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Highly Enantioselective Hydrogenation of Ethyl 5,5-Dimethoxy-3-oxopentanoate and its Application for the Synthesis of a Statin Precursor[‡]

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The highly enantioselective hydrogenation of ethyl 5,5-dimethoxy-3-oxopentanoate (**3**) to ethyl 3-hydroxy-5,5-dimethoxypentanoate (**4**) – a key intermediate in the synthesis of pharmacologically important statin drugs – has been investigated. The stereochemistry of the catalytic hydrogenation of the β-keto ester in the presence of a number of homogeneous chiral Rh^{I} and Ru^{II} complexes with phosphane ligands has been studied. The highest enantioselectivity for the homogeneous hydrogenation of **3** (up to 98.7 % *ee*) was achieved through an optimized version of Genêt's procedure with a Ru[(*R*)-BINAP]Cl_2 pre-catalyst (substrate/catalyst ratio up to 20 000:1, 50 bar H_2, 50 °C, in MeOH). The transformation of alcohol *R*-(**4**) into ylide *R*-(**6**) as an important precursor of the chiral side chain of rosuvastatin is also illustrated.

Introduction

Asymmetric reactions catalyzed by transition metals represent one of the most powerful tools for the synthesis of enantiomerically pure compounds.[1] In particular, enantioselective hydrogenation can be conducted on a large scale by use of hydrogen as a cheap reducing agent.[2] Various β-keto esters have thus been hydrogenated with excellent enantioselectivities in the presence of Ru-diphosphane catalysts to afford β-hydroxy esters.[3] These compounds can serve as valuable building blocks for the synthesis of natural and biologically active compounds.[4] Starting with the pioneering experiments with a Ru catalyst based on the atropisomeric ligand BINAP performed by Noyori et al.,[5] a wide variety of other chiral phosphorus ligands have been developed, including other biaryl diphosphanes,[6] bisphospholanes,[7] *P*-chiral ligands,[8] monodentate phosphanes,[9] planar chiral diphosphanes derived from ferrocene,[10] and paracyclophane.[11] In contrast, the array of substrates investigated is rather limited, usually restricted to simple β-alkyl or aryl residues. Only a few investigations have been dedicated to the use of substrates bearing functional groups – such as a benzyloxy group,[4a,4b,5a] halogen atoms,[6c,9,12] or double bonds[12c] – in the vicinity of the keto group.

Recently we reported on the preparation and highly stereoselective hydrogenation of ethyl (5*S*)-5,6-isopropylidenedioxy-3-oxohexanoate (**1**)[13] as a key intermediate on the pathway to the chiral side chain of pharmaceutically important atorvastatin (Scheme 1).[14,15]

Systematic investigation of the diastereoselective hydrogenation of β-keto ester **1** in the presence of a number of homogeneous achiral and chiral Rh^{I} and Ru^{II} complexes with phosphane ligands showed that Ru[(*R*)-Tol-BINAP]-Cl_2, neutralized with one equivalent of AcONa, afforded the most efficient catalytic system for the production of optically pure *syn*-(5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)-hexanoate (*syn*-**2**). At a preparative substrate/catalyst ratio of 1000:1, diastereoselectivities of up to >99% were achieved.[13] Chiral building block *syn*-**3** was successfully applied for the synthesis of atorvastatin by the lactol pathway.[14]

From the retrosynthetic analysis shown in Scheme 2 it follows that the chiral side chain of statins of general structure **A** (R is a hydrophobic heterocyclic or a carbocyclic moiety) can also be created by diastereoselective and chemoselective reduction of the carbonyl group in structure **B**. Protected hydroxy ylides **6** were postulated as possible building blocks for preparation of **B**, as long as the Wittig coupling reaction with the corresponding aldehyde could be performed and the HO-protecting groups subsequently cleaved.[16] This approach would give access to the newest statin, rosuvastatin,[17] also known as *super-statin*.[18]

Our strategy for the synthesis of the chiral side chain of statins is also shown in Scheme 2. It includes two-carbon

