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Facile biocatalytic syntheses of optically active 4-hydroxycyclohex-2-enone and 4-benzylthiacyclopent-2-enone

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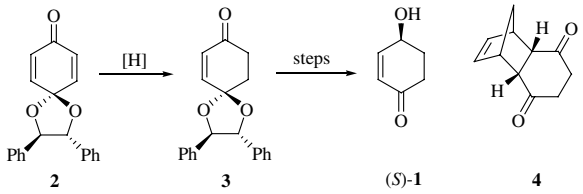
Abstract—Novozyme 435® (*Candida antarctica* Lipase B) effects the kinetic resolution of both 3-benzylthia-4-hydroxycyclopentanone and its six-membered ring analogue, providing a novel route to both enantiomers of 4-benzylthiacyclopent-2-enone and the two enantiomers of 4-hydroxycyclohex-2-enone, all in a state of very high optical purity.

1. Introduction

The diverse synthetic utility of optically active 4-hydroxycyclohex-2-enone and cyclohex-2-ene-1,4-diols has been summarised by Figueredo et al.[1] Not surprisingly, therefore, compounds such as (4*R*)- and (4*S*)-4-hydroxycyclohex-2-enone **1** have been the focus of a number of synthetic endeavours. For example, (4*S*)-**1** is available in six steps from a member of the chiral pool [(D)-quinic acid].[2] Both enantiomers of the hydroxy ketone **1** are available by a protocol using a chiral auxiliary[3] or by a pathway involving a stereoselective deprotonation of 4-benzyloxycyclohexanone using a chiral lithium amide reagent.[4] One of the most recently reported methods utilises a chiral derivative of 1,4-benzoquinone;[1] unfortunately the partial reduction of **2** to afford the enone **3** is difficult to control, with over-reduction to the saturated ketone occurring readily (Scheme 1).[5]

There are three routes to optically active **1** involving biotransformations described in the literature. The first method describes the Bakers' yeast reduction of the *meso*-diketone **4** to give the hydroxy ketone, followed by a retro-Diels–Alder reaction.[6] However, the yield of the reduction process is low (32%) and the enantiomeric excess of the desired product is only ca. 67%.



Scheme 1.

A better enzymatic method involves the kinetic resolution of 6-acetoxy-3-methoxycyclohex-2-enone;[7] finally desymmetrisation of *cis*-1,4-diacetoxycyclohex-2-ene using *Pseudomonas cepacia* lipase provided a three step pathway to (4*R*)-**1**;[8] unfortunately in both these cases the starting materials are not readily available on a large scale.

2. Results and Discussion

In contrast, racemic 4-hydroxycyclohex-2-enone is very easy to make from anisole **5** (Scheme 2).[9] While we considered that the enzyme-catalysed kinetic resolution of **6** would not be easy (vide infra: attempted resolution of the five-membered ring analogue) we recognised that a simple reversible Michael-type derivatisation of **6** would serve temporarily to distinguish the topology around the carbon atoms at positions 3 and 5. Thus to investigate this strategy enone **6** was first reacted with benzylthiol to give the *cis*-substituted compound **7** in 84% yield.

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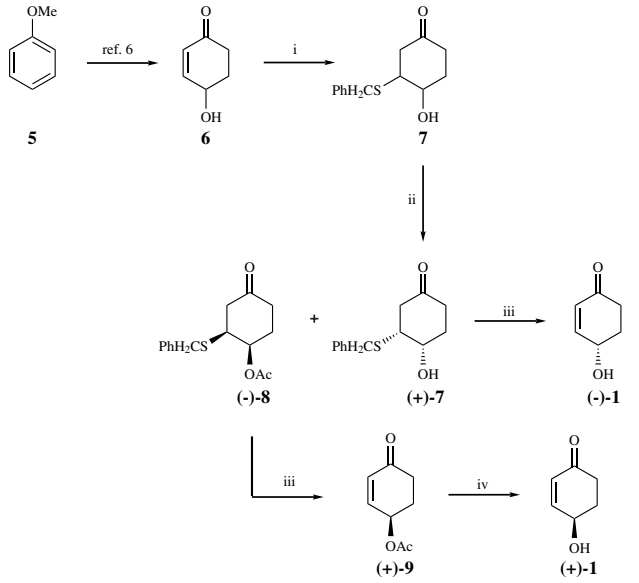


