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Chemo-enzymatic asymmetric total synthesis of penienone

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ABSTRACT

An asymmetric synthesis of penienone has been accomplished from (*R*)-5-hydroxymethyl-2-cyclohexenone by adopting a linear strategy. Lipase-PS-catalyzed enzymatic kinetic resolution (EKR) and Julia–Kocienski olefination followed by substrate-directed anionic hydroxymethylation have been successfully employed to achieve the target molecule.

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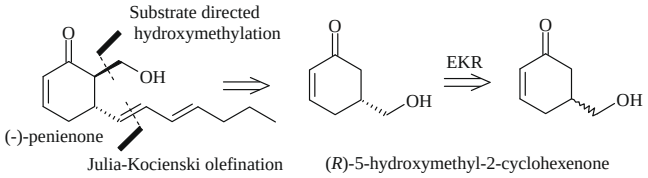
Penienone and penihydrone, the cyclohexane-based fungal metabolites have been isolated in 1997 by Kimura et al., from the metabolite of the fungus *Penicillium* sp. no. 13, and these were found to have plant growth regulatory activity.[1] Their structures have been elucidated on the basis of NMR and CD spectral studies. To date two asymmetric syntheses of (−)-penienone and one asymmetric synthesis of (+)-penihydrone have been reported in the literature. The first synthesis of both the molecules is reported by Sato and co-workers, in which an efficient cuprate addition of (1*E*,3*E*)-hepta-1,3-dienyl group to chiral 5-substituted-2-cyclohexenone has been accomplished.[2] Meyers and Waterson, in 2000 reported the asymmetric synthesis of (−)-penienone by employing bicyclic chiral lactams as a homoenolate equivalent to access a properly substituted chiral 5-substituted-2-cyclohexenone which is the core structure of penienone.[3] We have recently developed a chemo-enzymatic strategy for the synthesis of chiral 5-hydroxymethyl-2-cyclohexenone in both enantiomeric forms. Retrosynthetic analysis of penienone reveals that it can be easily accessed from (*R*)-5-hydroxymethyl-2-cyclohexenone by functional group manipulation (Scheme 1).

The starting compound (*R*)-5-hydroxymethyl-2-cyclohexenone (**3**) has been prepared by lipase-catalyzed (*Burkohedria cepacica*, Lipase-PS) kinetic resolution of the parent racemic compound (**1**).[4] In the irreversible trans-esterification reaction with vinyl acetate as the acylating agent the fast reacting (*S*)-enantiomer is converted to the corresponding acetate (**2**) (yield = 47%, ee = 99%) whereas the slow reacting enantiomer yielded (*R*)-5-hydroxymethyl-2-cyclohexenone (**3**) in 48% yield (ee = 98%).[5] The acetate group in the (*S*)-enantiomer is deacetylated with PPL (*Porcine pancreatic* lipase) to afford (*S*)-5-hydroxymethyl-2-cyclohexenone (**4**) in 82% yield. The primary hydroxyl group is oxidized with PCC (pyridinium chlorochromate) to yield the (*S*)-ketoaldehyde (**5**).[6] The racemization of (*S*)-ketoaldehyde to the corresponding racemic mixture (**1**) is achieved by treatment with catalytic DBU (1,8-diazabicyclo-undec-7-ene) in tetrahydrofuran[7] at room temperature. Chemoselective reduction of the aldehyde functionality is achieved with $NaCNBH_3$ in methanol. So by a three-step methodology the undesired (*S*)-5-hydroxymethyl-2-cyclohexenone (**2**) has been racemized to (±)-5-hydroxymethyl-2-cyclohexenone (Scheme 2). This can be used again in the initial kinetic resolution step.

