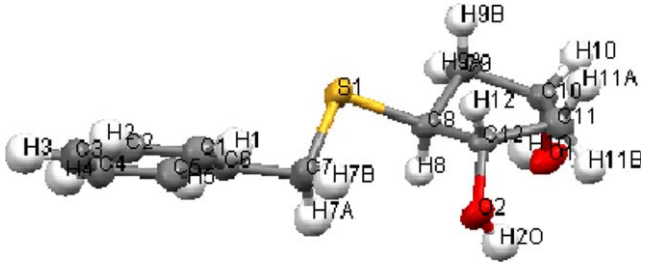
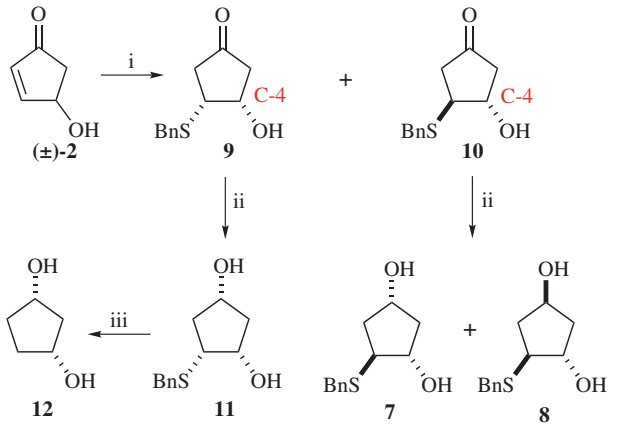


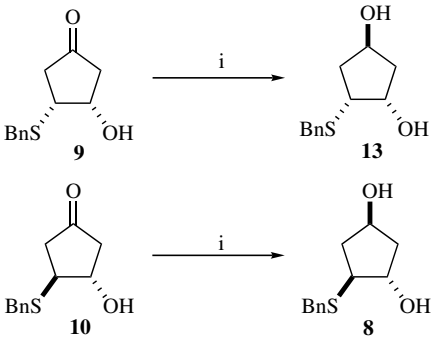
Figure 2.

gave rise to a second, minor product while the proportion of this minor product was substantially increased when the enone was reacted with the thiol using dimethylsulfoxide as the solvent. The ^{13}C NMR spectra of the two adducts formed from enone **2** were compared to the 'standard' *anti*-adduct **4**. The signal assigned to C-4 in compound **4** was observed at 74.9 ppm. The equivalent signal from the major adduct derived from the combination of compound **2** and benzylthiol appeared at 68.4 ppm; the minor adduct showed a signal in the ^{13}C NMR spectrum at 74.2 ppm. Thus it began to appear that the major adduct may in fact be the *syn*-adduct **9** while the minor adduct may be the *anti*-adduct **10**. Further transformations of the adducts confirmed this postulate. Thus the reduction of the minor adduct with $NaBH_4$ and cerium(III) chloride gave a mixture of diols **7** (53%) and **8** (43%). In contrast, the major *syn*-adduct gave a different diol **11** as the sole product. Desulfurization confirmed the relative orientation of the two hydroxy groups in the latter compound through the formation of the known *meso*-diol **12**[8] (Scheme 2). In order to confirm this hypothesis and to extend the synthetic utility of this sequence the reduction of **9** under Evans' conditions[9] was considered. Pleasingly under these conditions reduction of **9** furnished the remaining diastereomer **13** selectively (Scheme 3).

The reaction of hydroxy ketone **2** with dodecylthiol, or *para*-chlorobenzylthiol or cyclopentylthiol in dichloromethane containing triethylamine gave a single adduct

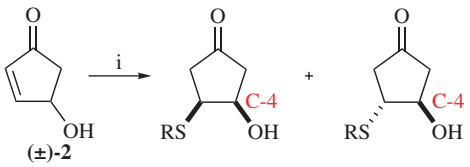


Scheme 2. Reagents and conditions: (i) (a) BnSH (1 equiv), DCM, Et_3N (0.1 equiv), rt, **9** 91%, (b) BnSH (1 equiv), DMSO, rt, **10** 59% (**9** 24% as the faster eluting diastereomer); (ii) $NaBH_4$ (1 equiv), $CeCl_3{\cdot}7H_2O$ (0.5 equiv), MeOH, 99%; (iii) Raney nickel (1 equiv), EtOH, 90%.



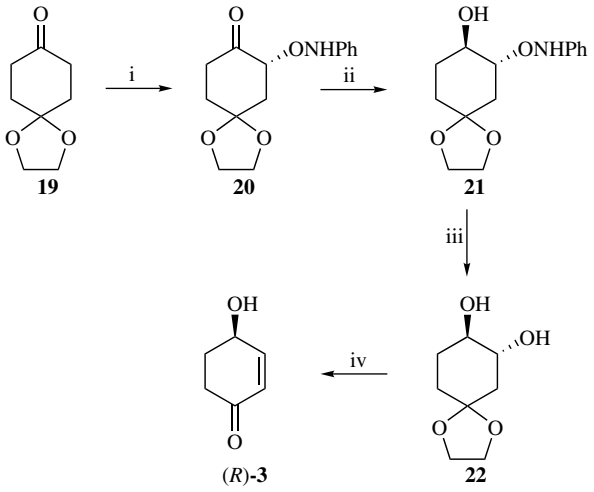
Scheme 3. Reagents and conditions: (i) $NMe_4(OAc)_3BH$ (5 equiv), AcOH (10 equiv), CH_3CN, 0 °C, 48 h, 86–91%.

in each instance (de >95%). In all cases, the ^{13}C NMR signal for C-4 appeared in the range 68.3–68.5 ppm and consequently the products **14**–**16** were assigned the *syn*-configuration. Under these standard conditions, however, reaction of compound **2** with 2-naphthylthiol produced the *syn*-adduct **17** (C-4 signal at 68.95) and the *anti*-adduct **18** (C-4 signal at 73.1) in the ratio ca. 1:1, possibly reflecting the reversibility of the conjugate addition in this instance (Scheme 4). The ratios of **17** and **18** were ca. 1:1 and ca. 1:2 when the reaction was conducted in DCM/Et_3N and DMSO, respectively.