[‡] Part III of a series of manuscripts dedicated to the synthesis of statins. Part II: Ref.[14]

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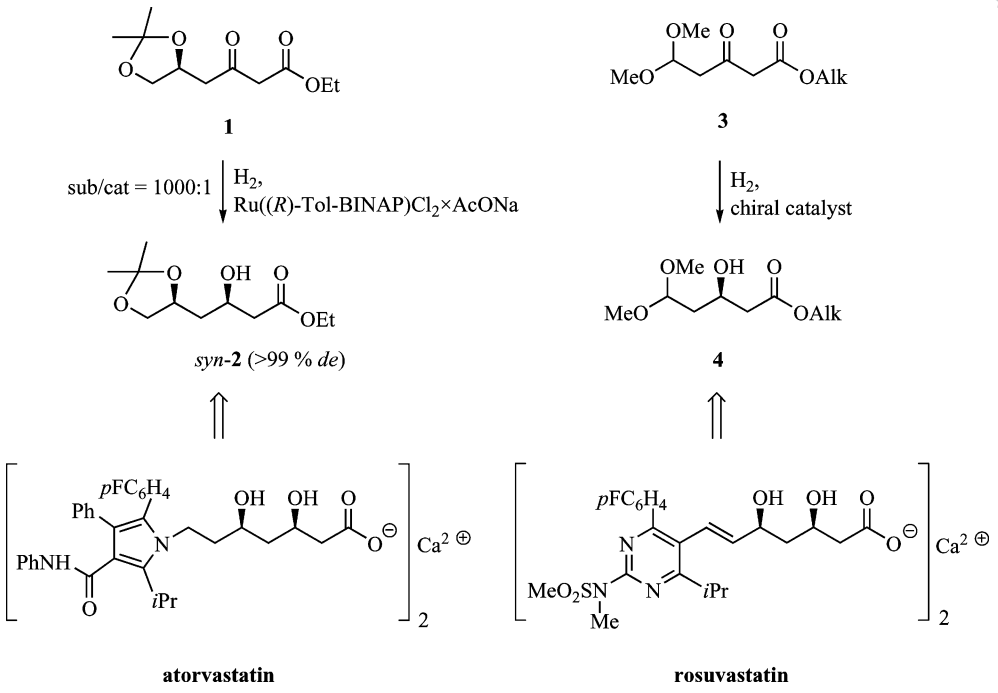
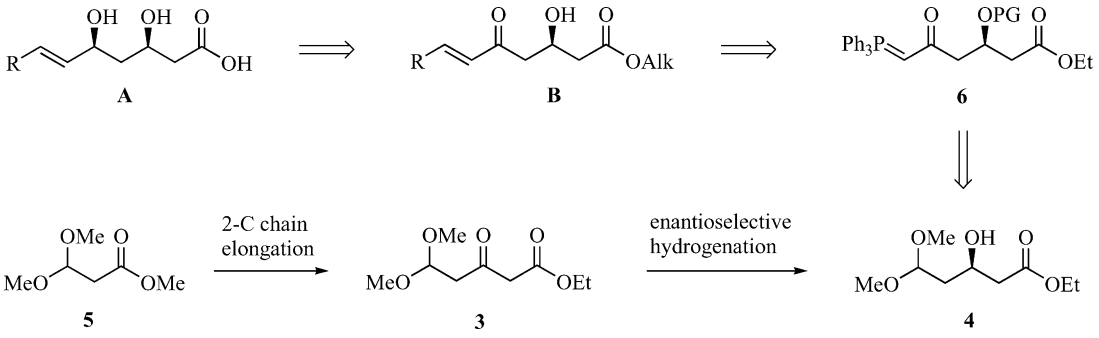


Scheme 1. Alternative pathways for the total synthesis of statins such as atorvastatin and rosuvastatin with stereoselective hydrogenations as key steps.



Scheme 2. Retrosynthetic pathway to the enantiopure side chain of statins [Alk = Et as follows below, or other alkyl group could also be used; *tert*-butyldiphenylsilyl (TBDPS) was considered as protecting group (PG)].

