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Review Article

Highly Stereoselective Hydrogenations—As Key-Steps in the Total Synthesis of Statins

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ABSTRACT Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase) and became the standard of care for treatment of hypercholesterolemia because of their efficacy, safety, and long-term benefits. They are administered as diastereo- and enantiomerically pure compounds. We summarize here two new approaches for the total synthesis of the most important representatives, atorvastatin, and rosuvastatin, based on highly stereoselective hydrogenations as key-steps. *Chirality 22:534–541, 2010.*

KEY WORDS: drug synthesis; atorvastatin; rosuvastatin; asymmetric hydrogenation; enantioselectivity; stereoselectivity; statins; asymmetric catalysis

INTRODUCTION

Statins[1–3] are effective inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme reductase (HMG-CoA reductase)[4] and are a class of hypolipidemic drugs used to lower level of cholesterol[5] in the blood by reducing the production of cholesterol by the liver in people with or at risk of cardiovascular disease.[6–8] Recently, statins have become the standard of care for treatment of hypercholesterolemia and hyperlipidaemia[9–12] due to their efficacy, safety, and long-term benefits.[13] Among the statin class of drugs, atorvastatin[14–21] and rosuvastatin[22–30] are the most powerful lipid-lowering agents (Fig. 1).

Atorvastatin calcium[13] was the first totally synthetic HMG-CoA-reductase inhibitor developed and marketed as a single enantiomer.[17–21] Currently, it ranks at the top of the drugs best sold in the world (Atorvastatin calcium tablets are currently marketed by Pfizer under the trade name *Lipitor*. According to a recent article in Forbes—*The World's Ten Best-Selling Drugs*: "Pfizer's cholesterol pill Lipitor remains the best-selling drug in the world for the fifth year in a row. Its annual sales were $12.9 billion, more than twice as much as its closest competitors.").[31] Rosuvastatin calcium is the newest among statins and it was approved as the cholesterol-lowering drug Crestor in August 2003. Rosuvastatin has been called a super-statin, because it appears to reduce low-density lipoprotein (LDL) cholesterol to a greater degree than rivals in its class without additional adverse effects. A number of new methods for the synthesis of rosuvastatin and its precursors has been published recently.[26–30]

SYNTHESIS OF ATORVASTATIN

We recently reported a new approach for the total synthesis of atorvastatin[32] via highly stereoselective hydrogenation of the statin precursor ethyl (5*S*)-5,6-isopropylidenedioxy-3-oxohexanoate[33] as a key-step. The retrosynthetic pathway to the enantiopure side chain of atorvastatin is depicted on Scheme 1. This involves two-carbon elongation of methyl (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (**1**) to afford alkyl (*S*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxobutanoate (**2**) followed by catalytic hydrogenation of the keto group to afford the corresponding hydroxy ester **D**. The protection of the HO-group in compound **D** and the subsequent cleavage of acetal-moiety gives lactone **C**, which may then be used for the preparation of atorvastatin precursor **B**.

As methyl (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (**1**) is commercially available at a rather high price, it was prepared in our lab starting from (*S*)-malic acid by a known sequence (Scheme 2). (*S*)-Malic acid was esterified with methanol in the presence of dimethyl orthoformate to obtain dimethyl (*S*)-malate (**3**). This material was regioselectively reduced using Moriwake's procedure ($sBH_3 \times SMe_2$, THF, cat. $NaBH_4$).[34,35] The resulting crude methyl (*S*)-3,4-dihydroxybutanoate was directly transformed without purification into the acetonide (*S*)-**1**[33] with a yield of 74% after distillation. Saponification of ester (*S*)-**1** with aqueous NaOH and subsequent neutralization gave the corresponding acid (*S*)-**4** in a chemical yield of 71–

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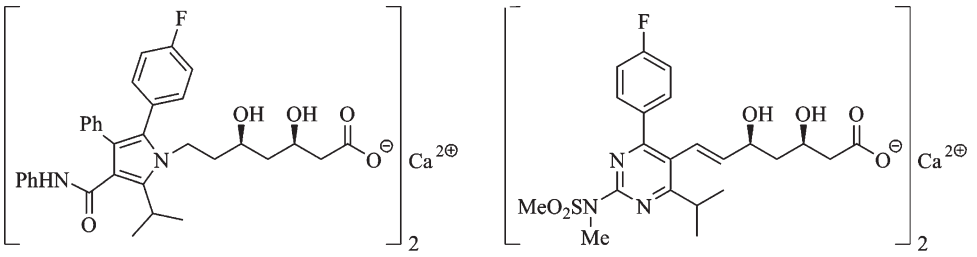


Fig. 1. Structures of atorvastatin calcium and rosuvastatin calcium.

78%. Acid (*S*)-**4** was elongated by application of a general protocol developed for the synthesis of β-keto esters[36] via intermediate formation of imidazolide (*S*)-**5**. After work-up keto ester (*S*)-**2** was obtained after distillation in good yield.[33]

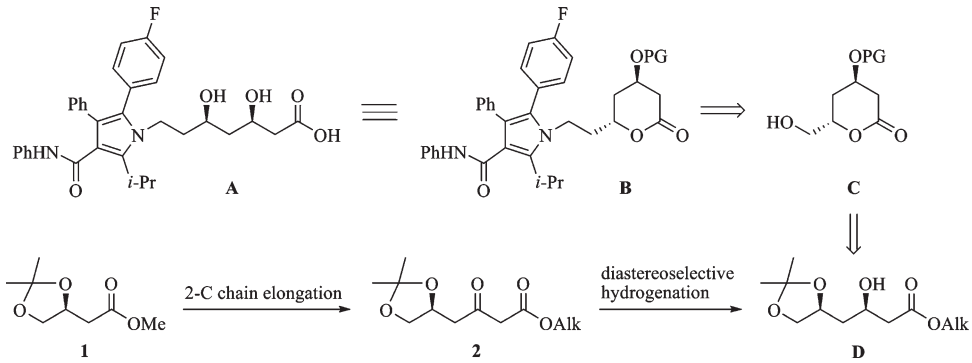
To define optimal conditions for the stereoselective hydrogenation of β-keto ester (*S*)-**2** into the desired protected polyol (3*R*,5*S*)-**6** (Scheme 3), we studied the performance of several homogeneous chiral Rh and Ru catalysts.