The primary hydroxyl group in **3** was protected as its TBDPS (*tert*-butyl diphenylsilyl) ether by treatment with imidazole and TBDPS–Cl to afford compound **6** in 90% yield. The keto protection in compound **6** was problematic in our hands and after the failure of numerous literature procedures, we achieved the desired transformation by a three-step protocol as described by Smith.[8] Bromination and dehydrobromination of compound **6** with Br_2–CCl_4/Et_3N afforded (*R*)-2-bromo-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone (**7**) in 88% yield.[9] Compound **7** when refluxed with ethylene glycol and PPTS (pyridinum *para*-toluene sulfonate) in benzene afforded the corresponding ketal **8** in 72% yield. Debromination of **8** was achieved by treatment with *n*-BuLi at −78 °C and quenching with NH_4Cl to afford compound **9** in 78% yield. Deprotection of the TBDPS group was achieved by treatment of **9** with TBAF (tetrabutylammonium fluoride) in tetrahydrofuran[10] to yield alcohol **10**.[11] Oxidation of **10** with TPAP/NMO (tetrapropyl ammonium perruthenate/*N*-methyl morpholine-N-oxide)[12] in the presence of powdered molecular sieves afforded the aldehyde **11** in 88% yield.[13] Wittig olefination of aldehyde **11** with phospho-



Scheme 1. Retrosynthetic analysis of penienone.

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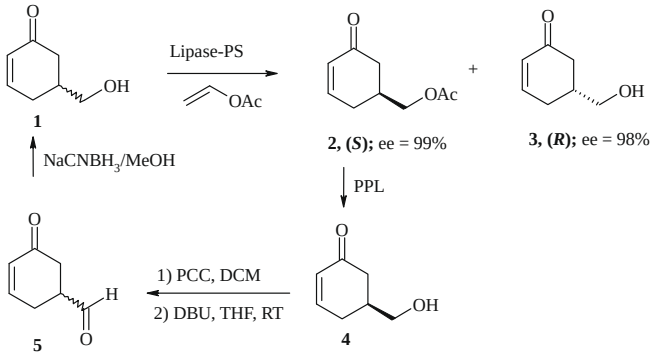
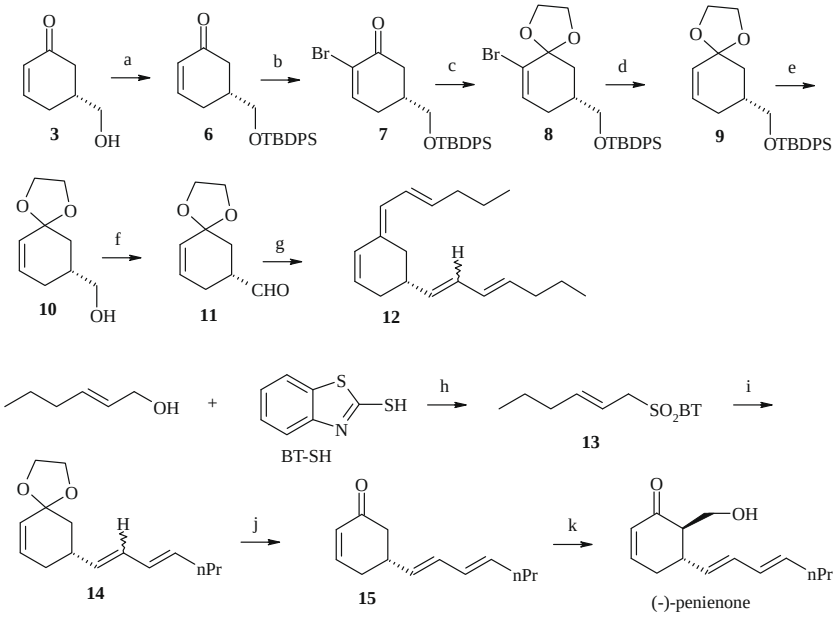


Scheme 2. Synthesis of (*R*)-5-hydroxymethyl-2-cyclohexenone by lipase-catalyzed kinetic resolution and recycling of the (*S*)-enantiomer.

achieve the total synthesis of (−)-penienone. An organocatalytic asymmetric variant of the aldol reaction was first tried with compound **15** and formaldehyde in the presence of (*S*)-proline.[21] After the usual work-up and purification (−)-penienone was obtained in 30% yield only. The unusual low yield of this organocatalytic aldol reaction forced us to adopt a different strategy for the introduction of the required hydroxymethyl functionality. Base-induced, substrate-directed hydroxymethylation was attempted.[22] Hence when compound **15** was treated with LiTMP (lithium tetramethylpiperidide) at −78 °C and the generated enolate was treated with benzotriazol-1-yl-methanol at the same temperature, (−)-penienone was obtained in 70% yield. The other diastereomer *epi*-penienone was obtained in 15% yield. The stereochemical course of the reaction was governed by the presence of the bulky (1*E*,3*E*)-hepta-1,3-dienyl moiety. The overall yield of (−)-penienone was 16% starting