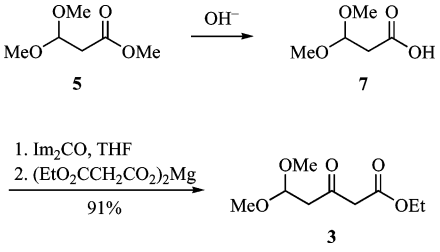
elongation of methyl 3,3-dimethoxypropanoate (**5**) to afford β-keto esters **3**, followed by enantioselective hydrogenation of the prochiral keto group to furnish β-hydroxy esters **4**. Protection of the HO functionality and transformation of the $(MeO)_2CH$ moiety affords the desired Wittig reagent **6**.

A route to the required chiral methyl 3-hydroxy-5,5-dimethoxypentanoate (**4**) had been already reported by Genêt et al., who hydrogenated the corresponding β-keto ester **3** in the presence of $Ru(BINAP)Br_2$ (2 mol-% catalyst, room temperature, 1 atm H_2 pressure) and obtained **4** in 86% yield and with >95% *ee*.[19]

Here we report on our efforts towards the highly enantioselective preparation of β-hydroxy ester **4** and its subsequent transformation into the Wittig reagent **6**. Both chiral compounds are not only useful for the synthesis of enantiopure statins, but can also be applied as versatile chiral building blocks for the synthesis of other β-substituted carboxylic acid derivatives.[20]

Results and Discussion

β-Keto ester **3**, serving as a prochiral substrate for the subsequent enantioselective hydrogenation, was assembled by a two-carbon chain elongation of 3,3-dimethoxypropionic acid (**7**, Scheme 3). The latter compound was easily available from ester **5** by hydrolysis. A modified two-step



Scheme 3. Synthesis of the prochiral substrate **3**.

Masamune procedure,[13,21] which first involved the activation of acid **7** with *N*,*N*′-carbonyldiimidazole, followed by subsequent treatment with $Mg(O_2CCH_2CO_2Et)_2$ prepared in situ, afforded ethyl 5,5-dimethoxy-3-oxopentanoate (**3**) in 91% yield.

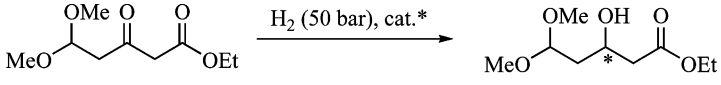
Results of the catalytic enantioselective hydrogenation of **3** are summarized in Table 1. Hydrogenation catalyzed by commercial Ru[(*R*)-BINAP]Cl_2 proceeded smoothly at room temp. and confirmed the results of Genêt et al. with the related bromide-based catalyst.[19] In MeOH with an initial H_2 pressure of 50 bar, β-hydroxy ester **4** was obtained with an enantioselectivity of 98.7% *ee* (Entry 3). The reaction was complete within 3 hours at a ratio of S/C = 500 (Entry 3) and within 10 hours at a ratio of S/C = 1000 (Entry 4). An increase in the temperature to 70 °C made it possible to complete the reaction in 1 h with a S/C ratio as high as 10000 (Entry 8), thus achieving a turnover frequency (TOF) of 10000 h^{-1}. Turnover numbers (TONs) of up to 20000 could be reached at this temperature, and the reaction was complete within 8 h (Entry 9). Enantioselectivities at increased temperatures were slightly lower, but still above 95% *ee* in all trials. 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 1) or ethanol (Entry 2).