14 R = $C_{12}H_{24}$
15 R = CH_2-C_6H_4Cl
16 R = cyclopentyl
17 (*syn*) and **18** (*anti*) R = 2-naphthyl

Scheme 4. Reagents and conditions: (i) RSH (1 equiv), Et_3N (0.1 equiv), DCM, rt.

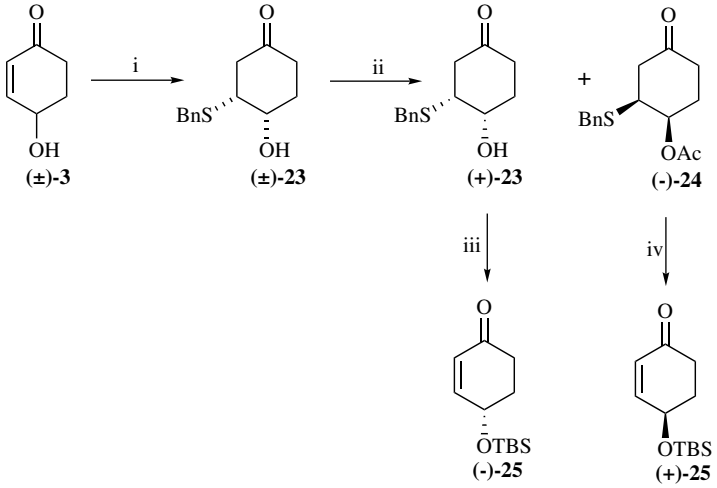


Scheme 5. Reagents and conditions: (i) PhNO, L-Pro (30 mol %), DMF; (ii) $NaBH_4$ (2.1 equiv), $CeCl_3 \cdot 7H_2O$ (2.1 equiv), MeOH; (iii) $CuSO_4$ (30 mol %), MeOH; (yield 40% for three steps); (iv) 2 M $HCl_{(aq)}$, THF/H_2O (1:1), 69%.

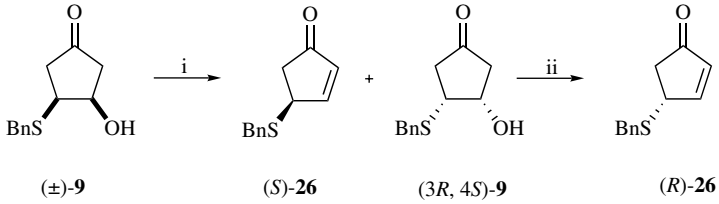
Our new approach to the formation of optically active 4-hydroxycyclohex-2-enone **3** commenced with oxidation of the mono-ketal **19** using nitrosobenzene with L-proline as the catalyst as described previously (Scheme 5).[10] The resultant optically active hydroxylamine **20** was reduced to afford a single alcohol **21** using Lűche conditions. The resulting alcohol **21** was treated with catalytic copper sulfate to produce diol **22**. A one-pot deketalisation/elimination cascade produced (*R*)-4-hydroxycyclohex-2-enone (*R*)-**3** in 69% yield and 93.9% ee. We have shown in an earlier paper that 4-hydroxycyclohex-2-enone reacts with benzylthiol to produce the *syn*-3-benzylthia-4-hydroxycyclohexanone as part of an alternative process to provide optically active 4-hydroxycyclohex-2-enone, optionally isolated as the TBS protected compound **25** (Scheme 6).[6]

3. Conclusion

A new route to optically active 4-hydroxycyclohex-2-enone (27% from **19**, Scheme 5) is competitive to an earlier route to this building block that we recently reported (15% from **3**, Scheme 6). Contrary to our early expectations,[6] 4-hydroxycyclopent-2-enone **2** reacts with thiols in a relatively nonpolar solvent (DCM) to give the *syn*-adducts predominantly or exclusively. Presumably the thiol/thiolate is encouraged to approach the enone moiety from the more hindered face by hydrogen bonding to the OH group and to the best of our knowledge this type of 'directed' conjugate addition has not been reported previously. In a polar solvent, such as dimethylsulfoxide, the key intermolecular interaction is reduced or even eliminated. The substitution pattern is important in connection with the conversion of optically active 4-hydroxycyclopent-2-enone **2** into optically active 4-benzylthiacyclopent-2-enone **26** (Scheme 7).[6]



Scheme 6. Reagents and conditions: (i) BnSH (1 equiv), Et_3N (0.1 equiv), DCM, rt; (ii) Novozym 435, vinyl acetate (5 equiv), DIPE, 30 °C; (iii) TBSCl (3 equiv) DBU (4 equiv), DCM, rt, 16 h; (iv) (a) $NaIO_4$ (1 equiv), MeOH/H_2O (1:1), 0 °C > rt, 16 h, (b) toluene, Δ 16 h, (c) K_2CO_3 (1 equiv), MeOH, rt, 2 h, (d) TBSCl (1.1 equiv), DBU (1.2 equiv), rt, 16 h.



Scheme 7. Reagents and conditions: (i) (a) Novozym 435, vinyl acetate (5 equiv), DIPE, 30 °C, (b) Et_3N (0.1 equiv) 30 min; (ii) Ac_2O, Et_3N, DCM, rt.