Scheme 3. Reagents and conditions: (a) TBDPS–Cl, imidazole, DMF, 90%; (b) Br_2–CCl_4, Et_3N, 0 °C, 2 h, 88%; (c) $(CH_2OH)_2$, PPTS, benzene, reflux, 48 h, 72%; (d) *n*-BuLi, −78 °C to rt, NH_4Cl, 78%; (e) TBAF/THF, 90%; (f) TPAP, NMO, MS (4 Å), rt, 6 h, 88%; g) *n*-BuLi, −78 °C; 1*E*,3*E*-hepta-1,3-dienylphosphoniumbromide; (h) Ph_3P, DIAD (diisopropylazodicarboxylate), THF, rt; $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, 78%; (i) LHMDS, −78 °C, 1 h, then add **7**, 2 h, 70%; (j) PTSA, $CHCl_3$, 2 h, 0.1 equiv I_2, 100 W tungsten lamp, 2 h; 88%; (k) LiTMP, benzotriazol-1-yl-methanol, 70%.

nium ylide derived from (*E*)-1-bromo-hex-2-ene at −78 °C afforded the undesired compound **12** instead of the desired compound **14**. The formation of **12** can be explained as follows. During the preparation of the Wittig ylide 1*E*,3*E*-hepta-1,3-dienylphosphoniumbromide, the presence of some triphenylphosphine causes deketalization[14] and subsequent olefination yielded compound **12** in 70% yield (*E*,*E*/*E*,*Z* = 3:1). The installation of the required 1*E*,3*E*-hepta-1,3-dienyl group was successfully accomplished by a Julia–Kocienski protocol.[15] The desired sulfone (**13**)[16] was prepared from (*E*)-2-hexenol[17] and 2-mercaptobenzothiazole by a standard method.[18] The sulfone was subjected to the olefination reaction with aldehyde **11** in the presence of LHMDS (lithiumhexamethyldisilazide) to afford compound **14**. The ketal moiety in **14** was removed by treating the compound with PTSA (*para*-toluenesulfonic acid) in $CHCl_3$ to afford compound **15** (mixture of geometrical isomers) in 95% yield. The undesired *E*,*Z* component in compound **15** was photoisomerized to the desired *E*,*E* component[19] by treatment of 0.1 equiv I_2.[20] After successful installation of the (1*E*,3*E*)-hepta-1,3-dienyl moiety in a stereocontrolled way the remaining task is to introduce the required hydroxymethyl group at the α-carbon in a stereoselective way to from compound **3** (Scheme 3). Our synthesized (−)-penienone shows comparable spectral characteristic values as those reported in the literature.[1–3,23,24]

In conclusion we have described an efficient asymmetric synthesis of the natural enantiomer of (−)-penienone by adopting an enzymatic kinetic resolution–racemization protocol and Julia–Kocienski olefination strategy followed by substrate-directed anionic hydroxymethylation strategy.

