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13 Employment of Catalysts Working in Tandem

CONTENTS

13.1 A ONE-POT SEQUENTIAL ASYMMETRIC HYDROGENATION UTILIZING Rh(I)- AND Ru(II)-CATALYSTS

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Asymmetric hydrogenation of enamido β-keto esters was carried out in the presence of both Rh(I)- and Ru(II)-chiral phosphine complexes as catalysts[1]. This is the efficient method to prepare statin analogues. The process independently induces two stereo centres in a molecule in a simple manner.

13.1.1 SYNTHESIS OF ETHYL (Z)-4-ACETAMIDO-3-OXO-5-PHENYL-4-PENTENOATE[1]

Materials and equipment

- (Z)-2-Acetamino-cinnamic acid[2,3], 1.03 g, 5.0 mmol
- Dry tetrahydrofuran, 20 mL
- 1,1′-Carbonyldiimidazole, 1.28 g, 5.5 mmol
- Lithiated ethyl acetate, 15 mmol
- Saturated aqueous ammonium chloride solution, 20 mL

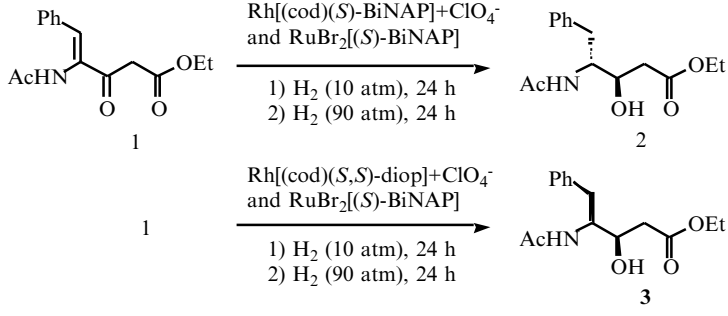
- Saturated aqueous sodium bicarbonate solution, 30 mL
- Brine, 30 mL
- Magnesium sulfate, 3 g
- Ethyl acetate, hexane
- Silica gel 60
- Column chromatography
- Test tubes, 25 mL × 50

- 100 mL Three-necked and 50 mL two-necked round-bottom flask with magnetic stirrer bars
- Magnetic stirrer
- Dry ice–acetone cooling bath
- Thermometer, −80 °C to 30 °C
- Syringes
- TLC
- Separatory funnel
- Cannula
- Rotary evaporator

Procedure[4]

1. To (*Z*)-2-acetamino-cinnamic acid (1.03 g, 5.0 mmol) in dry THF (20 mL) was added 1,1′-carbonyldiimidazole (1.28 g, 5.5 mmol) at room temperature; then lithiated ethyl acetate (15 mmol) was added via cannula at −78 °C.
2. The reaction mixture was stirred at the same temperature for 30 min, then stirred at 0 °C for 30 min, and poured into NH_4Cl aq. solution.
3. The aqueous layer was extracted with ethyl acetate and combined organic layer was washed with $NaHCO_3$ and brine, then dried over $MgSO_4$.
4. After removal of the solvent, the residue was chromatographed over silica gel to afford ethyl (*Z*)-4-acetamido-3-oxo-5-phenyl-4-pentenoate (870 mg, 63 %).

13.1.2 ASYMMETRIC HYDROGENATION OF ETHYL 4-ACETAMIDO-3-OXO-5-PHENYL-4-PENTENOATE



Materials and equipment

- Ethyl (*Z*)-4-acetamido-3-oxo-5-phenyl-4-pentenoate, 275 mg, 1.0 mmol
- [Rh(cod)(*S*)-BiNAP]$^{+}$CiO$_4^{-}$[5], 9.3 mg, 0.01 mmol
- RuBr$_2$(*S*)-BiNAP[6,7], 8.8 mg, 0.01 mmol
- Distilled triethylamine, 0.14 mL, 1.0 mmol
- Distilled ethanol, 10 mL
- 1 N HCl solution, 20 mL
- Brine, 30 mL
- Ethyl acetate, hexane
- Silica gel 60

- 50 mL Autoclave with glasstube and a magnetic stirrer bar
- Hydrogen gas tank
- Gas connector from tank to autoclave
- Magnetic stirrer
- Oil-bath
- Thermometer
- Syringes
- TLC
- Rotary evaporator

Procedure

1. In a 50 mL autoclave containing a glass tube and magnetic stirrer bar were placed [Rh(cod)(*S*)-BiNAP]$^{+}$CiO$_4^{-}$ and RuBr$_2$[(*S*)-BiNAP] as catalysts.
2. To this mixture were added the substrate **1**, triethylamine, and ethanol. The autoclave was filled with hydrogen (10 atm) after repeated (4–5 times) filling and purging of hydrogen.
3. The reaction was carried out under 10 atm H_2 at 40 °C for 24 h and under 90 atm at 40 °C for an additional 24 hours.
4. The solvent was removed under reduced pressure.
5. The residue was diluted with ethyl acetate before being washed with 1 N HCl at 0 °C. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine and dried over Na_2SO_4.
6. After removal of the solvent, the residue was eluted through a short silica gel column to remove the catalyst (elution with hexane:ethyl acetate = 1:2). The eluent was concentrated *in vacuo* to give the product **2** (99 % yield) and the diastereoselectivity was determined by HPLC analysis (99 %). The enantioselectivity of the product was determined by ^1H NMR analysis with chiral shift reagent (+)-Eu(dppm) in $CDCl_3$ and by chiral HPLC analysis (Chiralcel-OD).