In contrast to our earlier report, the lipase-mediated kinetic resolution of the benzylthiol adduct **9** derived from racemic 4-hydroxycyclopent-2-enone **2** produces (4*S*)-benzylthiacyclopent-2-enone (*S*)-**26** and (3*R*,4*S*)-3-benzylthia-4-hydroxycyclopentanone (3*R*,4*S*)-**9**. Treatment of the latter compound with acetic anhydride and triethylamine affords (4*R*)-benzylthiacyclopent-2-enone (*R*)-**26**.

4. Experimental

4.1. (±)-*syn*-3-Benzylthio-4-hydroxycyclopentanone 9

In a dry 250 mL round-bottomed flask, a solution of benzyl mercaptan (6.95 g, 56 mol equiv) in anhydrous dichloromethane (5 mL) and triethylamine (0.52 g, 5.6 mmol, 0.1 equiv) was added to a solution of enone **2** (5.0 g, 56 mmol, 1 equiv) in anhydrous dichloromethane (120 mL). The reaction mixture was stirred under argon at room temperature for 16 h. Solvent was removed in vacuo and the resultant residue purified by column chromatography (1% MeOH in CH_2Cl_2, $R_f = 0.42$) to afford the title compound (92%) as a white solid mp 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (1H, ddd, $J = 1.5$, 12.0, 18.5 Hz, CH_AH_B), 2.27 (1H, dd, $J = 4.5$, 18.5 Hz, CH_AH_B), 2.39 (1H, ddd, $J = 1.0$, 8.0, 18.5 Hz, CH_AH_B), 2.50 (1H, dd, $J = 1.25$, 18.5 Hz, CH_AH_B), 2.70 (1H, s, OH), 3.28 (1H, ddd, $J = 3.5$, 8.25, 11.75 Hz, C*H*S), 3.76 (1H, d, $J = 13.75$ Hz, CH_AH_B), 3.82 (1H, d, $J = 13.75$ Hz, CH_AH_B), 4.16 (1H, apparent t, $J = 3.85$ Hz, C*H*OH) 7.25–7.36 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 213.4 (C=O), 137.7 (C), 128.9 (CH), 128.6 (CH), 127.7 (CH), 68.0 (CHOH), 47.1 (CHS), 46.5 (CH_2), 40.3 (CH_2), 35.5 (CH_2). IR *v*max (neat, cm^{-1}) 3478, 3055, 2985, 2921, 2305, 1748, 1602, 1264, 735. HRMS calcd for $C_{12}H_{18}NO_2S$ (CI, MNH_4^+) requires 240.1058; found 240.1058. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.86; H, 6.31. Found: C, 64.60; H, 6.31.

4.2. (1*R*,3*S*,4*R*)-4-(Benzylthio)cyclopentane-1,3-diol 11

In a dry 250 mL round-bottomed flask, a solution of **9** (50 mg, 0.23 mmol, 1 equiv) methanol (4 mL) and cerium trichloride heptahydrate (84 mg, 0.23 mmol, 1 equiv) was stirred at −78 °C. To this solution sodium borohydride (8.5 mg, 0.23 mmol, 1 equiv) was added portionwise. The reaction mixture was stirred for a further 15 min. Water (10 mL) was added to quench the reaction. The resultant biphasic solution was extracted with ethyl acetate (4 × 15 mL). The combined organic extractions were washed with brine (sat.), dried over magnesium sulfate and filtered. Solvent was removed in vacuo. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1, $R_f = 0.47$). Yield = 94%. $[\alpha]_D = +97.1$ (*c* 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (1H, ddt, $J = 2.0$, 9.75, 16.75 Hz, CH_AH_B), 1.74 (1H, ddd, $J = 3.75$, 6.5, 14.75 Hz, CH_AH_B), 2.05–2.15 (1H, m, CH_AH_B), 2.48 (1H, ddd, $J = 7.0$, 10.0, 16.75 Hz, CH_AH_B), 2.92 (1H, m, C*H*S), 2.93 (1H, s, OH), 3.70 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.75 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.92 (1H, m apparent t, $J = 3.5$ Hz, C*H*OH), 4.17–4.25 (1H, m, C*H*OH), 7.24–7.36 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C), 129.2 (CH), 129.0 (CH), 127.8 (CH), 72.7 (CHOH), 72.0 (CHOH), 50.2 (CHS), 42.6 (CH_2), 41.0 (CH_2), 36.8 (CH_2). IR *v*max (neat, cm^{-1}) 3451, 3030, 2970, 2932. HRMS calcd for $C_{12}H_{17}O_2S$ (CI+NH_3) requires 225.09494; found 225.09514.

4.3. (±)-*anti*-3-Benzylthio-4-hydroxycyclopentanone 10

In a dry 10 mL round-bottomed flask, a solution of benzyl mercaptan (188 mg, 1.53 mmol, 1 equiv) in anhydrous dimethyl sulfoxide (4 mL) was added to a solution of enone **2** (150 mg, 1.53 mmol, 1 equiv) in anhydrous dimethyl sulfoxide (5 mL). The reaction mixture was stirred under argon at room temperature for 16 h. To the reaction mixture were added dichloromethane (40 mL) and water (40 mL). The biphasic solution was then partitioned. The aqueous layer was further extracted with dichloromethane (3 × 30 mL.). The organic extractions were combined and dried over magnesium sulfate and filtered. The filtrate was absorbed onto silica and purified by column chromatography (% MeOH in CH_2Cl_2, $R_f = 0.29$) to give ketone **10** (59%) as a clear oil. (±)-*syn*-3-Benzylthio-4-hydroxycyclopentanone **9** (24%) was the faster eluting diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13–2.27 (2H, m, 2 × CH_AH_B), 2.69–2.78 (2H, m, 2 × CH_AH_B), 3.13–3.19 (1H, m, C*H*S), 3.79 (1H, d, $J = 13.75$ Hz, CH_AH_B), 3.87 (1H, d, $J = 13.75$ Hz, CH_AH_B), 4.32–4.38 (1H, m apparent q, $J = 4.75$ Hz, C*H*OH), 7.32–7.56 (5H, m, Ar*H*) ^{13}C NMR (100 MHz, $CDCl_3$) 214.1 (C=O), 138.1 (C), 129.2 (CH), 128.6 (CH), 127.8 (CH), 74.2 (CHOH), 47.9 (CHS), 46.0 (CH_2), 43.8 (CH_2), 36.5 (CH_2). HRMS calcd for $C_{12}H_{18}NO_2S$ (CI, MNH_4^+) requires 240.1058; found 240.1050.