Acknowledgements

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5. The enantioselectivity of the lipase-PS-catalyzed trans-esterification step was measured by chiral HPLC (OJ-H, hexane:2-propanol/9:1) of the benzoate derivative of (*R*)-**1** and (*S*)-**1**.
6. (*R*)-5-oxo-cyclohex-3-ene-carbaldehyde (**5**):^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.63 (s, 1H, –C*H*O), 6.92 (dt, *J* = 10.0, 3.6 Hz, 1H, olefinic-*H*), 6.0 (d, *J* = 10.0 Hz, 1H, olefinic-*H*), 3.0 (m, 1H, –C*H*–CHO), 2.7–2.6 (m, 4H, ring-*H*).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 200.55, 196.34, 147.25, 130.30, 46.53, 36.73, 24.50.
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9. (*R*)-2-Bromo-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone (compound **7**): a solution of compound **6** (2 g, 5.5 mmol) in 4 mL of carbon tetrachloride is prepared in a two-necked round-bottomed flask. The solution is cooled to 0 °C with an ice bath and a solution of bromine (0.3 mL in 4 mL of CCl_4, 6 mmol) is added dropwise for 15 min. A solution of 1.2 mL of Et_3N (8.25 mmol) in 4 mL of CCl_4 is then added dropwise with vigorous stirring. The stirring is continued for an additional 2 h at room temperature. The resulting dark suspension is washed with dil. HCl (2 × 10 mL), saturated $NaHCO_3$ (20 mL) and brine solution. The resultant solution is dried over $MgSO_4$, and the solvent is evaporated under reduced pressure. The compound is purified by chromatography.^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.65 (m, 4H, Ar–*H*), 7.5–7.3 (m, 7H, Ar–*H* and olefinic-*H*), 3.6 (m, 2H, –C*H*$_2$–OTBDPS), 2.8–2.6 (m, 2H, ring-*H*), 2.5–2.4 (m, 3H, ring-*H*), 1.0 (s, 6H).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 191.17 (*C*=O), 150.01, 135.47, 133.05, 129.82, 127.76, 123.54, 66.16 (CH_2), 40.99 (CH_2), 37.54 (CH), 31.03 (CH_2), 26.78 (CH_3), 19.23 (*C*).
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11. (*R*)-1-(1,4-Dioxa-spiro-[4.5]-dec-9-en-7-yl)-methanol(**10**): compound **9** (1.21 g, 2.98 mmol) was taken in dry THF (30 mL). TBAF (1 M in THF, 2.98 mL) was added to it, and the reaction mixture was stirred for 3 h at room temperature. After that, THF was evaporated, and water (20 mL) was added to it, the reaction mixture was extracted with EtOAc (2 × 50 mL), the organic layer was washed with $NaHCO_3$ and brine and dried (Na_2SO_4). It was purified by flash chromatography (1:1; hexane/EtOAc) to afford 375 mg of compound **10** (90%).^{1}H NMR ($CDCl_3$, 400 MHz), δ: 5.95 (m, 1H, olefinic-*H*), 5.59 (d, *J* = 10.0 Hz, 1H, olefinic-*H*), 4.0–3.8 (m, 4H, ketal ring-*H*), 3.6 (d, *J* = 6.0 Hz, 2H, –C*H*$_2$OH), 2.2–2.1 (m, 2H, ring-*H*), 1.94 (m, 1H, ring-*H*), 1.7–1.5 (m, 3H, ring-*H*).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 131.48 (*C*H=C), 127.38 (*C*H=C), 105.90 (–O–*C*–O), 66.76 (–CH_2OH), 64.68 (–O–CH_2–), 64.30 (–O–CH_2–), 36.07 (CH_2), 35.26 (*C*H), 27.93 (CH_2).$[\alpha]_D^{28}$ −12.2 (*c* 1.0, MeOH).
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16. 2-[((*E*)-Hex-2-ene)-1-sulfonyl]-benzothiazole (**13**): to a solution of DIAD (1.28 mL, 6.5 mmol) in 20 mL of dry THF were added benzothiazole-2-thiol (1 g, 6 mmol), *E*-2-hexen-1-ol (0.5 g, 5 mol) and TPP (1.5 g, 6 mmol) at 0 °C. The reaction mixture was allowed to attain room temperature for 4 h, after that it was evaporated and the crude product was taken in 50 mL of ether, washed successively with 1 N NaOH (20 mL), water and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude sulfide (110 mg, 0.44 mmol) was taken in 5 mL of ethanol and treated with ammonium molybdate (54 mg, 0.044 mmol) and 0.5 mL of 30% H_2O_2. The reaction mixture was stirred at room temperature overnight. After that, the solution was evaporated and purified through silica-gel chromatography (1:3; hexane/EtOAc) to afford the sulfone **13** in 82% yield.