The hydrogenations were performed under mild conditions (50 bar initial H_2 pressure, room temperature). The results are listed in Table 1. The syn/anti ratios were determined on the basis of NMR data. Hydrogenation of (*S*)-**2** catalyzed with chiral Rh(I) catalysts showed only moderate diastereoselectivities (entries 1–9). Structures of chiral ligands are illustrated on Fig 2. Higher activities were observed in aprotic solvents (compare, entry 1 and 2). The Rh(I) catalyst with (*S,S*)-Et-DUPHOS or (*S,S*)-Me-DUPHOS as ancillary ligands induced reasonable syn-selectivity. At the same time, with (*R,R*)-Et-DUPHOS and (*R,R*)-Me-DUPHOS as ligands, completely opposite results were observed.

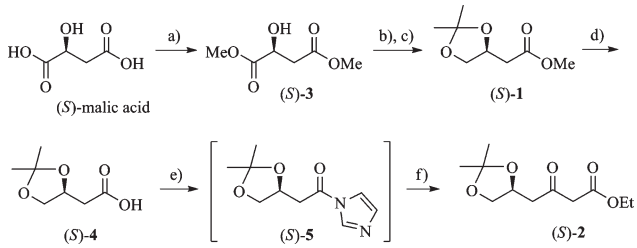
Ru(II) catalysts based on diphosphines BINAP and Tol-BINAP gave markedly varying results (entries 10–22). Particularly, it was found that the application of commercial or in-house prepared[37] Ru[(*R*)-BINAP]Cl_2 afforded a complex mixture of products although the conversion of β-keto ester **2** was complete (entry 10).

In comparison with the related Rh(I) complex (entries 1 and 2), the Ru(II) complex did not work in AcOEt (entry 11). Besides the desired (3*R*,5*S*)-**6** (syn) alcohol, a side product was formed in MeOH. On the basis of the NMR data,[33] we assumed that a thermodynamic equilibrium is established between (3*R*,5*S*)-**6** (syn) and the rearrangement product (*S,R*)-**7** during the hydrogenation reaction (Scheme 4). This assumption was confirmed by *O*-silylation of the mixture of alcohols (3*R*,5*S*)-**6** and (3*R*,5*S*)-**7** followed by chromatographic separation of products **8** and **9**. Structures of both isomers **8** and **9** were confirmed by elemental analysis, mass-spectra, and NMR data. It is remarkable that 1,3-dioxolane **8** as well as 1,3-dioxane **9** showed only one set of signals in the NMR spectrum. This gives clear evidence that the hydrogenation protocol used produced alcohols (3*R*,5*S*)-**6** and (3*R*,5*S*)-**7** with excellent diastereomeric purity. The same rearrangement was also observed with the Ru[(*R*)-Tol-BINAP]Cl_2 catalyst.

It became obvious that these catalysts have acidic properties and it is thus necessary to neutralize them before use. For this reason, we tested several nitrogenous bases (Et_3N, $BnNH_2$, imidazole, piperazine). These bases had an uniform influence on the activity of the catalysts. In Table 1 only examples with Et_3N are listed (entries 12–15). The addition of Et_3N completely inhibited the formation of the transacetalization product (*S,R*)-**7**. It was shown also that increasing the concentration of Et_3N affected the activity of the catalyst and at a ratio of Ru/Et_3N = 1/2, there was complete inhibition of hydrogenation. It is interesting to note that imidazole and piperazine, which possess two basic centers, behaved similarly to Et_3N. The (*R*)-BINAP complex induced exclusively (within analytical error) the syn-configuration in the product **6**. No significant influ-



Scheme 1. Retrosynthetic pathway to the enantiopure side chain of atorvastatin.

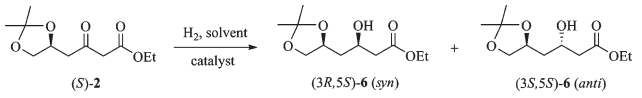


Scheme 2. Synthesis of ethyl (*S*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxobutanoate (**2**) [(a) MeOH, $HC(OMe)_3$, cat. HCl, RT, (93%); (b) $BH_3{\cdot}SMe_2$, THF, cat. $NaBH_4$ (1 mol %), RT; (c) $Me_2C(OMe)_2$, Me_2CO, cat. *p*-TsOH, RT, (74%); (d) 2N NaOH, RT, and neutralization with 2N $NaHSO_4$, (78%); (e) CDI (*N,N*′-carbonyldiimidazole), THF, RT; (f) $(EtO_2CCH_2CO_2)_2Mg$, THF, RT, 12h, (90%).]

ence of the chiral backbone of the substrate was observed. Partial neutralization of Ru[(*R*)-BINAP]Cl_2 (dimer) could also be achieved by prior treatment with an excess of Et_3N in CH_2Cl_2 followed by evaporation and drying in vacuum. The resulted solid, designated as Ru[(*R*)-BINAP]$Cl_2\times$ Et_3N, was tested in the hydrogenation of β-keto ester (*S*)-**2**. Particularly, it was shown that the activity of this complex is comparable to the activity of the catalytic system arising after neutralization in solution (compare with entries 12 and 13).

