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Enantioselective enzymatic approach to (+)- and (−)-2-acetoxy/hydroxycyclopentanones†

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Abstract—A new practical enzymatic approach to (+)- and (−)-2-acetoxy/hydroxycyclopentanones with 96–98% ee has been described via enzymatic hydrolysis of the *meso*-diacetate **2**, Swern oxidation of the thus formed (±)-hydroxy acetates **3** and **4**, followed by re-enzymatic resolution. Enantiomerically pure (+)- and (−)-2-hydroxycyclopentanones are in equilibrium with enediol **9** and slowly undergo racemisation, a process which could be arrested by protecting the hydroxyl group as the acetate.

1. Introduction

The utilities of (±)-2-hydroxy- and (±)-2-acetoxycyclopentanones have been well proven in practice[1] and several methods for synthesis of them are known in the literature.[2] To date there are five reports on the preparation of enantiomerically pure (*R*)-/(*S*)-2-hydroxycyclopentanones. The first reports[3] an enzymatic oxidation of *cis*-cyclopentanediol using whole cells to obtain enantiomerically pure 2-hydroxycyclopentanone. The second report[4] describes the preparation of (2*R*)-hydroxycyclopentanone by enantioselective reduction of (±)-2-hydroxycyclopentanone using glucose-6-phosphate dehydrogenase (G-6-PDH) or glucose dehydrogenase with 16–22% yield and 70–86% ee. The third one demonstrates[5] an elegant asymmetric oxidation of a homochiral ketal by rhenium(VII) oxide to obtain the ketal of enantiomerically pure 2-hydroxycyclopentanone with 98% yield and >99% ee. The fourth report[6] illustrates *Pseudomonas cepacia* lipase (PSL)-induced transesterification of *cis*-1,2-cyclopentanediol using vinyl acetate to obtain (1*S*)-acetoxy-(2*R*)-hydroxycyclopentane with 82% chemical yield and 79% ee,[7] which can be oxidized to the desired (2*S*)-acetoxycyclopentanone using CrO_3/Py. The fifth report[8] details an enzymatic oxidation of *anti*-1,2-cyclopentane diol with *Bacillus stearothermophilus* diacetyl reductase to obtain (2*S*)-hydroxycyclopentanone in 16% yield with 99% ee. Recently, the asymmetric rearrangement of a benzyloxy-substituted oxirane has been reported[9] to yield the desired enantiomerically pure benzyloxycyclopentanone. It is noteworthy that 2-hydroxycyclopentanones are not very stable compounds and at ambient conditions they are known to undergo self-coupling reactions to form 1,4-dioxane derivatives.[10,11] Similarly, in basic aqueous solutions they are known[4] to undergo a decomposition reaction with darkening to a black colour. Hence the provision of an unambiguous and facile route to (+)- and (−)-2-hydroxycyclopentanones and their derivatives is a challenging task of current interest.[2–9] In continuation of our earlier studies[12] on the chemo-, regio- and enantioselective hydrolysis of vicinal diacetyl derivatives by enzymes, we investigated an enzymatic route to these unstable but useful building blocks, and we herein report an easy access to (+)- and (−)-2-acetoxy/hydroxycyclopentanones (Scheme 1).

2. Results and discussion

In our hands the Amano PS-catalyzed biphasic hydrolysis of *cis* diacetate **2** at pH 7 furnished a mixture of hydroxy acetates **3** and **4** in 65% yield and was found to be optically inactive.[13–15] The formation of a racemic mixture of **3** and **4** could be a result of either non-selective random enzymatic hydrolysis of both acetates or alternatively, the enzyme is enantioselective in its action, but the product mixture is formed by the instantaneous in situ intramolecular acyl migration in a cyclic-*cis*-vicinal hydroxy acetate system. At this stage,

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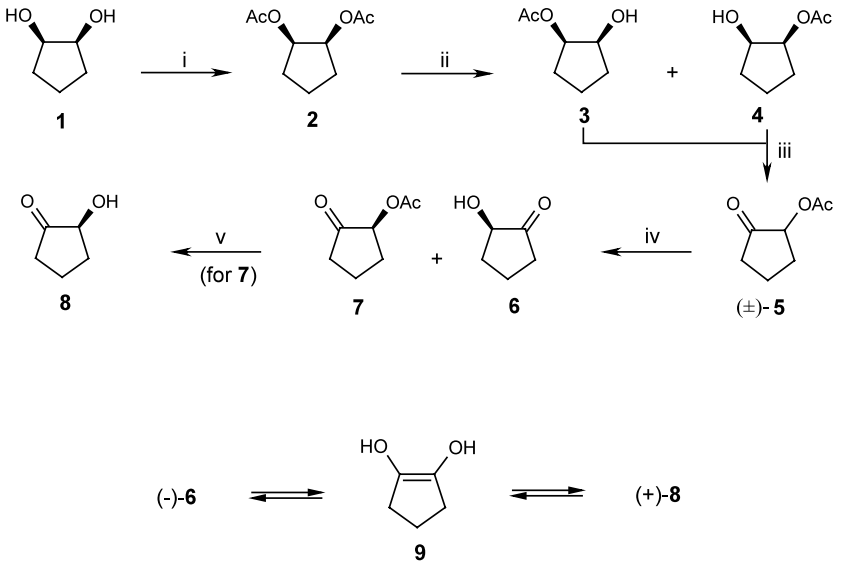