4.4. (3*S*,4*S*)-3-(Benzylthio)-4-(*tert*-butyldimethylsilyloxy) cyclopentanone 4

In a dry 50 mL round-bottomed flask, a solution of benzyl mercaptan (1.22 g, 9.8 mmol, 1 equiv) in anhydrous dichloromethane (5 mL) and triethylamine (49 mg, 0.98 mmol, 0.1 equiv) was added to a solution of enone **1** (2.08 g, 9.8 mmol, 1 equiv) in anhydrous dichloromethane (20 mL). The reaction mixture was stirred under argon at room temperature for 16 h. Solvent was removed in vacuo and the resultant residue purified by column chromatography (19:1, *n*-hexane/ethyl acetate, $R_f = 0.33$) to provide compound **4** (88%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1 (6H, 2 × s, $(CH_3)_2$), 0.87 (9H, s, *tert*-butyl), 2.06–2.16 (2H, m, 2 × CH_AH_B), 2.65 (1H, m, CH_AH_B), 2.71 (1H, m, CH_AH_B), 3.17 (1H, ddd, $J = 1.5$, 4.25, 8.5 Hz, C*H*S), 3.74 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.82 (1H, d, $J = 13.5$ Hz, CH_AH_B), 4.32 (1H, ddd, $J = 3.0$, 6.0, 8.5 Hz, C*H*OH), 7.20–7.31 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 215.0 (C=O), 138.0 (C), 129.1 (CH), 129.0 (CH), 127.7 (CH), 74.9 (CHOH), 48.1 (CHS), 46.6 (CH_2), 43.1 (CH_2), 36.6 (CH_2), 26.0 (^{t}Bu), 18.3 (C), −4.4 (2 × CH_3). IR *v*max (neat, cm^{-1}) 3054, 2984, 1747, 1422, 1205, 836. HRMS calcd for $C_{18}H_{32}O_2SSiN$ (CI, MNH_4^+) requires 354.19232; found

354.19144. Anal. Calcd for $C_{18}H_{28}O_2SSi$: C, 64.24; H, 8.39. Found: C, 64.10; H, 8.36.

4.5. (1*R*,3*S*,4*S*)-3-(Benzylthio)-4-(*tert*-butyldimethylsilyloxy)cyclopentanol 5 and (1*S*,3*S*,4*S*)-3-(benzylthio)-4-(*tert*-butyldimethylsilyloxy)cyclopentanol 6

In a dry 50 mL round-bottomed flask, a solution of **4** (500 mg, 1.5 mmol, 1 equiv) and methanol (20 mL), and cerium trichloride heptahydrate (569 mg, 1.5 mmol, 1 equiv) were stirred at −78 °C. To this solution, sodium borohydride (57 mg, 1.5 mmol, 1 equiv) was added portionwise. The reaction mixture was stirred for a further 15 min. Water (20 mL) was then added to quench the reaction. The resultant solution was extracted with ethyl acetate (4 × 15 mL). The combined organic extractions were washed with brine (satd), dried over magnesium sulfate and filtered. Solvent was removed in vacuo. The residue was purified by column chromatography (0.5% methanol in CH_2Cl_2, $R_f = 0.47$ **5** and 0.43 **6**) to yield compound **5** (49%) and **6** (38%). Data for compound **5** ^{1}H NMR (400 MHz, $CDCl_3$) **5** δ 0.1 (6H, 2 × s, $(CH_3)_2$), 0.9 (9H, s, *tert*-butyl), 1.76–1.87 (2H, m, 2 × CH_AH_B), 2.11 (1H, dt, $J = 5.0$, 14.0 Hz, CH_AH_B), 2.32 (1H, ddt, $J = 1.75$, 8.25, 14.75 Hz, CH_AH_B), 3.16 (1H, ddd, 1.75, 5.5, 8.0 Hz, C*H*S), 3.73 (1H, d, $J = 13.75$ Hz, CH_AH_B), 3.79 (1H, d, $J = 13.75$ Hz, CH_AH_B), 4.20–4.23 (1H, m, C*H*OTBS), 4.28–4.33 (1H, m, C*H*OH), 7.22–7.35 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C), 129.2 (CH), 128.9 (CH), 127.5 (CH), 80.6 (CHOH), 73.8 (CHOH), 50.4 (CHS), 43.2 (CH_2), 42.8 (CH_2), 37.0 (CH_2), 25.1 (^{t}Bu), 18.2 (C), −4.2 (CH_3), −4.4 (CH_3). HRMS calcd for $C_{18}H_{34}O_2SSiN$ (CI, M+NH_3) requires 356.20798; found 356.20704. Data for compound **6** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1 (6H, 2 × s, $(CH_3)_2$), 0.9 (9H, s, *tert*-butyl), 1.52 (1H, ddd apparent dt, $J = 5.0$, 14.25 Hz, CH_AH_B), 1.81 (1H, m, CH_ACH_B), 1.92–1.99 (1H, m, CH_ACH_B), 2.40 (1H, dt, 1H, $J = 7.25$, 14.25 Hz, CH_AH_B), 2.80 (1H, ddd, $J = 4.5$, 6.0, 10.5 Hz, C*H*S), 3.72 (1H, d, J = 13.25 Hz, CH_AH_B), 3.78 (1H, d, $J = 13.25$ Hz, CH_ACH_B), 4.18–4.23 (1H, m, C*H*OTBS), 4.32 (1H, dddd, $J = 2.5$, 4.5, 6.5, 14.25 Hz, C*H*OH), 7.15–7.30 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 137.2 (C), 127.8 (CH), 127.5 (CH), 126.0 (CH), 77.5 (CHOH), 70.5 (CHOH), 49.0 (CHS), 43.8 (CH_2), 39.6 (CH_2), 35.3 (CH_2), 24.8 (^{t}Bu), 16.9 (C), −5.6 (CH_3), −5.7 (CH_3). IR *v*max (neat, cm^{-1}) 3416, 2928, 2856, 1361, 1256, 836. HRMS calcd for $C_{18}H_{34}O_2SSiN$ (CI, M+NH_3) requires 356.20798; found 356.20686.