As pointed out by Brown, the presence of additional functional groups may seriously affect the enantioselectivity of hydrogenation, due to competitive ligation to the catalytically active metal.[23] This rule was confirmed by us in the hydrogenation of a related β-keto ester bearing neighboring hydroxy groups.[13] However, this effect could be diminished by protection of these hydroxy groups as an acetonide. A similar observation was made by Jendralla et al. in the hydrogenation of a 5-benzyloxy-3-oxopentanoate, where no influence of the protected HO group on the course of the hydrogenation was noted.[24] Also in the case of substrate **3** considered here, the presence of the acetal group did not prevent the achievement of excellent *ee* values. Moreover, Noyori et al. found that the highest *ee* values and shortest reaction times (5 min) with related substrates were obtained when the hydrogenations were run at 100 °C and 100 bar H_2 initial hydrogen pressure.[25] When the hydrogenation of **3** was performed under these conditions, incomplete conversion and diminished enantioselectivity (90% *ee*) was obtained (Entry 10). In contrast, at low hydrogen pressure (10 bar), β-keto ester **3** could be successfully reduced without any loss of enantioselectivity, but the reaction was significantly slower than under a pressure of 50 bar (compare Entries 6 and 7).

The use of the related Ru((*R*)-Tol-BINAP)Cl_2 complex improved neither the activity nor the stereoselectivity of the hydrogenation (Entry 12). The results were identical to those obtained with Ru(BINAP)Cl_2.

Homogeneous ruthenium complexes are not the only metal catalysts able to mediate the hydrogenation of ketones to alcohols. Togni et al. reported the highly enantioselective reduction of β-keto esters (up to 97% *ee*) catalyzed by a rhodium complex based on Josiphos as a chiral ligand under mild conditions (room temp., 20 bar H_2, 15 h).[26] Therefore, we also screened a set of analogous rhodium complexes with several commercially available chiral diphosphanes. Ethyl acetate was found to be the solvent of

Table 1. Enantioselective hydrogenation of functionalized β-keto ester **3**.[22]

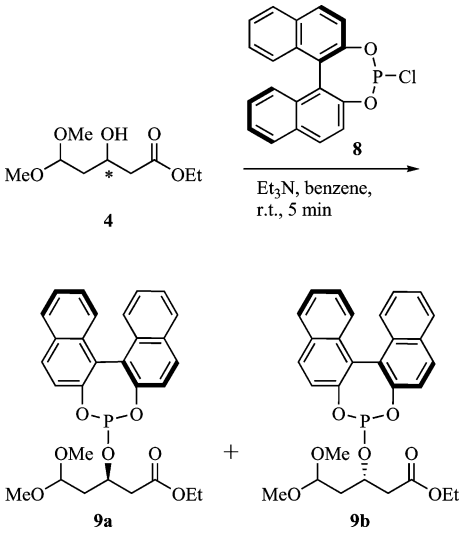


3 **4**

Entry	Catalyst	Solvent	S/C ratio	*T* [°C]	Time [h]	% Conversion	% *ee*
1	Ru((*R*)-BINAP)Cl_2	CH_2Cl_2	200	room temp.	20	46	n.d.
2	Ru((*R*)-BINAP)Cl_2	EtOH	500	room temp.	20	68	n.d.
3	Ru((*R*)-BINAP)Cl_2	MeOH	500	room temp.	3	>99	98.7 (*R*)
4	Ru((*R*)-BINAP)Cl_2	MeOH	1000	room temp.	10	>99	98.7 (*R*)
5	Ru((*R*)-BINAP)Cl_2	MeOH	2000	room temp.	24	35	n.d.
6	Ru((*R*)-BINAP)Cl_2	MeOH	2000	50	1	>99	97.8 (*R*)
7	Ru((*R*)-BINAP)Cl_2 (10 bar)	MeOH	2000	50	4	>99	98.4 (*R*)
8	Ru((*R*)-BINAP)Cl_2	MeOH	10000	70	1	>99	97.0 (*R*)
9	Ru((*R*)-BINAP)Cl_2	MeOH	20000	70	8	>99	95.8 (*R*)
10	Ru((*R*)-BINAP)Cl_2 (100 bar)	MeOH	20000	100	0.3	73	90.0 (*R*)
11	Ru((*R*)-Tol-BINAP)Cl_2	CH_2Cl_2	200	45	6	82	n.d.
12	Ru((*R*)-Tol-BINAP)Cl_2	MeOH	500	room temp.	3	>99	98.2 (*R*)
13	[Rh((*R*,*S*)-Josiphos)COD]BF_4	AcOEt	500	room temp.	2	>99	15.2 (*R*)
14	[Rh((*R*,*S*)-Josiphos)COD]BF_4	AcOEt	1000	room temp.	20	88	n.d.
15	[Rh((*R*,*R*)-DIOP)COD]BF_4	AcOEt	500	room temp.	4	>99	7.6 (*S*)
16	[Rh((*R*,*R*)-DIOP)COD]BF_4	AcOEt	1000	room temp.	20	64	n.d.
17	[Rh((*R*)-BINAP)COD]BF_4	AcOEt	500	room temp.	20	>99	58.6 (*S*)
18	[Rh((*S*,*S*)-Chiraphos)COD]BF_4	AcOEt	500	room temp.	20	>99	29.4 (*S*)
19	[Rh((*S*,*S*)-Deguphos)COD]BF_4	AcOEt	500	room temp.	18	<5	n.d.
20	[Rh((*S*,*S*)-Me-DuPhos)COD]BF_4	AcOEt	200	45	6	78	n.d.
21	[Rh((*R*,*R*)-Me-catASiumM)COD]BF_4	AcOEt	500	room temp.	10	>99	6.4 (*S*)