The activity of the complex is strongly dependent upon the polarity of the alcohol and follows the order: MeOH > EtOH >> *i*-PrOH (compare entries 16–18).

We noticed that all previously studied catalysts were poorly soluble in the reaction mixture. To overcome this problem we studied the influence of AcONa on the catalytic performance of Ru[(*R*)-BINAP]Cl_2 (runs 19–20). It is interesting to note that AcONa acted in the same way as Et_3N, for example, lowering the activity with an increase



Scheme 3. Hydrogenation of β-keto ester (*S*)-**2** under homogeneously catalyzed conditions.

in the AcONa/Ru ratio and complete inhibition of the hydrogenation at a ratio of 2 (runs 19–20). The parent Ru[(*R*)-Tol-BINAP]$Cl_2\times Et_3N$ complex exhibited similar activity and syn-selectivity (entry 21, compare with entry 16). The solubility of this precatalyst in MeOH was better than the analogous BINAP complex.

Finally, we found that application of Ru[(*R*)-Tol-BINAP]$Cl_2\times$ AcONa (entry 22) showed results similar to Ru[(*R*)-BINAP]Cl_2 (dimer) with addition of 1 equiv. of AcONa (compare with entry 19).

To optimize the substrate to catalyst ratio, several Ru(II) precatalysts, additives, solvents, and conditions (like, temperature and initial H_2-pressure) have been tested. Finally, the best results were achieved with Ru[(*R*)-Tol-BINAP]$Cl_2\times$ AcONa in EtOH at 50°C and 100 bar initial H_2-pressure. Under these conditions it was possible to run the hydrogenation of (*S*)-**2** at a substrate to catalyst ratio of 1000:1 with complete conversion within 4 h. The product (3*R*,5*S*)-**6** (syn) was obtained with at least 99% *de* and ca. 98% chemical purity.

The subsequent transformation of (3*R*,5*S*)-**6** (syn) into the atorvastatin precursor **15** was accomplished as shown in Scheme 5.[32] Protection of the HO-group of (3*R*,5*S*)-**6** followed by reduction of the ester-moiety gave aldehyde (3*R*,5*S*)-**10** in good yield. Upon subsequent cleavage of the acetal, the lactol **11** was obtained. Esterification of the primary hydroxyl group with 4-chlorotoluenesulfonyl chloride, followed by treatment of the sulfonate obtained with NaCN

TABLE 1. Stereoselective hydrogenation of β-keto ester (*S*)-2 with chiral Rh(I) and Ru(II) catalysts[33]

Entry	Precatalyst	Solvent	Time (min)	Conversion (%)	*de* (%)
1	{Rh[(*S*)-BINAP](COD)}BF_4	MeOH	1000	> 99	54 (syn)
2	{Rh[(*S*)-BINAP](COD)}BF_4	AcOEt	120	> 99	52 (syn)
3	{Rh[(*R*)-BINAP](COD)}BF_4	AcOEt	120	> 99	50 (anti)
4	{Rh[(*S,S*)-Et-DUPHOS](COD)}BF_4	AcOEt	70	> 99	36 (syn)
5	{Rh[(*R,R*)-Et-DUPHOS](COD)}BF_4	AcOEt	70	> 99	18 (anti)
6	{Rh[(*S,S*)-Me-DUPHOS](COD)}BF_4	AcOEt	120	> 99	40 (syn)
7	{Rh[(*R,R*)-Me-DUPHOS](COD)}BF_4	AcOEt	150	> 99	12 (anti)
8	Rh[(*R*)-Tol-BINAP](COD)]BF_4	AcOEt	80	> 99	50 (anti)
9	{Rh[(*R,S*)-JOSIPHOS](COD)}BF_4	AcOEt	50	> 99	40 (syn)
10	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	80	> 99	(*S,R*)-**6** (syn) and **9**
11	Ru[(*R*)-BINAP]Cl_2 (dimer)	AcOEt	940	< 10	n.d.
12	Ru[(*R*)-BINAP]Cl_2 (dimer) + 0.5 Et_3N	MeOH	100	> 99	> 99 (syn)
13	Ru[(*R*)-BINAP]Cl_2 (dimer) + 1.0 Et_3N	MeOH	200	> 99	98.2 (syn)
14	Ru[(*R*)-BINAP]Cl_2 (dimer) + 2.0 Et_3N	MeOH	1310	0	–
15	Ru[(*S*)-BINAP]Cl_2 (dimer) + 1.0 Et_3N	MeOH	380	> 99	2.3 (syn)
16	Ru[(*R*)-BINAP]$Cl_2\times Et_3N$	MeOH	120	> 99	> 99 (syn)
17	Ru[(*R*)-BINAP]$Cl_2\times Et_3N$	EtOH	300	> 99	> 99 (syn)
18	Ru[(*R*)-BINAP]$Cl_2\times Et_3N$	*i*-PrOH	340	0	–
19	Ru[(*R*)-BINAP]Cl_2 (dimer) + 1.0AcONa	MeOH	140	> 99	> 99 (syn)
20	Ru[(*R*)-BINAP]Cl_2 (dimer) + 2.0AcONa	MeOH	1000	0	–
21	Ru[(*R*)-Tol-BINAP]$Cl_2\times Et_3N$	MeOH	100	> 99	> 99 (syn)
22	Ru[(*R*)-Tol-BINAP]$Cl_2\times$AcONa	MeOH	130	> 99	> 99 (syn)