Scheme 2. Reagents and conditions: (i) $PhCH_2SH$ (1 equiv), Et_3N (0.1 equiv), CH_2Cl_2, rt, 16 h; (ii) vinyl acetate (5 equiv), Novozyme 435®, diisopropyl ether (DIPE), 30 °C, 16 h; (iii) DBU (2 equiv), CH_2Cl_2, rt, 24 h; (iv) K_2CO_3, MeOH, rt, 15 min.

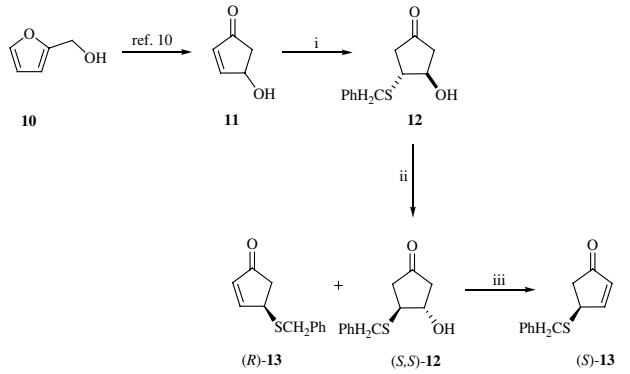
The racemic hydroxy ketone **7** was enantioselectively esterified employing Novozyme 435® and vinyl acetate to furnish optically active alcohol (+)-**7** (44% yield; >99% ee, CHPLC)[10] and the ester (−)-**8** (48% yield; >99% ee),[11] enantioselectivity, $E > 200$,[12] which were readily separated by flash column chromatography. Desulfurisation of (+)-**7** was effected using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the (*S*)-alcohol (*S*)-**1** $[\alpha]_D = -120$ (*c* 1.68, $CHCl_3$); lit.[5] $[\alpha]_D = -92.3$ (*c* 1.3, $CHCl_3$). Similarly the acetate (−)-**8** was converted into the (*R*)-acetoxy enone (*R*)-**9** and thence by a literature procedure into the (*R*)-hydroxy enone (*R*)-**1**.[4]

We have used a related strategy to prepare both enantiomers of 4-benzylthiacyclopent-2-enone **13**. The simplicity of the protocol suggests it would be the method of choice for the synthesis of other 4-thiacyclopent-2-enones.

While optically active 4-hydroxy and 4-alkoxycyclopent-2-enone (and its silylated derivatives) are well-known intermediates (e.g., in prostaglandin synthesis),[13] the preparation of optically active 4-alkylthiacyclopent-2-enone is much more obscure. Indeed, to our knowledge, there is only one paper detailing the isolation of an optically active 4-thiacyclopent-2-enone (a derivative of (1*S*)-10-mercaptoisoborneol).[14] Even in this paper the formation of the 4-thiacyclopent-2-enone was incidental to the main thrust of the study.

In order to establish a general route to the latter compounds, racemic 4-hydroxycyclopent-2-enone **11** was prepared from furfuryl alcohol **10** (Scheme 3).[15]

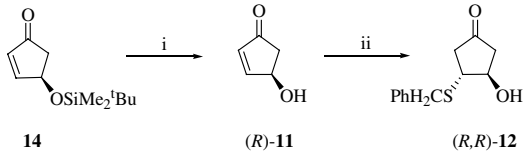
Treatment of the enone **11** with benzylthiol produced only *trans*-3-benzylthia-4-hydroxycyclopentanone **12** (86% yield).[16] Reaction of this racemic compound with



Scheme 3. Reagents and conditions: (i) $PhCH_2SH$ (1 equiv), Et_3N (1 equiv), CH_2Cl_2, rt, 16 h, 86%; (ii) a. vinyl acetate (5 equiv), Novozyme 435®, DIPE, 30 °C, 16 h, b. Et_3N (1 equiv), 1 h; (iii) Ac_2O in pyridine, Et_3N (2 equiv) rt, 6 h, 87%.

vinyl acetate in the presence of Novozyme 435® then base gave recovered (3*S*,4*S*)-alcohol (−)-**12** (49% yield; >99% ee) and 4(*R*)-benzylthiacyclopent-2-enone (*R*)-**13** (43% yield; >99% ee), $E > 200$. The (*S*,*S*)-alcohol **12** was converted into (4*S*)-benzylthiacyclopent-2-enone (*S*)-**13**[17] in 87% yield using acetic anhydride in pyridine.

