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An Efficient Synthesis of (2*S*,3*R*)-3-Hydroxylysine *via* Ruthenium Catalyzed Asymmetric Hydrogenation

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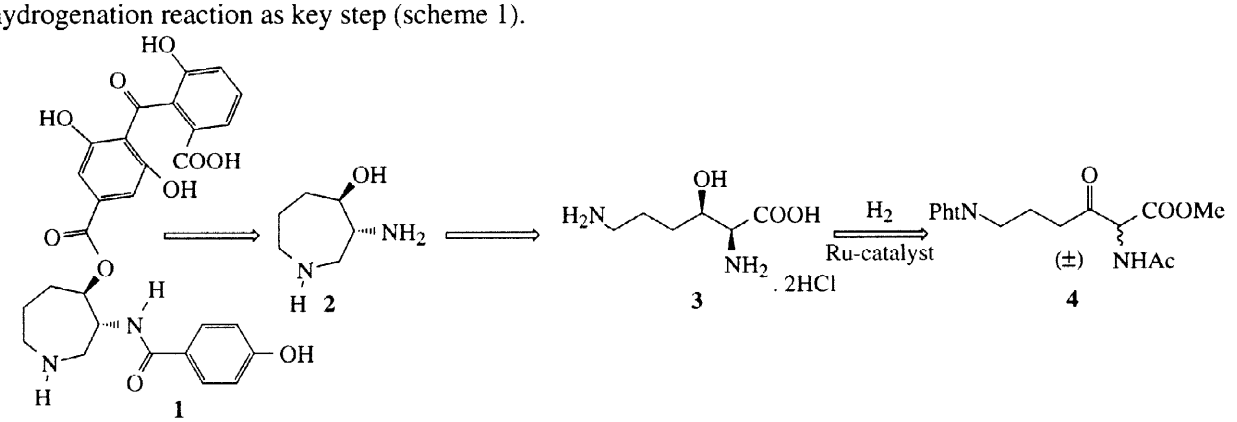
Abstract: *An efficient synthesis of the natural occuring amino acid (2S,3R)-3-hydroxylysine is reported. The five step sequence features a highly enantioselective dynamic kinetic resolution of racemic α-acetamido β-keto phtalimidohexanoate using ruthenium(II) catalyzed hydrogenation reaction.*

(-)-Balanol **1**, a fungal metabolite isolated[1] in trace amounts from *Verticillium balanoïdes* is a potent protein kinase C (PKC) inhibitor which is involved in cell growth, metabolism and differenciation.[2] Activated PKC has been implicated in number of severe disease states including central nervous system, cancer, cardiovascular disorders, inflammation, asthma and HIV infections.[3] Several examples of total synthesis of (-)-balanol[4] and analogues have been reported.[5] Most of them involved the chiral hexahydroazepine-containing fragment[6] **2** as synthetic intermediate. Some approaches to the synthesis of the azepane core structure have been described *via* multistep reactions. An alternative route to the azepane moiety consists in a cyclisation of the naturally occuring aminoacid (2*S*,3*R*)-3-hydroxylysine **3**. To the best of our knowledge, this β-hydroxy α-amino acid has been synthesized with 80% d.e. in a 12 steps sequence from L-serine[7] and more recently from 4-aminobutanol in 9 steps by chiral Sharpless *cis*-hydroxylation.[8] However, because of multistep reactions, alternative sources of (2*S*,3*R*)-3-hydroxylysine **3** are still relevant for a large scale production of **3**. We now report a catalytic approach to the synthesis of (2*S*,3*R*)-3-hydroxylysine **3** *via* ruthenium-mediated hydrogenation reaction as key step (scheme 1).