^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.3 (m, 1H, Ar–H), 8.1 (m, 1H, Ar–H), 7.7–7.5 (m, 2H, Ar–H), 5.8 (m, 1H, olefinic-H), 5.5 (m, 1H, olefinic-H), 4.3 (d, *J* = 7.2 Hz, 2H, –C*H*$_2$–SO$_2$–), 2.1 (q, *J* = 7.6 Hz, 2H), 1.4 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 165.25, 152.58, 143.34, 141.03, 136.76, 127.59, 125.34, 122.32, 114.31, 58.51, 34.48, 21.66, 13.28.
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19. (*R*)-((1*E*,3*E*)-5-Hepta-1,3-dienyl)-cyclohex-2-enone (**15**).^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.0 (m, 1H, olefinic-*H*), 6.1–5.97 (m, 3H, olefinic-*H*), 5.65 (dd, *J* = 14.8, 7.2 Hz, 1H, olefinic-*H*), 5.5 (dd, *J* = 14.8, 7.2 Hz, 1H, olefinic-*H*), 2.85 (m, 1H, ring-*H*), 2.5 (m, 2H), 2.3–2.0 (m, 4H), 1.48 (q, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 199.11 (C=O), 149.36, 134.60, 132.84, 130.39, 129.84, 129.75, 43.96 (CH_2), 38.02 (*C*H), 34.71 (CH_2), 32.16 (CH_2), 22.43 (CH_2), 13.74 (CH_3).$[\alpha]_D^{28}$ −50.6 (*c* 1.0, MeOH).HRMS (ESIMS) calcd for $C_{13}H_{18}ONa$ (M+Na)$^+$ 213.1249, found 213.1261.
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23. (5*S*,6*R*)-5-((1*E*,3*E*)-Hepta-1,3-dienyl)-6-hydroxymethyl-cyclohex-2-enone (penienone): to a stirred solution of *n*-BuLi (0.28 mL, 0.17 mmol) in anhydrous THF (4 mL) was added dropwise 2,2,6,6-tetramethylpiperidine (0.026 mL, 0.17 mmol) at −10 °C. The solution was allowed to stir at 0 °C for 30 min and was then cooled to −78 °C. Compound **15** (30 mg, 0.16 mmol) in anhydrous THF (2 mL) was added dropwise and stirred for an additional 1 h. Benzotriazol-1-yl-methanol (48 mg, 0.32 mmol) in anhydrous THF (3 mL) was added dropwise over 10-min period and kept for 2 h at this temperature. The reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (50 mL) and was then washed successively with 4 N NaOH (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography (1:5; hexane/EtOAc) to afford 24 mg (70%) of (−)-penienone.
^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.0 (m, 1H), 6.15–6.0 (m, 3H), 5.68 (dt, *J* = 13.6, 7.2 Hz, 1H), 5.48 (dd, *J* = 14.8, 8.8 Hz, 1H), 3.9 (m, 1H, –C*H*$_2$OH), 3.78 (m, 1H, –C*H*$_2$OH), 2.92 (m, 1H), 2.7 (br s, 1H, –OH), 2.5–2.35 (m, 3H), 2.0 (q, *J* = 7.2 Hz, 2H), 1.4 (q, *J* = 7.2 Hz, 2H), 0.9 (t, *J* = 7.2 Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz), δ: 202.36 (*C*=O), 149.95 (*C*H), 135.08 (*C*H), 132.73 (*C*H), 131.33 (*C*H), 129.57 (*C*H), 129.41 (*C*H), 60.92 (CH_2), 52.85 (*C*H), 40.98 (*C*H), 34.70 (CH_2), 33.06 (CH_2), 22.39 (CH_2), 13.73 (CH_3).$[\alpha]_D^{28}$ −39.4 (*c* 0.5, MeOH).HRMS (ESIMS) calcd for $C_{14}H_{20}O_2Na$ (M+Na)$^+$ 243.1355, found 243.1361.
24. (5*S*,6*S*)-5-((1*E*,3*E*)-Hepta-1,3-dienyl)-6-hydroxymethyl-cyclohex-2-enone(*epi*-penienone):
^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.93 (m, 1H), 6.07–5.88 (m, 3H), 5.66 (dt, *J* = 13.6, 7.2 Hz, 1H), 5.52 (dd, *J* = 14.6, 9.2 Hz, 1H), 3.96 (m, 1H, –C*H*$_2$OH), 3.48 (m, 1H, –C*H*$_2$OH), 2.94 (m, 1H), 2.87–2.75 (m, 2H), 2.67 (br s, 1H, –OH), 2.44 (m, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.4 (q, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz), δ: 202.30 (*C*=O), 148.85 (*C*H), 135.18 (*C*H), 133.43 (*C*H), 129.83 (*C*H), 129.67 (*C*H), 128.41 (*C*H), 62.62 (CH_2), 52.65 (*C*H), 40.82 (*C*H), 34.86 (CH_2), 32.60 (CH_2), 22.59 (CH_2), 13.93 (CH_3).