4.6. (±)-*syn*-3-(Dodecylthio)-4-hydroxycyclopentanone 14

Enone **2** (500 mg, 5.1 mmol, 1 equiv) was reacted with dodecylthiol (1.03 g, 5.1 mmol, 1 equiv) as described above. Purification by column chromatography (1% MeOH in CH_2Cl_2, $R_f = 0.25$) gave the title compound **14** as a white solid (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.8 (3H, t, $J = 6.75$ Hz, CH_3), 1.23–1.35 (18H, m, CH_2), 1.36–1.44 (2H, m, CH_2), 1.59–1.68 (2H, m, CH_2), 2.19 (1H, ddd, $J = 1.4$, 11.75, 18.5 Hz, CH_AH_B), 2.36 (1H, dd, $J = 4.5$, 18.5 Hz, CH_AH_B), 2.49 (1H, ddd, J = 0.8, 8.0, 18.5 Hz, CH_AH_B), 2.56–2.62 (2H, m, CH_2), 3.40 (1H, ddd, $J = 3.25$, 8.0, 11.25 Hz, C*H*S), 4.36 (1H, dd apparent t, $J = 4.0$ Hz, C*H*OH). ^{13}C NMR (100 MHz, $CDCl_3$) 214.0 (C=O), 68.3 (CHOH), 48.3 (CHS), 46.9 (CH_2), 41.0 (CH_2), 32.3 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 30.0 (CH_2), 29.95 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 23.0 (CH_2), 14.5 (CH_3). IR *v*max (neat, cm^{-1}) 3477, 2926, 2855, 1749, 1466, 1394, 1332, 1283, 1212, 1152, 1009, 909, 733. HRMS calcd for $C_{17}H_{36}O_2SN$ (CI, M+NH_3) requires 318.24670; found 318.24718.

4.7. (±)-*syn*-3-(4-Chlorobenzylthio)-4-hydroxycyclopentanone 15

Enone **2** (1.0 g, 10.2 mmol, 1 equiv) was reacted with *para*-chlorobenzyl thiol (1.62 g, 10.2 mmol, 1 equiv) as described above. Purification by column chromatography (1% MeOH in CH_2Cl_2, $R_f = 0.25$) gave the title compound **14** as a yellow oil (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (1H, ddd, $J = 1.0$, 11.75, 18.5 Hz, CH_AH_B), 2.29 (1H, dd, $J = 4.5$, 18.5 Hz, CH_AH_B), 2.40 (1H, ddd, $J = 1.0$, 8.25, 18.5 Hz, CH_AH_B), 2.52 (1H, dd, $J = 1.0$, 18.5 Hz, CH_AH_B), 3.27 (1H, ddd, $J = 3.25$, 8.0, 11.75 Hz, C*H*S), 3.73 (1H, d, $J = 13.75$ Hz, CH_AH_B), 3.79 (1H, d, $J = 13.75$ Hz, CH_AH_B), 4.19–4.23 (1H, m, C*H*OH), 7.26–7.38 (4H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) 213.1 (C=O), 139.6 (C), 136.1 (C-Hal), 129.9 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 68.1 (CHOH), 47.0 (CHS), 46.5 (CH_2), 40.3 (CH_2), 34.7 (CH_2). IR *v*max (neat, cm^{-1}) 3425.6, 3054.9, 2951.4, 1679.2, 1491.7, 744.0. HRMS calcd for $C_{12}H_{17}ClO_2SN$ (CI, M+NH_3) requires 274.06686; found 274.06746.