*Ethyl (3R,4R)-4-(acetamido)-3-hydroxy-5-phenylpentanoate (**2**)*

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28 (3H, t, $J = 6.9$ Hz), 1.99 (3H, s), 2.38 (2H, ABX, $J = 3.0$, 17.3 Hz), 2.57 (1H, ABX, $J = 10.3$, 17.3 Hz), 2.91 (2H, d, $J = 7.6$ Hz), 3.60–4.05 (2H, m), 4.15 (2H, q, $J = 6.9$ Hz), 5.83–5.87 (1H, m), 7.19–7.49 (5H, m, aromatic).

^{13}C NMR (67.5 MHz, $CDCl_3$). δ 173.5, 170.0, 137.9, 129.3, 128.6, 126.5, 66.8, 60.9, 53.9, 38.6, 38.2, 23.4, 14.1.

IR($CHCl_3$) 3350, 2922, 1729, 1647, 1537, 1372, 1295 cm^{-1}; MS (EI, 70 eV) 279 (M^+, 11 %), 220 (9), 192 (14), 167 (19), 149 (68), 135 (49).

HRMS (EI, 70 eV) calculated for $C_{14}H_{15}NO_4$ 279.1471 (M^+), found 279.1434.

HPLC (Silica gel 60–5 mm, 7.5 o.d.x 300 mm, elution with 12 % 2-propanol in hexane, 3.0 mL/min) Rt 29–33 min; $[\alpha]_{D^{25}} = +69.0^\circ$ ($c = 0.116$, MeOH) (>95 % ee).

Use of [Rh(cod)(*S*, *S*)-diop]$^+$$CiO_4^-$[8] instead of [Rh(cod)(*S*)-BINAP]$^+$ CiO_4^- gave its diastereomer **3** with 72 % stereoselectivity and >95 % ee.

*Ethyl (3R,4S)-4-(acetamido)-3-hydroxy-5-phenylpentanoate (**3**)*

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28 (3H, t, $J = 6.9$ Hz), 1.88 (3H, s), 2.53 (3H, m), 2.87 (1H, ABX, $J = 8.6$, 14.0 Hz), 2.99 (1H, ABX, $J = 4.6$, 14.0 Hz), 3.76–4.15 (2H, m), 4.20 (2H, q, $J = 6.9$ Hz), 5.53–5.49 (1H, m), 7.19–7.53 (5H, m, aromatic).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ 172.9, 169.1, 141.5, 129.3, 128.6, 126.7, 68.9, 60.9, 54.2, 38.2, 35.1, 23.3, 14.1.

IR ($CHCl_3$) 3350, 2922, 1729, 1647, 1537, 1372, 1295 cm^{-1}.

MS (EI, 70 eV) 279 (M^+), 220, 192, 174, 163, 135.

HRMS (EI, 70 eV) calculated for $C_{14}H_{15}NO_4$ 261.1471 (M^+), found 261.1495.

HPLC (Silica gel 60–5 mm, 7.5 o.d.x 300 mm, elution with 12 % 2-propanol in hexane, 3.0 mL/min) Rt 34–40 min; $[\alpha]^{25}_{D} = -55.5^\circ$ ($c = 0.072$, MeOH) (>95 % ee).

Conclusion

A direct method for the respective preparation of the core units of statin analogues (3*R*,4*R*)-**2**, (3*S*,4*S*)-**2**, (3*R*,4*S*)-**3**, and (3*S*,4*R*)-**3** in enantiomerically pure form is described. These analogues are prepared from the same molecule **1** in a one-pot, sequential asymmetric hydrogenation process utilizing Rh(I)- and Ru(II)-chiral phosphine complexes. Some other examples are depicted in Table 13.1.

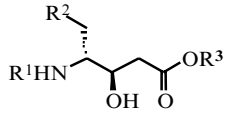


Table 13.1 Sequential asymmetric hydrogenation of γ-(acylamino)-γ, δ-unsaturated-β-keto esters catalysed by Rh[(cod)(*S*)-BiNAP]$^{+}$$ClO_4^{-}$ and $RuBr_2$[(*S*)-BiNAP].

Solvent	R^1	R^2	R^3	Yield %	ee %
EtOH	Ac	Ph	Et	99	>95
MeOH	Ac	Ph	Me	99	>95
t-BuOH	Ac	Ph	*t*-Bu	no reaction	–
Et	Boc	Ph	Et	99	>95
Et	Ac	4-Cl-C_6H_4	Et	90	>95

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