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Chemoenzymatic Synthesis of (2*S*,3*R*)-3-Hydroxyproline from Cyclopentadiene

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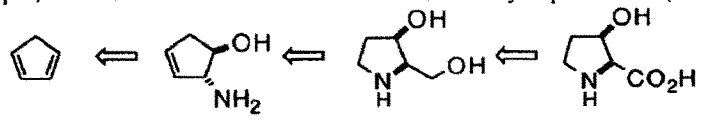
Abstract: Amido-alcohol **4**, derived from cyclopentadiene and resolved using *Candida antarctica* lipase B-mediated transacetylation, was transformed to (2*R*, 3*R*)-3-hydroxy-2-hydroxymethyl-pyrrolidine (**2**) and (2*S*, 3*R*)-3-hydroxyproline (**1**).

(2*S*, 3*R*)-3-Hydroxyproline (**1**) is a known, although rare, α-amino acid found in teleomycin antibiotics.[1,2] It can be easily transformed into the Geissman-Waiss lactone[3] and subsequently into a variety of pyrrolizidine alkaloids,[3, 4] including retronecine, platynecine, and croalbinecine. (2*S*, 3*R*)-3-Hydroxyproline (**1**) and (2*R*, 3*R*)-3-hydroxy-2-hydroxymethylpyrrolidine (**2**) are present as structural units in pyrrolizidine alkaloids (*e.g.*, australine[5] and alexine[6]), indolizidine alkaloids (*e.g.*, slaframine,[7] castanospermine[8]) and unusual amino acids (*e.g.*, detoxinine[9]). Several syntheses of *cis*-3-hydroxyproline have been reported.[4, 10] A new approach, presented in this paper, is based on amino alcohol **3**[11] derived from cyclopentadiene (Scheme 1).

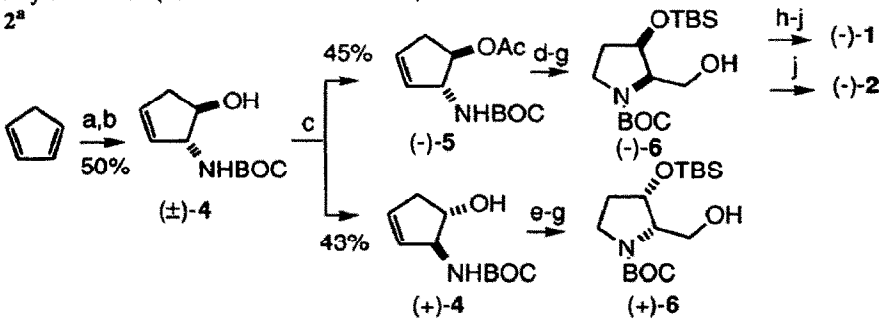
Scheme 1



3 **2** **1**

Enzymatic resolution of racemic alcohol **4** was achieved by *Candida antarctica* lipase B (Novo Nordisk SP 435)-mediated transacetylation in isopropenyl acetate to afford acetate (-)-**5** in 45 % yield (>98% ee) and alcohol (+)-**4** in 43% yield (93% ee) (Scheme 2).[12] The enantiopurity of alcohol (+)-**4** was increased to >98% by a single recrystallization (hexane : dichloromethane).

Scheme 2[a]



[a]Reagents and conditions: (a) AcOOH then NH_3/MeOH (ref.11); (b) BOC_2O, EtOAc; (c) *Candida antarctica* lipase B (Novo Nordisk SP 435), isopropenyl acetate, RT, 4 h; (d) KOH, MeOH (97%); (e) TBSCl, imidazole, DMF (98%) ; (f) O_3, MeOH - CH_2Cl_2 (1 : 1), then DMS; (g) $NaBH_3CN$, AcOH, MeOH (f + g: 71%); (h) NaOCl, TEMPO, KBr, $NaHCO_3$, Et_2O-H_2O; (i) $NaIO_4$, $RuCl_3$ (cat.), Me_2CO (h + i: 56%); (j) HCl, MeOH-H_2O (**1**: 91%; **2**: 88%).