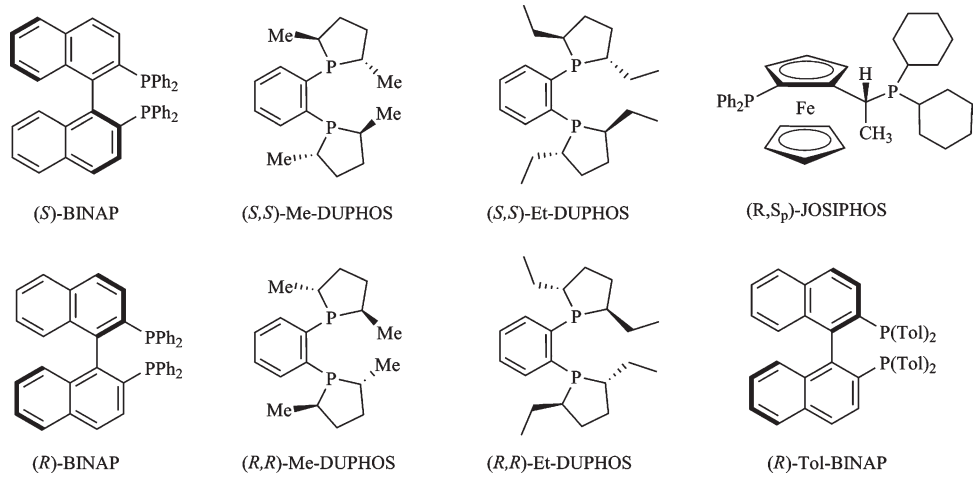
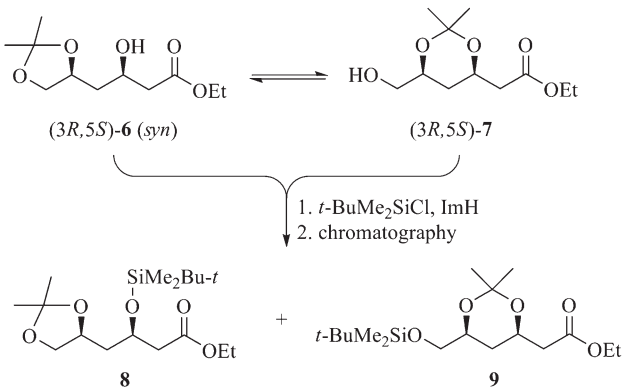


Fig. 2. Chiral diphosphine ligands applied for stereoselective Rh(I)- and Ru(II)-catalyzed hydrogenation of β-keto ester (*S*)-**2**.

gave the nitrile **12**. Raney nickel catalyzed hydrogenation of the latter afforded the desired amine **13**, which in turn was submitted to the Paal–Knorr condensation with the appropriate functionalized diketone **14** to give atorvastatin lactol **15** in 71% yield. Oxidation of the acetal and desilylation in order to obtain atorvastatin free acid can be conveniently performed as recently suggested.[38]

SYNTHESIS OF ROSUVASTATIN

Similarly, as shown earlier for the synthesis of atorvastatins we developed a new pathway for the production of rosuvastatin comprising two highly stereoselective hydrogenations as key-steps.[39,40] The first part covers the asymmetric hydrogenation of ethyl 5,5-dimethoxy-3-oxopentanoate (**17**) to ethyl 3-hydroxy-5,5-dimethoxypentanoate (**18**) (Scheme 6).[41] From the retrosynthetic analysis depicted in Scheme 6 it follows that the chiral side chain of rosuvastatin acid **A** can be created by diastereoselective and chemoselective reduction of the keto group in structure **B**. The protected hydroxy ylide (*R*)-**19** was postulated as a possible building block for the preparation of **B**, as long as the Wittig coupling reaction with the corresponding aldehyde could be performed and the HO-protecting group subsequently removed. Ylide (*R*)-**19** could be prepared[39] starting from methyl 3,3-dimethoxypropanoate (**16**) by two-carbon elongation followed by the enantioselective hydrogenation of the prochiral keto group in β-keto esters **17** to give finally β-hydroxy ester (*R*)-**18**. Protection of the HO-group and transformation of the $(MeO)_2CH$-moiety should accomplish the synthesis of ylide (*R*)-**19**.



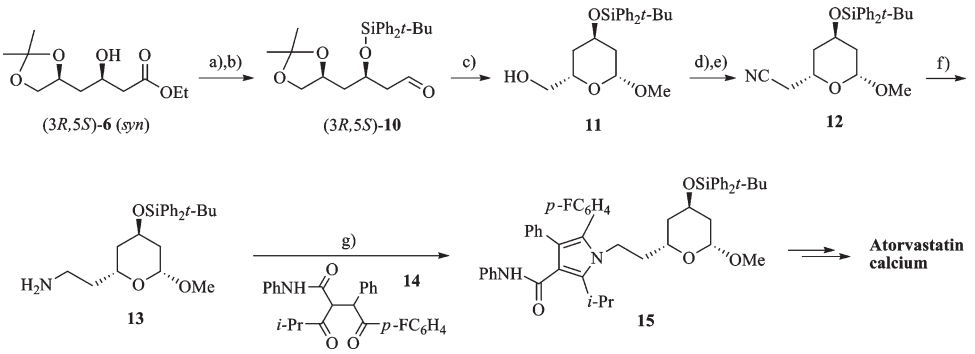
Scheme 4. Transacetalization reaction in acidic medium.

β-Keto ester **17**, serving as a prochiral substrate for the enantioselective hydrogenation, was assembled by a two-carbon chain elongation of 3,3-dimethoxypropionic acid **20** (Scheme 7). The latter was easily available from ester **16** by hydrolysis. A modified two-step Masamune procedure,[36] which involved first the activation of acid **20** with CDI (*N*,*N*-carbonyldiimidazole), followed by subsequent treatment with $Mg(O_2CCH_2CO_2Et)_2$ prepared in situ, afforded ethyl 5,5-dimethoxy-3-oxopentanoate (**17**) in 91% yield.

