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An Efficient Chemo-Enzymatic Synthesis of α-Amino-β-Hydroxy-γ-Butyrolactone

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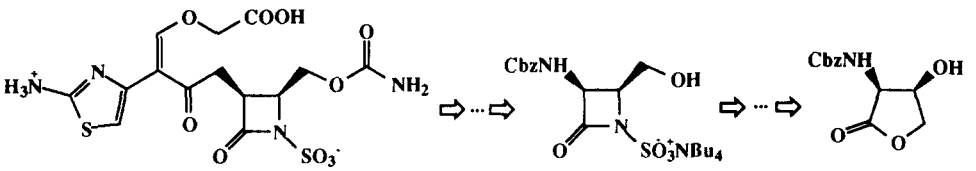
Abstract: The synthesis of *(2S,3R)*-2-amino-3-hydroxybutyrolactone, a precursor of the monobactam antibiotic Carunoman, has been accomplished in three steps involving the use of L-threonine aldolase.

Monobactams are monocyclic β-lactams having a sulfonic acid group on the nitrogen of the β-lactam ring[1]. The synthetic analogs of this class of compounds (Carunoman) **1** (Scheme 1) show strong antibacterial activity against gram-negative bacteria and high stability to β-lactamases from various bacterial spesies[1,2]. Different approaches had been developed [3,4] for the synthesis of the key precursor **2**, including the use of L-ascorbic acid[4] and *(2S,3R)*-2-amino-3-hydroxy-butyrolactone **3** derived from L-threonate[5,6] as starting materials.

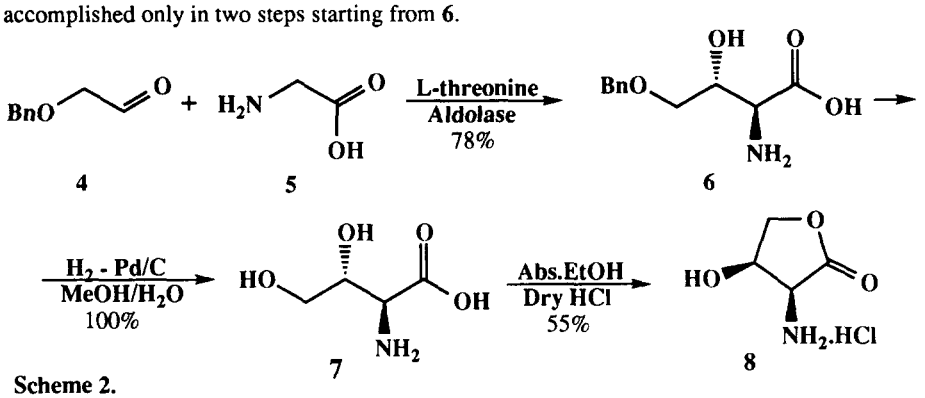


1 **2** **3**

Scheme 1.

We report here a highly efficient synthesis of *(2S,3R)*-2-amino-3-hydroxybutyrolactone **3** by using L-threonine aldolase as a catalyst for the synthesis of a β-hydroxy-α-amino acid with desired stereochemistry of both chiral centers found in **3** (Scheme 2). This achievement is based on our discovery [7] that an oxygen at the β-position of an aldehyde is very important for obtaining a high diastereoisomeric *erythro/threo* ratio in the enzymatic aldol addition reaction. Simple recrystallizatiom of the enzyme product with 92:8 *erythro/threo* ratio, for example, affords pure benzyloxyprotected hydroxy amino acid **6**. Compound **8** was readily converted to **3** for use in the

synthesis of **1** and analogs. The synthesis of aminolactone **8** was straightforward[8] and accomplished only in two steps starting from **6**.



Scheme 2.

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8. Procedures for the enzyme preparation and the enzymatic synthesis are as reported previously[7]. Compound **6**: ^{1}H NMR, CD_3OD/D_2O ~ 3/1) δ 7.29-7.38 (m, 5H), 4.55 (s, 2H), 4.24-4.29 (dd, 1H *J* = 4 .0 and 4.3 Hz), 3.84 (d, 1H *J* = 4.3 Hz), 3.70 (d, 2H, *J* = 4.0 Hz); m.p. 201-202 °C (dec) H_2O/EtOH; $[\alpha]_D$=+20.1 (c=0.88 1N HCl); TOFMS $[M+H]^+$ calc. 226.1 found. 226.
7 : The reduction was carried out at atmospheric pressure in 50% MeOH/H_2O untill deprotection was completed (TLC). Yield 100%. M.p. 194 °C (dec) H_2O/MeOH, (ref.[9] 194-195 °C); $[\alpha]_D$ = - 11.6 (c, 1.06 H_2O), (ref.[9] $[\alpha]_D$ =-11.3). ^{13}C NMR (D_2O, acetone as int. stand. $(CH_3)_2$ - 30.3 ppm) ; d 58.0 ($CHNH_2$), 62.8 (CH_2OH), 69.0 (CHOH), 171.5 (C=O). TOFMS $(M+H)^+$, calc. 136.0, found 136.0. **8** : The procedure follows the one previously described [10]. Yield 55%. M.p. 178-179 °C, lit.[9] 176 °C ; $[\alpha]_D$ =+59.7 (c, 1.06, H_2O), lit.[9] +55.6. ^{13}C NMR data are in good agreement with reported[6].
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