choice, since reactions in methanol and other solvents ran significantly more slowly. Even in ethyl acetate, however, Rh/Josiphos gave much lower activity than Ru/BINAP and only a disappointing 15% *ee* (Entries 13, 14). Other Rh catalysts provided low to moderate enantioselectivities and were less active than the Rh/Josiphos complex (Entries 15–21).

Interestingly, several trials of the analysis of the alcohol **4** by gas chromatography on various chiral columns gave no satisfactory resolution of enantiomers. As a convenient alternative, enantiomeric compositions of the product were determined with the help of the chiral derivatizing agent **8** (Scheme 4).



Scheme 4. Determination of the enantiomeric excess of alcohol **4** with the assistance of enantiopure phosphite **8**.

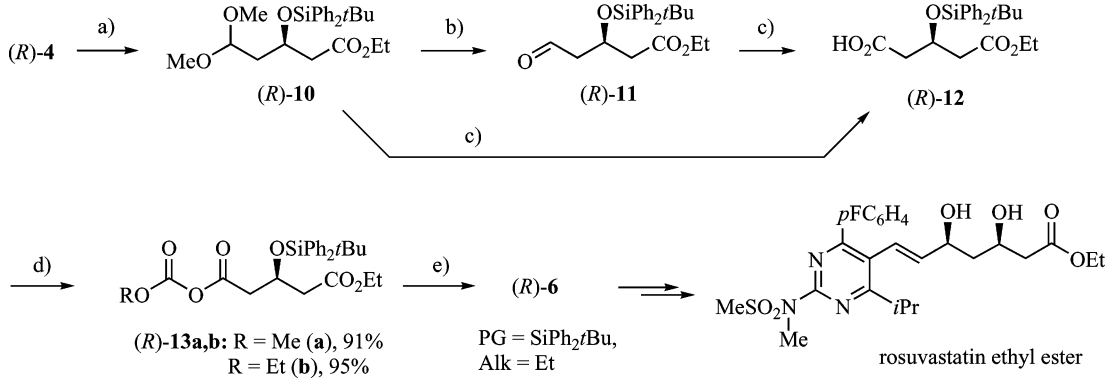
This chlorophosphite is readily available from (*R*)-BINOL in one step[27] and reacted quantitatively and rapidly with the alcohol **4** to give phosphites **9a** and **9b**. The ^{31}P NMR spectrum of the two diastereomeric compounds **9** is characterized by signals separated to the base line (δ_P 151.4 and 154.6 ppm), so it is possible to determine the enantiomeric composition of the catalytic hydrogenation product precisely. According to the well established general trend,[5a,12c] Ru((*R*)-BINAP)Cl_2 produced (*R*)-**4** as the predominant enantiomer.

