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SYNTHESIS OF STATINE AND ITS ANALOGUES BY HOMOGENEOUS ASYMMETRIC HYDROGENATION

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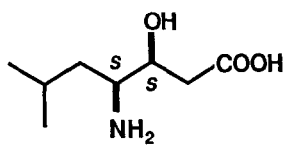
Summary: Diastereoselective hydrogenation of *N*-protected γ-amino β-keto esters catalyzed by BINAP—Ru(II) complexes provides an efficient entry to the statine series with high enantiomeric purities.

Statine (**1**) is an unusual γ-amino acid which is recognized as a key component of some low molecular-weight peptides such as the aspartic proteinase inhibitor pepstatin.[2] In view of the physiological significance of such peptides, particularly as therapeutic agents for human hypertension, and in the hope of developing new synthetic enzyme inhibitors, the opening of efficient entries to **1** and its analogues has been earnestly desired.[3] Described herein is a practical, highly stereoselective synthesis of β-hydroxy γ-amino acids in the *N*-protected form via homogeneous asymmetric hydrogenation.



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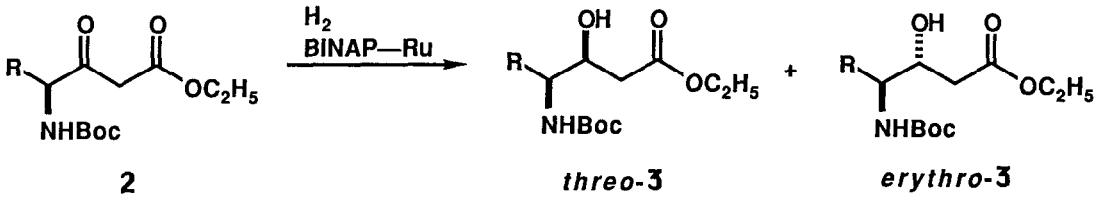
BINAP—Ru(II) complexes[4] are known to act as excellent catalyst precursors for the enantioselective hydrogenation of prochiral β-keto esters.[5] We examined the reaction of chiral ketonic substrates of type **2**,[6] leading to *threo*- and *erythro*-**3**, and found that the γ-stereogenic center in the substrates significantly affects the degree of the diastereoselectivity. Fortunately, as exemplified in Table I, the efficiency of the catalyst/substrate chirality transfer (catalyst control) and the intramolecular 1,2-asymmetric induction (substrate control) appear to cooperate to form the natural threo series with high stereoselectivity. For example, hydrogenation of the *N*-Boc derivative **2a** in the presence of $RuBr_2$[(*R*)-binap] afforded *threo*-**3a** having a 3*S*,4*S* configuration almost exclusively, whereas the reaction catalyzed by the enantiomeric Ru complex gave a 9:91 mixture of *threo*-**3a** and *erythro*-**3a**. The catalyst control effecting the hypothetical enantioface differentiation in this reaction is calculated to be >32:1 and the substrate control favoring the threo stereochemistry to be 3:1.[7] Obviously, the directing effect of the ester function is of overwhelming significance in the creation of the β-stereogenic center.[8] The γ-stereocenter in **2** is, configurationally, not very stable and



2 *threo*-3 *erythro*-3

a: R = $C_6H_5CH_2$
b: R = $(CH_3)_2CHCH_2$
c: R = cyclohexylmethyl

Table I. Asymmetric Hydrogenation of **2**[a]

		product **3**		*threo*-**3**	
substrate	catalyst[b]	% yield[c]	threo:erythro	% ee[d]	$[\alpha]_D^{26}$, deg[e]
2a	$RuBr_2$[(*R*)-binap]	97[f]	>99:1[g]	99	-36.9
2a	$RuBr_2$[(*S*)-binap]	96	9:91[g]	>99[h]	*i*
2b	$RuBr_2$[(*R*)-binap]	99	>99:1[j]	97	-38.3
2c	$RuBr_2$[(*R*)-binap]	92	>99:1[j]	100[k]	-32.6