The absolute configuration of compounds **12** and **13** was confirmed by deprotection then thiolation of commercially available (4*R*)-*tert*-butyldimethylsilyloxycyclopent-2-enone **14** (Scheme 4).[18]



Scheme 4. Reagents and conditions: (i) AcOH/THF/H_2O (3:1:1), rt, 48 h, 75%; (ii) $PhCH_2SH$ (1 equiv), Et_3N (0.1 equiv), CH_2Cl_2, rt, 16 h, 88%.

Note that in connection with this study, attempts made to resolve racemic **11** by lipase-catalysed kinetic resolution were generally unfruitful: in our hands *Aspergillus melleus* lipase-catalysed esterification of (±)-**11** gave the best, but still modest, enantioselectivity ($E = 15$, conversion = 47%).

3. Conclusion

In summary, in this study we have used Novozyme 435® to perform kinetic resolutions on racemic 3-benzylthia-4-hydroxycyclopentanone **12** and its six-membered ring homologue **7** to afford access to both enantiomers of 4-benzylthiacyclopent-2-enone **13** and both enantiomers of 4-hydroxycyclohex-2-enone **1**, respectively. We have also proved the concept of Michael-type addition to 4-hydroxycyclopent-2-enone and 4-hydroxycyclohex-2-enone in order to aid kinetic resolution by altering the substitution pattern *alpha* to the hydroxy group.