Alcohol (*R*)-**4** was transformed into ylide (*R*)-**6** by multistep synthesis by the route depicted in Scheme 5. Protection of the HO functionality of alcohol (*R*)-**4** was performed by treatment with *t*BuPh$_2$SiCl in DMF in the presence of imidazole as a base. The silyl ether (*R*)-**10** was obtained in a yield of 90%. Selective cleavage of the acetal moiety in (*R*)-**10** was performed in acetone/H_2O in the presence of a catalytic amount of *p*-toluenesulfonic acid hydrate. After purification, the aldehyde (*R*)-**11** was obtained in 98% yield. Oxidation was performed by treatment with Jones' oxidation reagent at 0 °C, proceeding without racemization at the C-3 carbon atom. It was found that both cleavage of the acetal moiety and oxidation of the aldehyde group could be performed in one-pot fashion under Jones' oxidation conditions in acetone at 0 °C.

Further transformations of (*R*)-3-(*tert*-butyldiphenylsilyloxy)-5-ethoxy-5-oxopentanoic acid ((*R*)-**12**) into ylide (*R*)-**6** were performed by a modified procedure reported by Konoike et al.[16] by preparation of mixed anhydrides (*R*)-**13a** or (*R*)-**13b** (for **13a**: R = Me; for **13b**: R = Et). Treatment of (*R*)-**12** with 1.5 equiv. of methyl or ethyl chloroformate proceeded in toluene in the presence of Et_3N. Compounds (*R*)-**13a** or (*R*)-**13b** were formed in 91–95% yields. Mixed anhydrides were obtained with 95–98% purity and were applied in the next step without additional purification. Treatment of (*R*)-**13a** or (*R*)-**13b** with methyltriphenylphosphonium bromide and *n*BuLi furnished the targeted Wittig reagent (*R*)-**6** in 45% yield.[28] The employment of ylide (*R*)-**6** for the synthesis of rosuvastatin, as well as the synthesis of the requisite heterocyclic part, will be described in a subsequent publication.[29]

Conclusions

The highly enantioselective homogeneous hydrogenation of ethyl 5,5-dimethoxy-3-oxopentanoate (**3**) can be carried out in the presence of Ru((*R*)-BINAP)Cl_2 as pre-catalyst at



Scheme 5. Synthetic pathway to rosuvastatin through the Wittig reaction between ylide (*R*)-**6** and the corresponding aldehyde; a) *t*BuPh$_2$SiCl, imidazole, DMF, 0 °C → room temperature, overnight, 90%; b) *p*TsOH·H_2O, acetone/H_2O (5:1), reflux, 2 h, 98%; c) Jones' oxidation: CrO_3, H_2SO_4, acetone/water, 0 °C → room temperature, 68%; d) AlkOC(O)Cl, NEt_3, toluene, 0 °C → room temperature, 1 h; e) Ph_3P^+–CH_3 Br^-, *n*BuLi, THF, –78 °C → 0 °C, then 15, –78 °C → 0 °C, overnight, 45%.

room temperature according to an optimized methodology by Genêt et al., affording the corresponding β-functionalized β-hydroxy ester (*R*)-**4** in up to 98.7% *ee*. TONs of up to 20000 were achieved. An increase in the temperature to 70 °C made it possible to complete the reaction up to ten times more rapidly, with enantioselectivities slightly lower, but still above 95% *ee*. The resulting chiral ethyl (*R*)-3-hydroxy-5,5-dimethoxypentanoate [(*R*)-**4**] represents a valuable chiral building block for further transformations. For example the conversion of alcohol *R*-(**4**) into ylide *R*-(**6**) as a versatile building block for the synthesis of the chiral side chain of statins has been demonstrated.

Experimental Section

General: MeOH and AcOEt (packed under N_2) for hydrogenation were purchased from Aldrich. CH_2Cl_2 was distilled from CaH_2, THF and Et_2O were distilled from Na·Ph_2CO under Ar, and DMF was dried with 3-Å molecular sieves for 72 h prior to vacuum distillation. Other commercial reagents were used without additional purification. NMR spectra were recorded with a Bruker ARX 400 spectrometer or a Bruker ARX 300 spectrometer. Chemical shifts (δ, in ppm) are given relative to TMS as internal standard for ^{1}H NMR and relative to the residual $CDCl_3$ peak for ^{13}C NMR (δ = 77.16 ppm) and C_6D_6 peak for ^{13}C NMR (δ = 128.06 ppm).[30] Spin–spin coupling constants (*J*) are given in Hz. The optical rotation was measured on a "gyromat-HP" instrument.