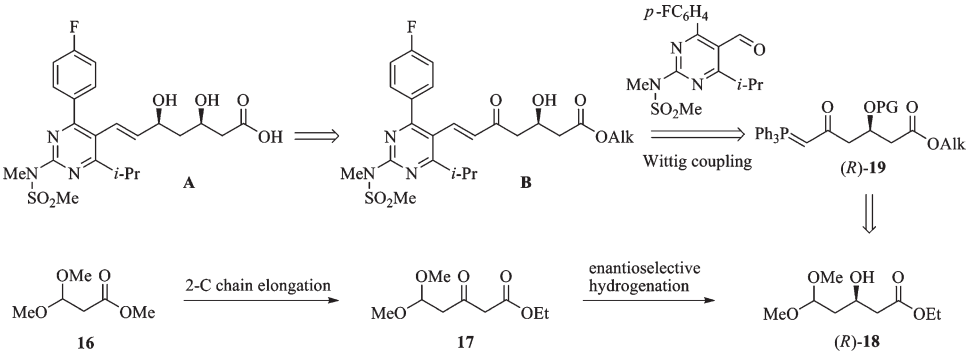
For the asymmetric hydrogenation of functionalized β-keto ester **17** (Scheme 8), a number of Rh(I) and Ru(II) catalysts were tested. Structures of applied chiral ligands are illustrated on Figs. 2 and 3. Selected results are summarized in Table 2.

Rh(I) complexes displayed good activities but only poor enantioselectivities (entries 1–8). Ethyl acetate was found to be the solvent of choice, since reactions in methanol and other solvents ran significantly more slowly.

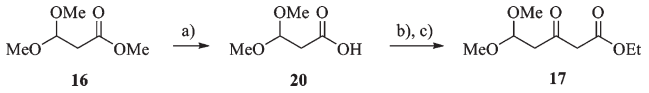
In strong contrast, hydrogenations catalyzed by commercial Ru[(*R*)-BINAP]Cl_2 proceeded smoothly at room temperature and confirmed the previously reported results with related bromide based catalyst.[42] A route to the required chiral methyl 3-hydroxy-5,5-dimethoxypentanoate (**18**) had been already reported by Genêt et al.[42] who hydrogenated the corresponding β-keto ester **17** in the presence of Ru(BINAP)Br_2 (2 mol % catalyst, room temperature, 1 atm H_2 pressure) and obtained **18** in 86% yield and with enantioselectivity >95% *ee*. According to our recently published results,[39] the hydrogenation of β-keto ester **17** proceed in MeOH with an initial H_2-pressure of 50 bar to give β-hydroxy ester (*R*)-**18** with an enantiose-



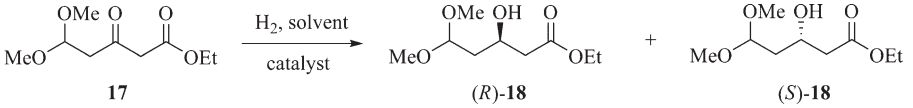
Scheme 5. Synthesis of atorvastatin by the lactol pathway [(a) *t*-$BuPh_2SiCl$, imidazole, DMF, 10°C, (94%); (b) DIBALH, Et_2O, −78°C, (77%); (c) $HC(OMe)_3$, MeOH, cat. *p*-TsOH×Py, 70°C, (64%); (d) *p*-$ClC_6H_4SO_2Cl$, Py, RT, (96%); (e) NaCN, DMSO, RT, (79%); (f) H_2, Ra−Ni, NH_3, MeOH, RT, (>99%); g) THF/toluene, reflux, 30h, (71%).]



Scheme 6. Retrosynthetic pathway to the enantiopure side chain of statins.



Scheme 7. Synthesis of the prochiral β-keto ester **17** [(a) 2N NaOH, RT, and then 2N $NaHSO_4$; (b) CDI (*N,N'*-carbonyl-diimidazole), THF, RT; (c) $(EtO_2CCH_2CO_2)_2Mg$, THF, RT, 12 h, (91%).]



Scheme 8. Enantioselective hydrogenation of functionalized β-keto ester **17.**

lectivity of 98.7% (entry 11). The reaction was complete within 3 h at a ratio of S/C = 500 (entry 11) and within 10 h at a ratio of S/C = 1000 (entry 12). An increase in the temperature to 70°C made it possible to complete the reaction in 1h with a S/C ratio as high as 10,000 (entry 16), thus achieving a turnover frequency (TOF) of 10,000 h^{-1}. Turnover numbers (TONs) of up to 20,000 could be reached at this temperature, and the reaction was complete within 8 h (entry 17). Enantioselectivities at increased temperatures were slightly lower, but still above 95% in all trials. After hydrogenation of **17** at 100°C and 100 bar of initial H_2-pressure in the presence of Ru[(*R*)-BINAP]Cl_2 (dimer) and a substrate/catalyst ratio = 20,000,

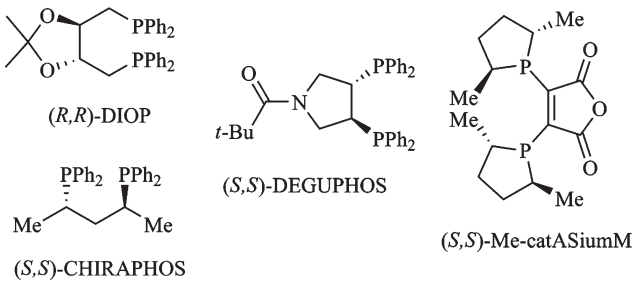
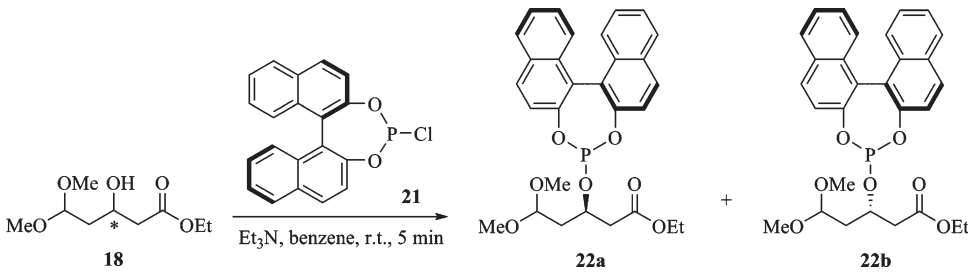