4.8. (±)-*syn*-3-(Cyclopentylthio)-4-hydroxycyclopentanone 16

Enone **2** (500 mg, 5.1 mmol, 1 equiv) was reacted with cyclopentyl thiol (521 mg, 5.1 mmol, 1 equiv) as described above. Purification by column chromatography (*n*-hexane/ethyl acetate, 1:1 $R_f = 0.25$) gave the title compound **15** as a clear oil (90%).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48–1.67 (4H, m, 2 × CH_2), 1.73–1.84 (2H, m, CH_2), 2.02–2.12 (2H, m, CH_2), 2.20 (1H, ddd, $J = 1.25$, 12.0, 18.5 Hz, CH_AH_B), 2.38 (1H, dd, 4.5, 18.5 Hz, CH_AH_B), 2.50 (1H, ddd, $J = 0.75$, 8.25, 18.5 Hz, CH_AH_B), 2.60 (1H, dd, $J = 1.5$, 18.5 Hz, CH_AH_B), 1.98 (1H, s, OH), 3.14–3.22 (1H, m apparent quint, $J = 7.25$ Hz, C*H*S), 3.47 (1H, ddd, $J = 3.5$, 8.25, 12.0 Hz, C*H*S), 4.36–4.40 (1H, m apparent t, $J = 4.0$ Hz, C*H*OH). ^{13}C NMR (100 MHz, $CDCl_3$) 214.0 (C=O), 68.4 (CHOH), 47.7 (CHS), 46.6 (CH_2), 43.2 (CHS), 40.6 (CH_2), 39.3 (CH_2), 34.3 (CH_2), 24.6 (CH_2). IR *v*max (neat, cm^{-1}) 3464, 2960, 1747. HRMS calcd for $C_{10}H_{20}O_2SN$ (CI, M+NH_3) requires 218.12148; found 218.12136. Anal. Calcd for $C_{10}H_{16}O_2S$: C, 59.96; H, 8.05. Found: C, 60.01; H, 8.05.

4.9. (±)-*syn*-3-Hydroxy-4-(naphthalene-2-ylthio)-cyclopentanone 17 and 18

Enone **2** (1.0 g, 10.2 mmol, 1 equiv) was reacted with 2-naphthyl thiol (1.63 g, 10.2 mmol, 1 equiv) as described

above. Purification by column chromatography (1% MeOH in CH_2Cl_2, $R_f = 0.27$) furnished a mixture of **17** and **18** as a pale, yellow oil (69%). Data for compound **17** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30–2.45 (2H, m, $2 \times CH_AH_B$), 2.54–2.65 (2H, m, CH_AH_B), 2.93 (1H, s, OH) 3.87 (1H, ddd, $J = 3.25$, 8.0, 11.5 Hz, C*H*S), 4.32–4.38 (1H, m, C*H*OH), 7.48–7.55 (3H, m, Ar*H*), 7.76–7.84 (3H, m, Ar*H*), 7.94–7.97 (1H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 213.5 (C=O), 134.1 (C), 133.0 (C), 131.6 (C), 130.2 (CH), 129.5 (CH), 129.4 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 68.8 (CHOH), 51.4 (CHS), 46.9 (CH_2), 40.7 (CH_2). IR *v*max (neat, cm^{-1}) 3444, 1749, 1393, 907, 731. HRMS calcd for $C_{15}H_{18}O_2SN$ (CI, M+NH_3) requires 276.10583; found 276.10613.

4.10. (1*R*,3*S*,4*S*)-4-(Benzylthio)cyclopentane-1,3-diol 7

To a solution (0 °C) of the silyl ether **5** (150 mg, 0.443 mmol, 1 equiv) in dry tetrahydrofuran (11.6 mL), was added tetra-*n*-butylammonium fluoride (TBAF) (1 M solution in tetrahydrofuran, 1.1 equiv); the resulting solution was stirred for 45 min allowing the mixture to warm to room temperature. The resulting solution was then diluted with dichloromethane (20 mL) and quenched with water (5 mL). The organic layer was extracted with brine (5 mL) and dried over magnesium sulfate, solvent was removed in vacuo. The crude product was purified by flash column chromatography (*n*-hexane/ethyl acetate, 3:1 $R_f = 0.20$) to give the diol **7** as a clear oil (87%). $[\alpha]_D = -39.3$ (*c* 0.89, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (1H, ddd, $J = 1.25$, 5.5, 14.5 Hz, CH_AH_B), 1.78–1.85 (1H, m, CH_AH_B), 2.12 (1H, dt, $J = 5.25$, 14.5 Hz, CH_AH_B), 2.25 (1H, ddt, $J = 1.75$, 8.25, 14.5 Hz, CH_AH_B), 3.15–3.21 (1H, m, C*H*S), 3.75 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.82 (1H, d, $J = 13.5$ Hz, CH_AH_B), 4.10–4.15 (1H, m, C*H*OH), 4.35–4.40 (1H, m, C*H*OH), 7.22–7.37 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 138.6 (C), 129.3 (CH), 129.0 (CH), 127.5 (CH), 79.9 (CHOH), 73.8 (CHOH), 50.2 (CHS), 42.4 (CH_2), 42.3 (CH_2), 37.2 (CH_2). IR *v*max (neat, cm^{-1}) 3441, 3054, 2986, 2928, 1422, 1266. HRMS calcd for $C_{12}H_{20}O_2SN$ (CI, MNH_4^+) requires 242.12148; found 242.12148.

4.11. (1*S*,3*S*,4*S*)-4-(Benzylthio)cyclopentane-1,3-diol 8

To a solution (0 °C) of silyl ether **6** (1 equiv) in dry tetrahydrofuran (11.6 mL), was added tetra-*n*-butylammonium fluoride (TBAF) (1 M solution in tetrahydrofuran, 1.1 equiv) and the resulting solution stirred for 45 min allowing the mixture to warm to room temperature. The resulting solution was diluted with dichloromethane (20 mL) and quenched with water (5 mL). The organic layer was extracted with brine (5 mL) and dried over magnesium sulfate, followed by solvent removal in vacuo. The crude product was purified by flash column chromatography (*n*-hexane/ethyl acetate, 3:1, $R_f = 0.17$) to give the diol **8** as a clear oil (83%). $[\alpha]_D = +40.9$ (*c* 0.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (1H, dddd, $J = 0.8$, 4.5, 7.0, 14.0 Hz, CH_AH_B), 1.90 (1H, m, CH_AH_B), 2.05 (1H, dddd, $J = 0.8$, 4.25, 6.75, 14.0 Hz, CH_AH_B), 2.48 (1H, ddd apparent dt, $J = 7.5$, 14.25 Hz, CH_AH_B), 2.81 (1H, ddd, $J = 5.25$, 7.50, 13.0 Hz, C*H*S), 3.78 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.85 (1H, d, $J = 13.5$ Hz, CH_AH_B), 4.24 (1H, dt, app. q, $J = 5.75$, 12.0 Hz, C*H*OH), 4.37 (1H, dddd, $J = 4.25$, 4.50, 8.50, 8.75 Hz, C*H*OH), 7.21–7.37 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 138.7 (C), 129.3 (CH), 129.0 (CH), 127.6 (CH), 78.0 (CHOH), 71.3 (CHOH), 50.4 (CHS), 44.0 (CH_2), 41.4 (CH_2), 36.4 (CH_2). IR *v*max (neat, cm^{-1}) 3441, 3054, 2986, 2928, 1422, 1266. HRMS calcd for $C_{12}H_{20}O_2SN$ (CI, MNH_4^+) requires 242.12148; found 242.12138.