Ethyl 5,5-Dimethoxy-3-oxopentanoate (3): Solid *N*,*N*′-carbonyldiimidazole (Im_2CO, 50.02 g, 0.308 mol) was added in portions over 5–10 min to a solution of acid **7** (41.45 g, 0.288 mol) in dry THF (200 mL, gas evolution). The mixture was then stirred at room temp. for 2 h to produce the corresponding imidazolide in situ.

In another flask, a mixture of monoethyl malonate (83.5 g, 0.632 mol) and commercial Mg powder of particle size <0.1 mm (10.24 g, 0.422 mol) in dry THF (300 mL) was stirred under reflux for 4 h to form $Mg(OOCCH_2COOEt)_2$ in situ; this was cooled down to room temp. and added to the former solution. The residual Mg powder was rinsed with THF (100 mL), and the washing solution was added to the reaction mixture. The mixture was stirred overnight at room temp. and concentrated in vacuo. The residue was dissolved in ethyl acetate (300 mL) and acidified with $NaHSO_4$ (620 mL, 2 M) with vigorous stirring. The organic layer was separated and washed successively with water, saturated $NaHCO_3$ (3 × 200 mL), and brine. It was subsequently dried with Na_2SO_4 and the solvents were removed. Vacuum distillation of the residue (b.p. 86–92 °C/0.06 mbar) afforded keto ester **3** (53.62 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.86 [d, *J* = 5.6 Hz, 2 H, $CH_2CH(OMe)_2$], 3.37 [s, 6 H, $CH(OCH_3)_2$], 3.49 (s, 2 H, CH_2CO_2Et), 4.20 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.78 [t, *J* = 5.6 Hz, 1 H, $CH(OCH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.34 (OCH_2CH_3), 46.88 [$CH_2CH(OMe)_2$], 50.40 (CH_2CO_2Et), 54.21 [$CH(OCH_3)_2$], 61.61 (OCH_2Me), 101.59 [$CH(OMe)_2$], 167.21 (CO_2Et), 200.08 [$C(O)CH_2CO_2Et$] ppm.

Catalytic Hydrogenation of 3. General Procedure: Keto ester **3** (2.04 g, 10 mmol) and Ru((*R*)-BINAP)Cl_2 (0.004 g, 0.005 mmol) were placed in an autoclave under argon, followed by addition of abs. MeOH (8 mL). The mixture was pressurized with hydrogen to 50 bar and stirred at 50 °C until the H_2 consumption stopped (1 h). Evaporation of the solvent in vacuo gave hydroxy ester **4** as yellowish oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.75–1.83 [m, 2 H, $CH_2CH(OMe)_2$], 2.60 (dd, *J* = 15.96 and 4.35 Hz, 1 H, $CH^aH^bCO_2Et$), 2.74 (dd, *J* = 15.96 and 8.26 Hz, 1 H, $CH^aH^bCO_2Et$), 3.42 [s, 3 H, $CH(OCH_3)^a(OCH_3)^b$], 3.45 [s, 3 H, $CH(OCH_3)^a(OCH_3)^b$], 3.76 (br s, 1 H, OH), 4.25 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.59–4.72 (m, 1 H, CHOH), 4.92 [t, *J* = 5.63 Hz, 1 H, $CH(OMe)_2$] ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 14.15 (OCH_2CH_3), 39.62 (CH_2CO_2Et), 41.91 [$CH_2CH(OMe)_2$], 52.88 [$CH(OCH_3)^a(OCH_3)^b$], 52.92 [$CH(OCH_3)^a(OCH_3)^b$], 60.35 (CHOH), 65.27 (OCH_2Me), 103.13 [$CH(OMe)_2$], 172.23 (CO_2Et) ppm.