Fig. 3. Chiral diphosphine ligands used for the Rh(I)- and Ru(II)-catalyzed enantioselective hydrogenation of β-keto ester **17** [for structures of other chiral diphosphines, like (*R,S*)-JOSIPHOS, (*S,S*)-Me-DUPHOS, and (*R*)-BINAP, see Figure 2].

TABLE 2. Enantioselective hydrogenation of β-keto ester 17 using chiral Rh(I) and Ru(II) catalysts[39] at 50 bar of initial H_2-pressure (if not otherwise noted)

Entry	Precatalyst	Solvent	S/C	T (°C)	Time (h)	Conversion (%)	*ee* (%)
1	{Rh[(*R,S*)-JOSIPHOS](COD)}BF_4	AcOEt	500	r. t.	2	> 99	15.2 (*R*)
2	{Rh[(*R,S*)-JOSIPHOS](COD)}BF_4	AcOEt	1000	r. t.	20	88	n.d.
3	{Rh[(*R,R*)-DIOP](COD)}BF_4	AcOEt	500	r. t.	4	> 99	7.6 (*S*)
4	{Rh[(*R*)-BINAP](COD)}BF_4	AcOEt	500	r. t.	20	> 99	58.6 (*S*)
5	{Rh[(*S,S*)-CHIRAPHOS](COD)}BF_4	AcOEt	500	r. t.	20	> 99	29.4 (*S*)
6	{Rh[(*S,S*)-DEGUPHOS](COD)}BF_4	AcOEt	500	r. t.	18	< 5	n.d.
7	{Rh[(*S,S*)-Me-DUPHOS](COD)}BF_4	AcOEt	200	45	6	78	n.d.
8	{Rh[(*S,S*)-Me-catASiumM](COD)}BF_4	AcOEt	500	r. t.	10	> 99	6.4 (*S*)
9	Ru[(*R*)-BINAP]Cl_2 (dimer)	CH_2Cl_2	200	r. t.	20	46	n. d.
10	Ru[(*R*)-BINAP]Cl_2 (dimer)	EtOH	500	r. t.	20	68	n. d.
11	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	500	r. t.	3	> 99	98.7 (*R*)
12	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	1000	r. t.	10	> 99	98.7 (*R*)
13	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	2000	r. t.	24	35	n.d.
14	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	2000	50	1	> 99	97.8 (*R*)
15	Ru[(*R*)-BINAP]Cl_2 (dimer; 10 bar)	MeOH	2000	50	4	> 99	98.4 (*R*)
16	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	10,000	70	1	> 99	97.0 (*R*)
17	Ru[(*R*)-BINAP]Cl_2 (dimer)	MeOH	20,000	70	8	> 99	95.8 (*R*)
18	Ru[(*R*)-BINAP]Cl_2 (dimer; 100 bar)	MeOH	20,000	100	0.3	73	90.0 (*R*)
19	Ru[(*R*)-Tol-BINAP]Cl_2 (dimer)	MeOH	500	r. t.	3	> 99	98.2 (*R*)



Scheme 9. Determination of the enantiomeric excess of alcohol **18** with the assistance of enantiopure phosphite (*R*)-**21.**

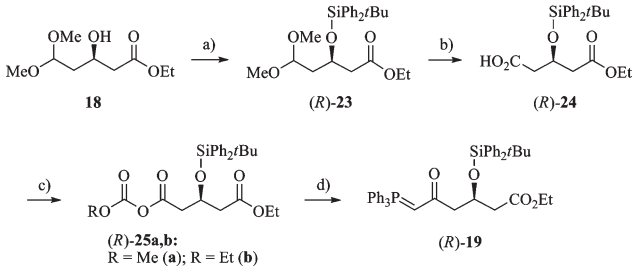
incomplete conversion and diminished enantioselectivity (90%) was noted (entry 18).

Methanol was found to be the solvent of choice, since the reaction rates dropped dramatically when the reaction was performed in CH_2Cl_2 (entry 9) or ethanol (entry 10).

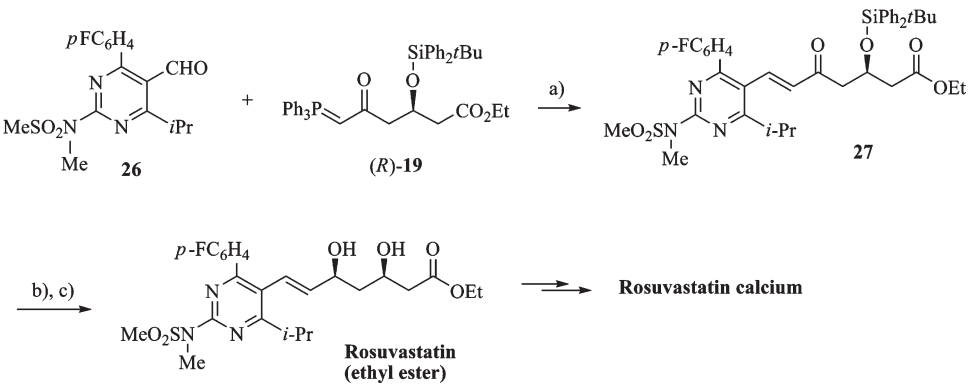
In contrast, at low hydrogen pressure (10 bar), β-keto ester **17** could be successfully reduced without any loss of enantioselectivity, but the reaction was significantly slower than under a pressure of 50 bar (compare entries 14 and 15). The use of the related Ru((*R*)-Tol-BINAP)Cl_2 complex improved neither the activity nor the stereoselectivity of the hydrogenation (entry 19). The results were identical to those obtained with Ru(BINAP)Cl_2.