Scheme 1. (i) Ac_2O, Py, rt, 48 h (93%); (ii) petroleum ether/benzene (2:1), Amano PS, rt, 18 h, pH 7.0 (65%); (iii) $(COCl)_2$, DMSO, TEA, DCM, −60°C, 15 min (86%); (iv) petroleum ether/benzene (2:1), Amano PS (800 U),[12] rt, 22 h, pH 6.5 (**6**, 28–32%; **7**, 45%); (v) aq. K_2CO_3, MeOH, 0°C, 4 h (77%).

we oxidized the mixture of hydroxy acetates **3** and **4** to the corresponding keto acetate **5**, for enzymatic resolution with two aims; viz (a) to draw conclusions about the enantioselectivity of the enzyme and (b) to develop a new enzymatic route to (+)- and (−)-2-acetoxy/hydroxycyclopentanones. Upon Swern oxidation, the mixture of **3** and **4** gave (±)-2-acetoxycyclopentanone **5** in 86% yield, which on Amano PS-catalyzed biphasic hydrolysis at pH 6.5[16] gave a mixture of enantiomerically pure 2-hydroxycyclopentanone **6** and 2-acetoxycyclopentanone **7**. Silica gel column chromatographic separation of the above mixture gave (−)-(2*R*)-hydroxycyclopentanone **6** in 28–32% yield and (+)-(2*S*)-acetoxycyclopentanone **7** in 45% yield. The 2-hydroxyketone **6** on reaction with (*R*)-Mosher's acid in the presence of DCC gave the corresponding MTPA derivative of **6**, the ^{1}H NMR spectrum of which revealed that it has an ee of 90–92%. Similarly, enantiomerically pure **6** on treatment with AcOH/DCC gave the acetyl derivative of **6** with 90–92% ee. The comparison of the specific rotation of **7** with the acetyl derivative of **6** revealed that **7** is obtained with 96–98% ee. The base-induced hydrolysis of **7** to **8** followed by MTPA derivatisation of **8** indicated that it possesses only 40% ee. The decline in the ee of **8** can be due to base-induced racemisation/1,2-carbonyl transposition.[17] During these studies, we also noticed that (−)-**6**, either neat or in chloroform solution at 0°C, slowly loses its enantiomeric purity and becomes completely racemic over a period of nearly two months, indicating that these isomers have a two months half life span as determined by measuring the specific rotations with time (Fig. 1). Enantiopure (−)-**6** was subjected to D_2O treatment at room temperature for 10 days and ^{1}H NMR spectra were scanned after each 24 h. Only the heteroatom proton (-OH) was exchanged. The α-methine proton did not show any exchange with deuterium atom, revealing that only intramolecular

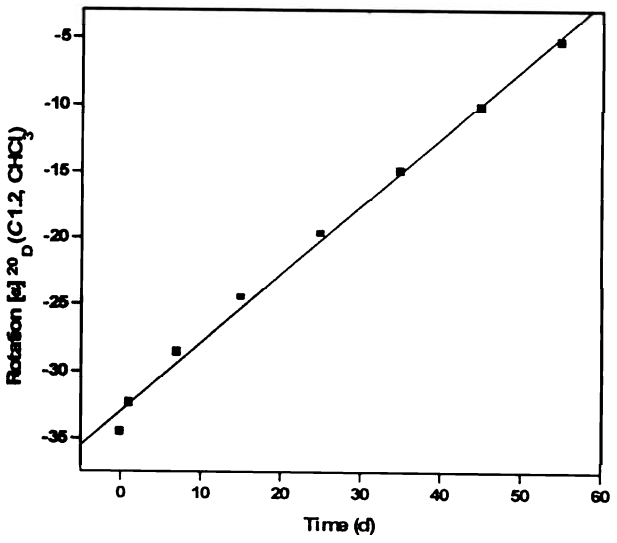

Figure 1.

prototropic shifts take place in the formation of enediol-**9**. The isolation of monodeuterated (−)-**6** from D_2O and determination of the optical rotation indicated that the process of racemisation of (−)-**6** was also relatively slow in D_2O, possibly because of extensive intermolecular hydrogen bonding. The (+)-(2*S*)-acetoxycyclopentanone **7** did not show any decline in enantiomeric purity and hence without chromatographic separation of **6** and **7**, the mixture was first treated with (*R*)-Mosher's acid and DCC to form a mixture of **7** and the MTPA derivative of **6**. The ^{1}H NMR spectrum of silica gel column-purified MTPA-ester of **6** revealed that it actually has an ee of 96–98%.