Processing of (-)-**5** by protective group exchange (O-Ac → O-TBS),[13] followed by ozonolysis and sodium cyanoborohydride reduction gave known prolinol (-)-**6**.[10c,14] Acidic hydrolysis afforded pyrrolidine **2**, while stepwise oxidation[15,16] (TEMPO, NaOCl then $RuCl_3$, $NaIO_4$) led, after deprotection, to 3-hydroxyproline (**1**).[14] The enantiomeric 3-hydroxyprolinol derivative (+)-**6**[14] was obtained from alcohol (+)-**4**.[14]

This chemoenzymatic method allows access to both enantiomers of 3-hydroxyproline (**1**) and the related 3-hydroxy-2-hydroxymethylpyrrolidines from cyclopentadiene. The lipase-mediated acetylation/resolution in organic media provides convenient access to enantiopure intermediates (+)- and (-)-**4** which should prove useful in the synthesis of a variety of enantiopure targets including pyrrolizidine and indolizidine alkaloids.

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12. The enzymatic acetylation of alcohol (±)-**4** was conducted as follows: alcohol (±)-**4** (500 mg, 2.6 mmol) was dissolved in isopropenyl acetate (3 mL) and to this solution SP-435 (immobilized recombinant *Candida antarctica* lipase B) (50 mg, 10 % by wt.) was added. The reaction progress was monitored by GC. At ca. 50% conversion (approx. 4.5 h) the reaction mixture was filtered, concentrated and chromatographed on silica gel (hexane : ethyl acetate; 5:1) to give acetate (-)-**5** (225 mg, 45% yield, 98% ee. by ^{19}F NMR of the Mosher ester) and alcohol (+)-**4** (260 mg, 43% yield, 93% ee.by ^{19}F NMR of the Mosher ester).

    For examples of other applications of the SP-435 biocatalyst from our laboratory see: Johnson, C. R. ; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11103; Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287; Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813.
13. This exchange resulted in improved yields in the subsequent TEMPO oxidation.
14. Physical Data: **1 as HCl salt:** mp 225 °C d.; $[\alpha]_D^{23}$ -95.5 (*c* 0.5, H_2O) [lit. 10b, $[\alpha]_D^{20}$ -101 (*c* 1.0, H_2O)]; ^{1}H NMR as reported.[10f]

    2 as HCl salt: mp 220 °C d.; $[\alpha]_D^{23}$ - 12.7 (*c* 0.2, MeOH); ^{1}H &^{13}C NMR as reported.[17]

    (±)-4: mp 76.0-77.0 °C; ^{1}H NMR: ($CDCl_3$) δ 5.75 (dd, J = 5.7, 2.1 Hz, 1H); 5.45 (d, J = 3.9 Hz, 1H); 5.00 (bs, 1H); 4.32 (bs, 1H); 4.15 (m, 2H); 2.65 (ddd, J = 17.1, 7.2, 1.8 Hz, 1H); 2.17 (dd, J = 17.1, 2.4 Hz, 1H); 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.6, 132.7, 128.2, 79.8, 79.7, 65.5, 39.4, 28.2.

    (-)-5: mp 71.0-72.0 °C; $[\alpha]_D^{23}$ -107.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H); 5.78 (m, 1H); 5.07 (m, 1H); 4.70-4.55 (m, 2H); 2.86 (dd, J = 17.7, 6.9 Hz, 1H); 2.27 (bd, J = 17.7 Hz, 1); 2.06 (s, 3H); 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.1, 131.8, 129.7, 79.6, 62.0, 38.0, 28.3, 21.1.

    (+)-4: mp 72.0-73.0 °C; $[\alpha]_D^{23}$ +19.1 (*c* 1.0, $CHCl_3$).

    (-)-6: oil; $[\alpha]_D^{23}$ -35.4 (*c* 3.1, $CHCl_3$) [lit. 10c, $[\alpha]_D^{25}$ -34.4 (*c* 1.9, $CHCl_3$)].

    (+)-6: oil; $[\alpha]_D^{23}$ +33.5 (*c* 5.0, $CHCl_3$)
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