Enantiomeric compositions for β-hydroxy ester **18** were determined with help of the chlorophosphite chiral derivatizing agent (*R*)-**21** (Scheme 9),[39] prepared from PCl_3 and (*R*)-BINOL. Chlorophosphite (*R*)-**21** reacted quantitatively and rapidly with alcohol **18** to give phosphites **22a** and **22b**. The ^{31}P NMR spectrum of the two diastereomeric compounds **22** is characterized by signals separated to the base line (δ_P 151.4 and 154.6 ppm), so it is possible to determine the enantiomeric composition of the catalytic hydrogenation product precisely.

Alcohol (*R*)-**18** was transformed into ylide (*R*)-**19** by the route depicted in Scheme 10. Protection of the HO-group was performed by treatment with *t*-BuPh_2SiCl in DMF in the presence of imidazole as a base. Selective cleavage of the acetal-moiety in (*R*)-**23** and oxidation was performed in one-pot by treatment with Jones' oxidation reagent at 0°C, proceeding without racemization at the C-3 carbon atom.



Scheme 10. Multistep synthesis of ylide (*R*)-**19** [(a) *t*BuPh_2SiCl, imidazole, DMF, 0°C to RT, overnight, (90%); (b) Jones' oxidation: CrO_3, H_2SO_4, acetone/water, 0°C to RT (68%); (c) AlkOC(O)Cl, NEt_3, toluene, 0°C to RT, 1 h; (d) Ph_3P^+–CH_3Br^-, *n*BuLi, THF, –78°C to 0°C, then 15, –78°C to 0°C, overnight, (45%).]



Scheme 11. Synthesis of rosuvastatin ethyl ester [(a) MeCN, reflux, 14 h, (70%); (b) HF (aq.), MeCN; (c) Et_2BOMe, $NaBH_4$, THF/MeOH, –78°C, (85%, over two steps).]

Mixed anhydrides (*R*)-**25a,b** [R = Me (a) or R = Et (b)], prepared by treatment of (*R*)-**24** with 1.5 equiv. of corresponding methyl or ethyl chloroformate in toluene in the presence of Et_3N, were submitted for the synthesis of ylide (*R*)-**19** without additional purification. Treatment of (*R*)-**25a** or (*R*)-**25b** with methyltriphenylphosphonium bromide and *n*BuLi furnished the targeted Wittig reagent (*R*)-**19** in 45% yield.

Wittig coupling of aldehyde **26** and ylide (*R*)-**19** was performed under reflux in CH_3CN over 14 h and gave the rosuvastatin precursor **27** in a yield of 70% (Scheme 11).[41] Removal of the *t*BuPh$_2$Si protective group by treatment with aqueous HF in CH_3CN and final exclusive diastereoselective reduction of the keto group with $Et_2B(OMe)$ and $NaBH_4$ in THF/MeOH at –78°C, afforded rosuvastatin ethyl ester in 85% yield.

We have presented here two new approaches for the total syntheses of atorvastatin and rosuvastatin, based on highly stereoselective hydrogenations of intermediate β-keto esters. Optimized syntheses of substrates and subsequent multistep transformations of the chiral hydrogenation products in the desired drug constituents show clearly the great value of stereoselective homogeneous catalysis for the establishment of new and patent-free routes to drugs.

LITERATURE CITED

1. Gaw A, Packard CJ, Shepherd J. Statins: the HMG CoA reductase inhibitors in perspective. London: Taylor & Francis; 2004. 262 p.
2. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423–1429.
3. Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. Am J Cardiol 2003;91 (5A Suppl S):11C–17C.
4. Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res 1992;33:1569–1582.
5. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–2827.
6. Cummings SR, Bauer DC. Do statins prevent both cardiovascular disease and fracture? JAMA 2000;283:3255–3257.
7. Zhou Z, Rahme E, Pilote L, Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention, Am Heart J 2006;151:273–281.
8. van der Harst P, Voors AA, van Gilst WH, Böhm M, van Veldhuisen DJ. Statins in the treatment of chronic heart failure: a systematic review. PLoS Med 2006;3:e333–e333; literature cited therein.
9. Kaye JA, Meier CR, Walker AM, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. Brit J Cancer 2002;86:1436–1439.
10. Ray SK, Rege NN. Atorvastatin: in the management of hyperlipidaemia. Drug Rev 2000;46:242–243.
11. Wierzbicki AS, Mikhailidis DP, Wray R, Schachter M, Cramb R, Simpson WG, Byrne CB. Statin-fibrate combination therapy for hyperlipidaemia: a review. Curr Med Res Opin 2003;19:155–168.
12. Rodenburg J, Vissers MN, Wiegman A, van Trotsenburg ASP, van der Graaf A, de Groot E, Wijburg FA, Kastelein JJP, Hutten BA. Statin treatment in children with familial hypercholesterolemia. Circulation 2007;116:664–668.
13. Li JJ, Johnson DS, Sliskovic DR, Roth BD, Atorvastatin calcium (*Lipitor*®). In: Contemporary drug synthesis. New York: Wiley-Interscience; 2004. p 113–124.
14. Maggon K, Best-selling human medicines 2002–2004. Drug Discov Today 2005;10:739–742.
15. Croom KF, Plosker GL. Atorvastatin: a review of its use in the primary prevention of cardiovascular events in patients with type 2 diabetes mellitus. Drugs 2005;65:137–152.
16. Law MR, Rudnicka AR, Statin safety a systematic review. Am J Cardiol 2006;97 (suppl 8A):52C–60C.
17. Brower PL, Butler DE, Deering CF, Le TV, Millar A, Nanninga TN, Roth BD. The synthesis of (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a key intermediate for the preparation of CI-981, a highly potent, tissue selective inhibitor of HMG-CoA reductase. Tetrahedron Lett 1992;33:2279–2282.
18. Baumann KL, Butler DE, Deering CF, Mennen KE, Millar A, Nanninga TN, Palmer CW, Roth BD. The convergent synthesis of CI-981, an optically active, highly potent, tissue selective inhibitor of HMG-CoA reductase. Tetrahedron Lett 1992;33:2283–2284.
19. Rádl S, Stach J, Hajicek J. An improved synthesis of 1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a key intermediate for atorvastatin synthesis. Tetrahedron Lett 2002;43:2087–2090.
20. George S, Sudalai A. An efficient organocatalytic route to the atorvastatin side-chain. Tetrahedron Lett 2007;48:8544–8546.
21. Pandey PS, Rao TS. An efficient synthesis of *N*3,4-diphenyl-5-(4-fluorophenyl)-2-isopropyl-1H-3-pyrrolecarboxamide, a key intermediate for atorvastatin synthesis. Bioorg Med Chem Lett 2004;14: 129–131.
22. Culhane NS, Lettieri SL, Skae JR. Rosuvastatin for the treatment of hypercholesterolemia. Pharmacotherapy 2005;25:990–1000; literature cited therein.