Scheme 1

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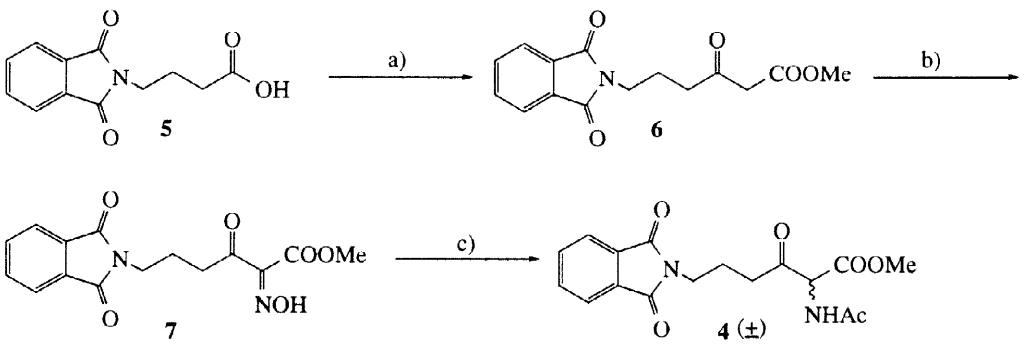
In previous work,[9] it was shown that the synthesis of *syn* β-hydroxy α-aminoacids is quite facile *via* dynamic kinetic resolution (DKR) of α-acetamido β-ketoester using ruthenium-catalyzed hydrogenation reaction. The chiral Ru(II) catalysts have been used *in situ*[10] in the synthesis of several chiral intermediates. The racemic methyl-2-acetamido-3-keto-6-phtalimidohexanoate **4** was prepared in 80% yield as shown in scheme 2. The β-ketoester **6** was prepared from the commercially available 4-phtalimidobutyric acid **5** by successive addition of carbonyldiimidazole and magnesium salt of ethylmalonic acid to afford **6**. Subsequent treatment with sodium nitrite in a mixture of acetic acid and water provided the oxime **7** (90% yield) which was then reduced to the desired racemic α-acetamido β-ketoester **4** by heterogeneous hydrogenation with Pd/C in acetic acid and *in situ* protection with acetic anhydride in 70% yield.



(a) ImCOIm then $Mg^{2+}(^{-}OOCCH_2COOMe)_2$, THF, 24 h (80%) (b) $NaNO_2$, AcOH, H_2O, 2 h (90%) (c) H_2, Pd/C, Ac_2O, AcOH, 18 h (70%).

Scheme 2

The next step was to synthesize the *syn* α-hydroxy β-ketoester **9** and different reaction conditions were tested. All reactions were performed with Ru(II)-catalyst prepared *in situ* by treatment of the chiral ligand (*R*)-MeO-BIPHEP and (COD)Ru(2-methylallyl)$_2$ and methanolic HBr. The hydrogenation was first carried out in methanol (table 1) with 1 mol% of the catalyst under hard conditions (entry 1, 100 bar, 80°C). A complete conversion was obtained with a moderate *syn* diastereoselectivity (d.e.=30%). The fact that the DKR depends on the relative rate of hydrogenation and racemization of the substrate suggested that a significant increase of the selectivity might be obtained by decreasing the catalyst concentration and temperature. Indeed, under 100 bar of hydrogen at room temperature and at a lower catalyst loading (0.5 mol%), an increased *syn* diastereoselectivity was observed with a lower conversion (entry 2). In dichloromethane under the same reaction conditions, the desired α-hydroxy β-ketoester **9** was obtained with a complete *syn* diastereoselectivity and a moderate conversion (entry 3). In order to enhance the conversion, 1% mol of catalyst was used in dichloromethane under 120 bar and at room temperature with a substantial loss of diastereoselectivity (entry 4). Finally, the dynamic kinetic resolution was achieved with 0.5 mol% of catalyst at 115 bar and 50°C : the optically pure *syn* α-hydroxy β-ketoester **9**[11] was isolated in quantitative yield (entry 5). The e.e. was determined by ^{19}F NMR of the corresponding (*R*)-MTPA ester.