4.12. (1*S*,3*S*,4*R*)-4-(Benzylthio)cyclopentane-1,3-diol 13

In a 25 mL round-bottomed flask, a solution of tetramethylammonium triacetoxyborohydride (600 mg, 2.3 mmol, 5 equiv) and acetic acid (0.26 mL, 4.5 mmol, 10 equiv) in 10 mL of acetonitrile was added to a solution of **9** (100 mg, 0.45 mmol, 1 equiv) in 1 mL of acetonitrile. The reaction mixture was stirred at 0 °C for 48 h before it was quenched with 3.0 mL of saturated aqueous ammonium chloride solution. After effervescence had ceased, the solution was treated with 3 mL of 1.0 M aqueous sodium/potassium tartrate solution and stirred for 20 min. The aqueous solution was extracted with dichloromethane (10×5 mL). The combined organic layers were washed with 5 mL of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1, $R_f = 0.16$) to give the diol **13** as a clear oil. Yield = 86%. $[\alpha]_D = +57.2$ (*c* 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (1H, apparent dt, $J = 4.25$, 14.75 Hz, CH_AH_B), 1.87 (2H, m, $2 \times CH_AH_B$), 2.24 (1H, ddd, $J = 2.0$, 6.75, 14.75 Hz, CH_AH_B), 3.32 (1H, m, C*H*S), 3.71 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.76 (1H, d, $J = 13.5$ Hz, CH_AH_B), 3.97–4.01 (1H, m, C*H*OH), 4.44–4.49 (1H, m, C*H*OH), 7.28–7.40 (5H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 138.6 (C), 129.1 (CH), 129.0 (CH), 127.7 (CH), 71.3 (CHOH), 71.1 (CHOH), 49.7 (CHS), 43.9 (CH_2), 40.0 (CH_2), 36.7 (CH_2). HRMS calcd for $C_{12}H_{17}O_2S$ (CI, MNH_4^+) requires 225.09494; found 225.09414.

4.13. *trans*-1,4-Dioxa spiro[4.5]decane-7,8-diol 22

To a 50 mL round-bottomed flask containing a solution of 1,4-cyclohexanedione monoethyleneketal **19** (1 g, 6.41 mmol) and L-proline (112 mg, 0.96 mmol) in dimethylformamide (15 mL) at 0 °C was added a solution of nitrosobenzene (343 mg, 3.2 mmol) in dimethylformamide (4 mL) over 15 h by syringe pump. The reaction mixture was stirred for 2 h. Methanol (8 mL) and cerium chloride heptahydrate (2.37 g, 7.05 mmol) were added to the reaction mixture before adding sodium borohydride (266 mg, 7.05 mmol). The reaction mixture was stirred for 30 min at 0 °C, before the addition of copper sulfate pentahydrate (240 mg, 0.96 mmol). The reaction mixture was stirred for 16 h at 0 °C. Water (10 mL) was added to

quench the reaction. The resultant biphasic solution was extracted with ethyl acetate (4×20 mL) and the combined organic extracts washed with brine (satd), dried over magnesium sulfate and filtered. Solvent was removed in vacuo and the residue purified by column chromatography (5% methanol in CH_2Cl_2, $R_f = 0.21$) to yield the title compound **22** (40%) as a light brown oil. $[\alpha]_D = 0$ (*c* 1, DCM) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (3H, m, $3 \times CH_AH_B$), 1.75 (1H, m, CH_AH_B), 1.93 (1H, m, CH_AH_B), 2.08 (1H, ddd, $J = 2.5$, 4.5, 13.0 Hz, CH_AH_B), 3.52 (1H, ddd, $J = 4.5$, 8.3, 13.0 Hz, C*H*OH), 3.66 (1H, ddd, $J = 4.2$, 8.0, 12.3, C*H*OH), 3.95 (4H, m, OCH_2CH_2O). ^{13}C NMR (100 MHz, $CDCl_3$) 109.1 (COO), 74.4 (CO), 73.1 (CO), 64.8 (CH_2), 64.8 (CH_2), 40.5 (CH_2), 32.7 (CH_2), 28.4 (CH_2). IR *v*max (neat, cm^{-1}) 3395, 2951, 2891, 1447, 1357, 1102, 1052; HRMS calcd for $C_8H_{15}O_4$ (Cl, MH^+) requires 175.09705; found 175.09709.