23. Hirsch M, O'Donnell J, Olsson A. Rosuvastatin is cost-effective compared with atorvastatin in reaching cholesterol goals. Int J Cardiol 2005;104:251–256.
24. Hoey S. The therapeutic benefits of rosuvastatin. Brit J Card Nurs 2008;3:482–484.
25. Quirk J, Thornton M, Kirkpatrick P. Rosuvastatin calcium. Nature Rev Drug Discov 2003;2:769–770; literature cited therein.
26. Pfefferkorn JA. Second-generation HMG-CoA reductase inhibitors. Synthesis of rosuvastatin. In: Johnson DS, Li JJ, editors. The art of drug synthesis. New Jersey: John Wiley; 2007. p 174–176; literature cited therein.
27. Casar Z, Mesar T. Processes for the preparation of statins, particularly rosuvastatin, and intermediates for the preparation thereof. EP1978020 A1, 2008.
28. Balanov A, Shenkar N, Niddam-Hildesheim V. Preparation of rosuvastatin. US Pat Appl, US2007167625 A1, 2007.
29. Radl S, Stach J, Klvana R, Jirman J. A method for the production of the hemi-calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl)amino]pyrimidine-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid. PCT Int Appl, WO 2007000121 A1, 2007.
30. Patel DJ, Kumar R, Dwivedi SPD. Process for preparing rosuvastatin calcium. WO2007099561 A1, 2007.
31. Available at: http://www.forbes.com.
32. Tararov VI, Andrushko N, Andrushko V, König G, Spannenberg A, Börner A. Synthesis of the chiral side chain of statins—lactone versus lactol pathway. Eur J Org Chem 2006:5543–5550.
33. Tararov VI, König G, Börner A. Synthesis and highly stereoselective hydrogenation of the statin precursor ethyl (5S)-5,6-isopropylidenedioxy-3-oxohexanoate. Adv Synth Catal 2006b;348:2633–2644.
34. Saito S, Hasegawa T, Inaba M, Nishida R, Fujii T, Nomizu S, Moriwake T. Combination of borane-dimethyl sulfide complex with catalytic sodium tetrahydroborate as a selective reducing agent for á-hydroxy esters. Versatile chiral building block from (S)-(−)-malic acid. Chem Lett 1984;13:1389–1392.
35. Saito S, Ishikawa T, Kuroda A, Koga K, Moriwake T. A revised mechanism for chemoselective reduction of esters with borane-dimethyl sulfide complex and catalytic sodium tetrahydroborate directed by adjacent hydroxyl group. Tetrahedron 1992;48:4067–4086.
36. Brooks DW, Lu LDL, Masamune S, C-Acylation under Virtually Neutral Conditions. Angew Chem Int Ed Engl 1979;18:72–74.
37. Kitamura M, Tokunaga M, Ohkuma M, Noyori R. Convenient preparation of binap-ruthenium(II) complexes catalyzing asymmetric hydrogenation of functionalized ketones. Tetrahedron Lett 1991;32:4163–4166.
38. Tararov V, Korostylev A, Börner A, Bobál P, Frantisek J, Stohandl J, Denike K, Jeker N. Process for preparing C5 products and their use for atorvastatin synthesis. EP1705175 A1, 2006.
39. Korostylev A, Andrushko V, Andrushko N, Tararov VI, König G, Börner A. Highly enantioselective hydrogenation of ethyl 5,5-dimethoxy-3-oxopentanoate and its application for the synthesis of a statin precursor. Eur J Org Chem 2008:840–846.
40. Andrushko V, Andrushko N, König G, Börner A. Highly enantioselective catalytic hydrogenation of a 5-amino-3,5-dioxopentanoic ester. Tetrahedron Lett 2008;49:4836–4839.
41. Andrushko N, Andrushko V, König G, Spannenberg A, Börner A. A new approach to the total synthesis of rosuvastatin. Eur J Org Chem 2008:847–853.
42. Poupardin O, Greck C, Genêt J-P. Rapid asymmetric synthesis of highly functionalized C5 chiral synthons. Practical preparation of trans-3-hydroxy-D-proline. Synlett 1998;11:1279–1281.