[a] Reactions were carried out in a 0.3–1.5 M ethanol solution of the substrate (0.6–5.7 mmol) under 100 atm of hydrogen at 18–21 °C for 60–180 h in the presence of 0.2 mol% of BINAP–Ru complex. [b] Empirical formula (see ref 5). [c] Isolated yield after silica-gel column chromatography. [d] HPLC analysis of the GITC derivatives. [e] Measured in methanol (*c* 1.0). [f] A 20 g-scale reaction. [g] HPLC analysis. [h] (3*R*,4*S*)-*erythro*-**3a** in >98% ee. [i] The value of a 9:91 threo–erythro mixture: $[\alpha]_D^{20}$ -16.1° (c 1.0, CH_3OH). The erythro isomer after purification by silica-gel column chromatography: $[\alpha]_D^{20}$ -14.3° (*c* 1.0, CH_3OH). [j] GC analysis (2% OV-225 chromosorb W, column temp 150–170 °C). [k] The minor isomer was not detectable by HPLC analysis of the GITC derivative.

the keto esters are known to undergo racemization under certain catalytic and stoichiometric reduction conditions.[3c,d] However, under the present hydrogenation conditions, the undesired stereomutation is minimized, as is seen from the high ee value of the product **3**.

Thus our hydrogenation methodology has realized a facile, stereocontrolled route to the statine series. We have performed the reaction only on a 20-g scale but, on the basis of our experience in related reactions, no problems are foreseen in scaling-up.

The experimental procedure is as follows. A solution of **2a** (20.0 g, 59.7 mmol) in degassed anhydrous ethanol (40 mL) was placed in a 80-mL Schlenk tube and degassed by three freeze-thaw cycles. $RuBr_2$[(*R*)-binap][5] (100 mg, 0.113 mmol) was then added to this solution under argon, and the catalyst was dissolved with the aid of an ultrasonicator. The resulting light brown solution was degassed by two freeze-thaw cycles. By means of a cannula this was then transferred to a glass vessel placed in a

100-mL stainless steel autoclave. Hydrogen was pressurized to 100 atm, and the solution was stirred at 20 °C for 145 h. The solvent was removed under reduced pressure, and the remaining solid was subjected to silica-gel column chromatography (Fuji Davison BW820 MH, 200 g; eluent, 1:1 ethyl acetate–hexane mixture) to give **3a** (19.5 g, 97% yield) as a >99:1 threo–erythro mixture (HPLC analysis: column, Senshu Pak ODS-1251-SH; eluent, 55:45 water–acetonitrile mixture; t_R of *threo*-**3a**, 18.6 min; t_R of *erythro*-**3a**, 15.8 min). An aliquot of the hydrogenation product was converted to the corresponding free base and condensed with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) by the reported method.[3c,d,9] The resulting thiourea was analyzed as a 99.5:0.5 diastereomeric mixture by HPLC, indicating a 99% ee (column, Senshu Pak silica-1251-N, eluent, 93:7 hexane–2-propanol mixture; t_R of (3*S*,4*S*)-isomer, 12.7 min; t_R of (3*R*,4*R*)-isomer, 10.9 min).

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6. Substrates were synthesized in 50–60% yield *via* PCC oxidation of the corresponding hydroxy esters.[3q,u,v] **2a**: mp 64–65 °C, $[\alpha]_D^{20}$ -58.5° (*c* 1.0, CH_3OH) [lit[3c]: mp 54–56 °C, $[\alpha]_D^{22}$ -56.3° (*c* 2.0, CH_3OH)]. **2b**: mp 41.0–42.5 °C, $[\alpha]_D^{20}$ -57.3° (*c* 1.0, CH_3OH) [lit[3c]: mp 36–38 °C, $[\alpha]_D^{22}$ -54.8° (*c* 2, CH_3OH)]. **2c**: $[\alpha]_D^{20}$ -41.1° (*c* 1.0, CH_3OH) [lit[3d]: $[\alpha]_D$ -38.4° (*c* 1, CH_3OH). The enantiomeric excesses of **2b** and **2c** were determined to be >98% in both cases by HPLC analysis (column, Sumipax OA-4100 4 mmϕ x 25 cm; eluent, 88:12 hexane–1,2-dichloroethane mixture; flow rate, 2.0 mL/min).
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