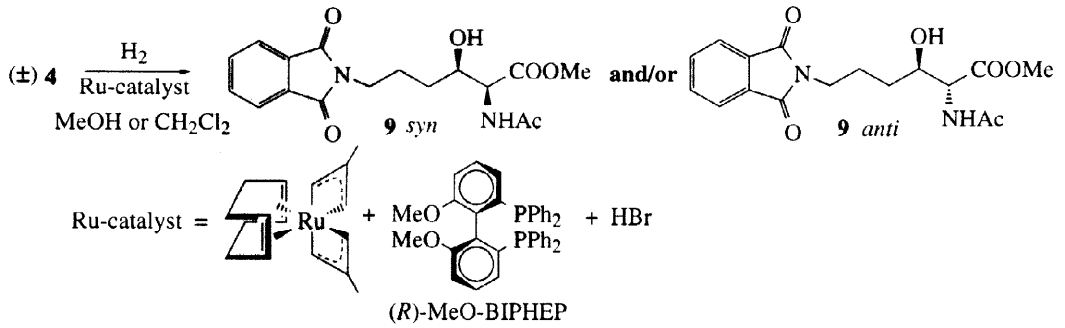
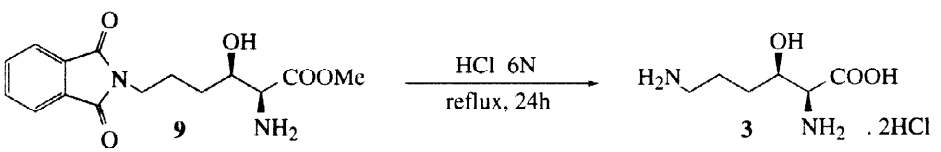


Table 1 : Dynamic Kinetic Resolution of α-acetamido β-ketoester **4** with chiral Ru(II)-catalyst [a]

Entry	Catalyst (% mol)	P (bar)	T (°C)	Time (h)	Solvent	Conv. (%)	*syn /anti*
1	1	100	80	89	MeOH	100	65/35
2	0.5	100	r.t.	66	MeOH	78	75/25
3	0.5	100	r.t.	66	CH_2Cl_2	61	>99/1
4	1	100	r.t.	90	CH_2Cl_2	74	69/31
5	0.5	115	50	108	CH_2Cl_2	100	>99/1[b]

(a) Conversions and diastereomeric excesses were measured by ^1H NMR. (b) Hydrogenation was carried out on a 500 mg scale.

With the enantiomerically pure compound *syn* **9** in hands, the preparation of (*2S,3R*)-**3** was performed in refluxing HCl 6N for 24 h (**Scheme 3**). The resulting crude material was then concentrated and passed through an anion-exchange resin (Cl^- form) to afford pure (*2S,3R*)-3-hydroxylysine bis hydrochloride **3** in 80% yield.



Scheme 3

In conclusion, the ruthenium-mediated dynamic kinetic resolution (DKR) allows the construction of both stereogenic centers of (*2S,3R*)-3-hydroxylysine in a single stereocontrolled catalytic step in a 40% overall yield. This route could allow the preparation of large quantities of (*2S,3R*)-3-hydroxylysine and is competitive compared to the previously reported syntheses which involved multisteps reactions. In addition, this methodology could be extended to the preparation of new synthetic intermediates with functionalized azepane cores which are currently under investigation.

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11. Compound **9** (*syn*) : ^{1}H NMR (250MHz, $CDCl_3$) δ: 1.50-1.57 (m, 2H); 1.75-1.86 (m, 2H); 2.05 (s, 3H); 3.76 (m, 2H); 3.77 (s, 3H); 4.20 (m, 1H); 4.64 (dd, J=2.2Hz and J=8.9Hz, 1H); 6.25 (d, J=8.9Hz, 1H); 7.70-7.75 (m, 2H); 7.80-7.85 (m, 2H). Anal. calcd. for $C_{17}H_{20}N_2O_6$ C,58.61; H,5.79; N,8.04. Found C,58.51; H,5.83; N,8.09. A 3:1 mixture *syn+anti* **9** has been obtained in reaction conditions of table 1 (entry 1) : the minor *anti* diastereomer shows characteristic signals at δ 4.0 ppm (m) and 6.6 ppm (bd).