Acknowledgements

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10. For compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67–1.77 (1H, m, CH_AH$_B$), 2.19 (1H, dddd, J = 2.0, 3.0, 7.0, 14.5 Hz, CH_AH$_B$), 2.29 (1H, dddd, J = 3.0, 4.0, 7.5, 14.0 Hz, CH$_A$$H_B$), 2.39 (1H, dddd, J = 0.75, 2.0, 5.0, 14.5 Hz, CH_AH$_B$), 2.57 (1H, dd, J = 12.75, 14.5 Hz, CH$_A$$H_B$), 2.62–2.71 (2H, m, CH$_A$$H_B$ and OH), 3.23 (1H, ddd, J = 2.5, 5.0, 12.75 Hz, CH), 3.74 (1H, d, J = 13.5 Hz, CH_AH$_B$), 3.81 (1H, d, J = 13.5 Hz, CH$_A$$H_B$), 3.97–4.01 (1H, m, CH), 7.26–7.33 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 30.5 (CH_2), 35.5 (CH_2), 35.6 (CH_2), 42.6 (CH_2), 48.8 (CH), 65.2 (CH), 127.8 (CH), 129.0 (CH), 129.2 (CH), 137.7 (C), 208.4 (CO); IR ν_{max} (neat, cm^{-1}) 3450, 3027, 2926, 1701, 1601, 1083; HRMS calcd for: $C_{13}H_{20}SO_2N$ (CI, MNH_4^+) requires 254.1215. Found 254.1217. $[\alpha]_D$ = +5.5 (*R*,*S*)-**7** (*c* 1.65, $CHCl_3$).
11. For compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75–1.86 (1H, m, CH_AH$_B$), 2.15 (3H, s, CH_3), 2.24–2.33 (2H, m, CH_2), 2.24–2.67 (5H, 2m, CH_2), 3.00 (1H, ddd, J = 2.5, 5.0, 12.0 Hz, CH), 3.75 (1H, d, J = 13.5 Hz, CH_AH$_B$), 3.81 (1H, d, J = 13.5 Hz, CH$_A$$H_B$) 5.31–5.37 (1H, m, CH), 7.21–7.33 (5H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) 207.0 (C=O), 170.1 (C=O ester), 137.3 (C), 128.8 (CH), 128.6 (CH), 127.3 (CH), 68.2 (CH), 44.8 (CH), 43.3 (CH_2), 35.8 (CH_2), 35.4 (CH_2), 28.5 (CH_2), 20.9 (CH_3). IR ν_{max} (neat, cm^{-1}) 3061, 2964, 1731, 1601, 1238; HRMS calcd for: $C_{14}H_{22}SO_3N$ (CI, MNH_4^+) 296.1321. Found 296.1316. $[\alpha]_D$ = −31.9 (*S*,*R*)-**8** (*c* 1.074, $CHCl_3$).
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15. Typical laboratory procedure for preparation of (±)-4-hydroxycyclopent-2-enone **11**: A 3 L five-necked round bottomed flask, equipped with long air condenser, thermometer pocket and a bubbler, was charged with furfuryl alcohol (25 g, 0.255 mol), potassium dihydrogen orthophosphate (6.3 g, 0.022 mol) and distilled water (1.5 L). The reaction was purged with a slow stream of nitrogen along with paddle stirring. It was heated to 99 °C for 48 h. The solution developed brown insoluble impurities during the reaction. It was cooled to room temperature and then washed twice with ethyl acetate. The aqueous layer was concentrated to almost dryness under reduced pressure. The residue was then thoroughly extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was distilled under high vacuum using a fractionating column. Enone **11** was obtained as a pale yellow coloured oil distilling at 95–100 °C at 0.5 mmHg (10.0 g, 40% yield).
16. For compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (1H, ddd, J = 1.5, 12.0, 18.5 Hz, CH_2), 2.27 (1H, dd, J = 4.5, 18.5 Hz, CH_2), 2.39 (1H, ddd, J = 1.0, 8.0, 18.5 Hz, CH_2), 2.50 (1H, dd, J = 1.25, 18.5 Hz, CH_2), 2.70 (1H, s, OH), 3.28 (1H, ddd, J = 3.5, 8.25, 11.75 Hz, CH), 3.76 (1H, d, J = 13.75 Hz, CH_AH$_B$), 3.82 (1H, d, J = 13.75 Hz, CH$_A$$H_B$), 4.16 (1H, apparent t, J = 3.85 Hz, CH) 7.25–7.36 (5H, m, ArH). ^{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 (CH), 47.1 (CH_2), 46.5 (CH_2), 40.3 (CH_2), 35.5 (CH_2). IR ν_{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. White solid, mp 50–52 °C. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.86; H, 6.31. Found: C, 64.60; H, 6.31. $[\alpha]_D$ = −60 (*S*,*S*)-**12** (*c* 1.0, $CHCl_3$).
17. For compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3 (1H, ddd, apparent dt, J = 2.25, 19.0 Hz, CH_2), 2.72 (1H, ddd, J = 2.25, 6.5, 19.0 Hz, CH_2), 3.76 (1H, d, J = 13.5 Hz, CH_AH$_B$), 3.82 (1H, d, J = 13.5 Hz, CH$_A$$H_B$), 3.88–3.95 (1H, m, CHS), 6.15–6.21 (1H, m, $CH_{olefinic}$) 7.21–7.38 (5H, m, ArH), 7.41–7.44 (1H, m, $CH_{olefinic}$). ^{13}C NMR (100 MHz, $CDCl_3$) 207.5 (C=O), 163.6 (C=C), 137.9 (C), 134.9 (CH), 129.3 (CH), 129.2 (CH), 127.9 (C=C), 43.7 (CH), 43.0 (CH_2), 36.0 (CH_2). IR ν_{max} (neat, cm^{-1}) 3059, 3027, 2918, 1950, 1713, 1658, 1581, 699. HRMS calcd for: $C_{12}H_{13}SO$ (CI, M^+) requires 205.06873. Found 205.06852. Compound (*S*)-**13** $[\alpha]_D$ = +178 (*c* 1.0, $CHCl_3$); (*R*)-**13** $[\alpha]_D$ = −178 (*c* 1.0, $CHCl_3$).
18. The silyl compound **14** is available from StylaCats Ltd, Runcorn, U.K.