These observations clearly suggest that intramolecular hydrogen bonding in **6**/**8** enhances the keto-enol tautomerism and the 2-hydroxycyclopentanones **6** and **8**

are in equilibrium with enediol **9** (Scheme 1). This is slowly transformed to the racemic mixture through keto-enol tautomerism.[18] These results show that the enzyme Amano PS is very specific in its hydrolytic action on the *meso*-diacatate **2** and the racemic mixture of products **3** and **4** is formed because of in situ intramolecular acyl migrations.[12b]

3. Conclusion

In summary, we have demonstrated a facile and unambiguous new practical chemoenzymatic approach to (−)-(2*R*)-hydroxycyclopentanone **6** with 28–32% yield and 90–92% ee, and (+)-(2*S*)-acetoxycyclopentanone **7** with 45% yield and 96–98% ee.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Brucker AC 200 (200 MHz) NMR spectrometer and Brucker MSL 300 (300 MHz) NMR spectrometer. The FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. The mass spectra were recorded on a Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Amano PS-800 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.

4.2. *cis*-1,2-Diacetoxycyclopentane, 2

To a stirred solution of diol **1** (2.04 g, 20 mmol) in pyridine (10 mL) was added acetic anhydride (8 mL) and the reaction mixture was kept in the dark for 24 h at rt. The reaction mixture was poured into water and extracted with ethyl acetate (15 mL×5). The combined organic layer was washed with a $CuSO_4$ solution, water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a 5–10% ethyl acetate:petroleum ether mixture as an eluent gave **2** (3.5 g, 93%). Thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50–2.10 (m, 6H), 2.04 (s, 6H), 5.00–5.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.8, 20.6, 27.9, 73.8, 170.0. MS (*m*/*e*) 143, 126, 101, 83, 67, 57. IR (neat) ν_{max} 1742 cm^{-1}.

4.3. (±)-*cis*-1-Acetoxy-2-hydroxycyclopentane 3 and 4

A solution of diacetate **2** (2.79 g, 15 mmol) in a petroleum ether:benzene (2:1) mixture (60 mL) was added to a suspension of Amano PS lipase (350 mg) in aq. sodium phosphate (0.01 M, 20 mL) at pH 7.0. The reaction mixture was stirred at 25°C for 18 h. The reaction mixture was filtered through Celite and the aqueous layer was extracted with ethyl acetate (15 mL×5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation of the residue using a 10–15% ethyl acetate:petroleum ether mixture as an eluent gave **2** (840 mg, 30%), **3** and **4** (1.4 g, 65%), respectively (increased reaction time resulted in the formation of **1**). Thick oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40–2.05 (m, 6H), 2.08 (s, 3H), 2.25 (bs, 1H), 4.15 (q, J=5 Hz, 1H), 4.87–5.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.0, 20.8, 27.7, 30.4, 72.5, 76.4, 171.0. MS (*m*/*e*) 101, 84, 73, 67, 57, 55. IR (neat) ν_{max} 3429, 1722 cm^{-1}.

4.4. (±)-2-Acetoxycyclopentanone, 5

To a solution of oxalyl chloride (0.74 mL, 8.4 mmol) in dry CH_2Cl_2 (5 mL) under argon at −60°C was added a solution of DMSO (0.8 mL, 11 mmol) in dry CH_2Cl_2 (5 mL) in a dropwise fashion over a period of 5 min. Hydroxy acetate **3** and **4** (1.0 g, 7 mmol) in dry CH_2Cl_2 was charged dropwise over a period of 5 min and the reaction mixture was stirred at −60°C for 15 min. Et_3N (4.9 mL, 35 mmol) was added and the reaction mixture was further stirred at rt for 5 min. Water (10 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (15 mL×5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue provided **5** (855 mg, 86%). Viscous oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70–2.00 (m, 2H), 2.13 (s, 3H), 2.20–2.50 (m, 4H), 5.07 (t, J=9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.0, 20.5, 28.2, 34.6, 75.5, 169.9, 212.2. MS (*m*/*e*) 142, 99, 86, 71. IR (neat) ν_{max} 1753, 1744 cm^{-1}.