4.14. (*R*)-4-Hydroxycyclohex-2-enone 3

In a 25 mL round-bottomed flask, a solution of **21** (50 mg, 0.29 mmol), 2 M HCl (0.36 mL, 0.73 mmol), THF (3 mL) and water (3 mL) were stirred at room temperature for 24 h. Ammonium sulfate (satd aq, 25 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried over magnesium sulfate and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (50% ethyl acetate in *n*-hexane, $R_f = 0.20$) to afford the title compound **3** (69%) as a light yellow oil, ee = 93.6% (chiral GC; Lipodex-C, 100 °C; (*S*) = 20.10 min, (*R*) = 20.82 min). $[\alpha]_D = +94$ (*c* 1.0, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (1H, dddd, $J = 1.25$, 3.5, 9.5, 12.75 Hz, CH_AH_B), 2.32–2.44 (2H, m, $2 \times CH_AH_B$), 2.59 (1H, dtd, $J = 1.0$, 4.5, 17.75, CH_AH_B), 4.59 (1H, m), 5.97 (1H, ddd, $J = 1.0$, 2.0, 10.25, C*H*), 6.92 (1H, ddd, $J = 1.75$, 2.5, 10.25, C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) 198.9 (C=O), 152.8 (CH), 129.7 (CH), 66.7 (CH), 35.7 (CH_2), 32.9 (CH_2). IR *v*max (neat, cm^{-1}) 3396, 2957, 1698, 1417, 1378, 1132, 1065, 970, 943, 862. HRMS calcd for $C_6H_{12}O_2N$ (Cl, MNH_4^+) requires 130.08681; found 130.08660.

4.15. (*S*)-4-(*tert*-Butyldimethylsilyloxy)cyclohex-2-enone (*S*)-25

To a stirred solution of (3*R*,4*S*)-**23**[6] (70 mg, 0.25 mmol, 1 equiv) and TBSCl (75 mg, 0.50 mmol, 2 equiv) in anhydrous dichloromethane (25 mL) was added DBU (95 mg, 0.625 mmol, 2.5 equiv) dropwise over 5 min. The resultant mixture was stirred for a further 16 h at rt. The reaction mixture was diluted with dichloromethane (50 mL) and washed with H_2O (40 mL), 0.1 M HCl (2×40 mL), satd $NaHCO_3$ (40 mL) and brine (40 mL), dried over magnesium sulfate and concentrated in vacuo. Purification by column chromatography (*n*-hexane/ethyl acetate, 19:1 $R_f = 0.16$) gave the title compound (*S*)-**25** in 70% yield. $[\alpha]_D = -109.6$ (*c* 1.46, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (6H, $2 \times$ s, $(CH_3)_2$), 0.92 (9H, s, ^{t}Bu), 2.01 (1H, tdd, $J = 4.25$, 9.0, 12.75 Hz, CH_AH_B), 2.21 (1H, dqd, $J = 1.6$, 4.75, 12.75 Hz, CH_AH_B), 2.36 (1H, ddd, $J = 4.75$, 12.75, 17.0 Hz, CH_AH_B), 2.58 (1H, dtd apparent dt, $J = 4.25$, 16.75 Hz, CH_AH_B), 4.53 (1H, dddd, $J = 2.0$, 2.4, 4.5, 9.0 Hz, C*H*OTBS), 5.92 (1H, apparent d, $J = 10.25$ Hz, $CH_{allylic}$), 6.83 (1H, ddd apparent dt, $J = 2.25$, 10.25 Hz, $CH_{allylic}$). ^{13}C NMR (100 MHz, $CDCl_3$) 199.2 (C=O), 154.3 (CH), 129.1 (CH), 67.4 (CHOTBS), 35.9 (CH_2), 33.3 (CH_2), 26.0 (^{t}Bu), 18.5 (C), −4.2 (CH_3), −4.4 (CH_3).

4.16. (*R*)-4-(*tert*-Butyldimethylsilyloxy)cyclohex-2-enone (*R*)-25

To a solution of 1*R*,2*S*-**24**[6] in MeOH/H_2O (1:1) was added $NaIO_4$ (1 equiv) portionwise at 0 °C and the resultant mixture was stirred for 16 h. The white slurry was filtered through a sintered funnel and the filtrate concentrated in vacuo. The residue was taken up in dichloromethane (50 mL) and water (50 mL) and extracted with dichloromethane (5×30 mL). The combined organic extracts were washed with brine (30 mL) and H_2O (30 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in toluene and heated to 115 °C for 16 h. The reaction mixture was allowed to cool and concentrated in vacuo. The residue was dissolved in dichloromethane (50 mL) and H_2O (40 mL) was added. The mixture separated and the aqueous phase was extracted with dichloromethane (4×30 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulfate and concentrated in vacuo. The resultant residue (crude 4-acetoxycyclohex-2-enone) was dissolved in MeOH (20 mL) and cooled to 0 °C. To this mixture K_2CO_3 (1 equiv) was added and stirred for 30 min. Brine (30 mL) and dichloromethane (40 mL) were added and stirred for 25 min. The biphasic mixture was extracted with dichloromethane (4×25 mL). The combined organic extracts were washed with brine (25 mL) and H_2O (2×25 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to furnish 4-hydroxycyclohex-2-enone (*R*)-**3** as a brown oil.

A solution of crude (*R*)-**3** (1 equiv) and TBSCl (1 equiv) in anhydrous dichloromethane (20 mL) was stirred at rt under argon. DBU (1.1 equiv) was added dropwise over 10 min. After 3 h at rt, the reaction mixture was diluted with dichloromethane (50 mL) and washed with H_2O (40 mL), 0.1 M HCl (2×40 mL), satd $NaHCO_3$ (40 mL) and brine (40 mL), dried over magnesium sulfate and concentrated in vacuo. Purification by column chromatography (*n*-hexane/ethyl acetate, 19:1) gave the title compound *R*-**25** in 39% yield (overall), $[\alpha]_D = +108.9$ (*c* 2.28, DCM). Data for compound (*R*)-**25** are consistent with (*S*)-**25** and the literature.

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