4.5. Amano PS-catalyzed hydrolysis of (±)-5

A solution of (±)-2-acetoxyketone **5** (710 mg, 5 mmol) in a petroleum ether:benzene (2:1) mixture (30 mL) was added to a suspension of Amano PS lipase (250 mg) in aq. sodium phosphate (0.01 M, 10 mL) at pH 6.5. The reaction mixture was stirred at 25°C for 22 h. The reaction mixture was filtered through Celite and the aqueous layer was extracted with ethyl acetate (15 mL×5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation using a 10–15% ethyl acetate:petroleum ether mixture as an eluent gave (+)-**7** (318 mg, 45%) and (−)-**6** (150 mg, 32%), respectively.

(−)-**6**: viscous oil; $[\alpha]_D^{20}$=−38.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60–1.95 (m, 2H), 1.95–2.60 (m, 4H), 2.92 (bs, 1H, D_2O exchangeable), 4.09 (t, J=10 Hz, 1H); ^{1}H NMR (D_2O, 200 MHz) δ 1.50–2.50 (m, 6H), 4.19 (t, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 30.7, 33.9, 75.7, 159.8. MS (*m*/*e*) 100, 84, 72, 57, 55. IR (neat) ν_{max} 3404, 1746 cm^{-1}. (+)-**7**: viscous oil; $[\alpha]_D^{20}$=+61.0 (*c* 2.0, $CHCl_3$).

4.6. Acetyl derivative of (−)-6

To a solution of acetic acid (10 mg), (−)-2-hydroxyketone **6** (10 mg, 0.1 mmol) and DMAP (cat.) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (15 mg) in dry CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 8 h. The urea formed was filtered off and the organic layer was concentrated in vacuo. Silica gel column chromatographic purification of the residue using a 10% ethyl acetate:petroleum ether mixture as an eluent gave the acetyl derivative of (−)-**6** in quantitative yield. Thick oil: $[\alpha]_D^{20} = -54.9$ (*c* 1.0, $CHCl_3$).

4.7. (+)-(2*S*)-Hydroxycyclopentanone 8

To a solution of (+)-acetoxyketone **7** (71 mg, 0.5 mmol) in MeOH (15 mL) and H_2O (15 mL) was added K_2CO_3 (70 mg, 0.6 mmol) and the reaction mixture was stirred at 0°C for 4 h. The reaction mixture was diluted with water (30 mL) and the aqueous solution was extracted with CH_2Cl_2 (15 mL×5). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a 15% ethyl acetate:petroleum ether mixture as an eluent gave **8** (39 mg, 77%). Thick oil; $[\alpha]_D^{20} = +20.3$ (*c* 1.2, $CHCl_3$).

4.8. General procedure for MTPA-ester preparation

To a solution of (*R*)-Mosher's acid (23 mg), (−)-2-hydroxyketone **6** (10 mg, 0.1 mmol) and DMAP (cat.) in dry CH_2Cl_2 (3 mL) was added a solution of DCC (15 mg) in dry CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 8 h. The urea formed was filtered off and the organic layer was concentrated in vacuo. Silica gel column chromatographic purification of the residue using a 10% ethyl acetate:petroleum ether mixture as an eluent gave the MTPA-ester in quantitative yield.

4.8.1. MTPA-ester of (±)-2-hydroxycyclopentanone. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70–2.60 (m, 12H), 3.58 (s, 3H), 3.64 (s, 3H), 5.25 (t, $J=8$ Hz, 1H), 5.35 (t, $J=8$ Hz, 1H), 7.30–7.75 (m, 10H). MS (*m*/*e*) 316, 286, 216, 189, 158, 139, 119, 105, 91, 77, 69, 55.

4.8.2. MTPA-ester of (−)-(2*R*)-hydroxycyclopentanone, 6. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75–2.50 (m, 6H), 3.64 (s, 3H), 5.35 (t, $J=8$ Hz, 1H), 7.30–7.70 (m, 5H). MS (*m*/*e*) 316, 286, 216, 189, 158, 139, 119, 105, 91, 77, 69, 55.

4.8.3. MTPA-ester of (+)-(2*S*)-hydroxycyclopentanone, 8. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.80–2.60 (m, 6H), 3.57 (s, 3H), 5.25 (t, $J=8$ Hz, 1H), 7.35–7.70 (m, 5H). MS (*m*/*e*) 316, 286, 216, 189, 158, 139, 119, 105, 91, 77, 69, 55.

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