Determination of the Enantiomeric Composition of Compound 4. General Procedure: A solution of (*R*)-**8**[27] (10%, 0.5 mL, 0.14 mmol) in dry benzene, the alcohol **4** (21 mg, 0.10 mmol), abs. Et_3N (20 mg, 0.19 mmol), and dry [D_6]benzene (0.1 mL) were mixed together in a vial. The resultant pale solution was immediately transferred into an NMR tube under argon, and the ^{31}P NMR spectrum was then recorded. Two singlet peaks at δ_P = 151.4 and 154.6 ppm and separated down to the baseline correspond to compounds **9a** and **9b**, respectively. The enantiomeric excess of the alcohol **4** was calculated from the integral intensities of the peaks.

Ethyl (*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5,5-dimethoxypentanoate (10): *tert*-Butyldiphenylsilyl chloride (4.15 g, 15.09 mmol) was added dropwise over 30 min at 0 °C to a solution of ethyl (*R*)-3-hydroxy-5,5-dimethoxypentanoate [(*R*)-**4**, 2.83 g, 13.72 mmol] and imidazole (2.05 g, 30.18 mmol) in dry DMF (15 mL). The reaction mixture was stirred for 2 h at room temp. and then diluted with H_2O (100 mL). The crude product was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed successively with water, saturated $NaHCO_3$ (2 × 100 mL), and brine and dried with Na_2SO_4. EtOAc was then evaporated. Column chromatography purification (silica gel, eluent *n*-hexane/EtOAc, 5:1) afforded (*R*)-**10** (5.49 g, 90% yield). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.9 (t, *J* = 7.17 Hz, 3 H, OCH_2CH_3), 1.17 [s, 9 H, $C(CH_3)_3$], 2.01–2.06 [m, 2 H, $CH_2CH(OMe)_2$], 2.57 (d, *J* = 1.16 Hz, 1 H, $CH^aH^bCO_2Et$), 2.59 (d, *J* = 1.26 Hz, 1 H, $CH^aH^bCO_2Et$), 2.95 [s, 3 H, $CH(OCH_3)^a(OCH_3)^b$], 2.99 [s, 3 H, $CH(OCH_3)^a(OCH_3)^b$], 3.87 (q, *J* = 7.17 Hz, 2 H, OCH_2CH_3), 4.54 [t, *J* = 5.71 Hz, 1 H, $CH(OCH_3)_2$], 4.60 (quintet, *J* = 6.11 Hz, 1 H, CHOSi), 7.17–7.21 (m, 6 H, Ar), 7.78–7.86 (m, 4 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.19 (OCH_2CH_3), 19.21 (CMe_3), 26.98 [$C(CH_3)_3$], 37.87 (CH_2CO_2Et), 42.40 [$CH_2CH(OMe)_2$], 52.05 [$CH(OCH_3)^a(OCH_3)^b$], 52.90 [$CH(OCH_3)^a(OCH_3)^b$], 60.36 (OCH_2Me), 67.50 (CHOSi), 101.58 [$CH(OMe)_2$], 133.76 (*C*, Ar), 133.95 (*C*, Ar), 134.92 (CH, Ar), 135.49 (*C*, Ar), 135.60 (CH, Ar), 135.97 (CH, Ar), 136.04 (CH, Ar), 171.26 (CO_2Et) ppm.

Ethyl (*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-oxopentanoate (11): *p*-Toluenesulfonic acid hydrate (*p*-TsOH·H_2O, 120 mg, 0.63 mmol) was added to a solution of (*R*)-**10** (1.2 g, 2.7 mmol) in acetone/H_2O (5:1, 28.8 mL). The reaction mixture was heated at reflux for 2 h until 100% conversion was achieved (reaction was monitored by TLC: toluene/EtOAc, 20:1), and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc, and washed successively with saturated $NaHCO_3$ and brine. The organic layer was subsequently dried with Na_2SO_4 and the solvents were evaporated. Purification of the crude product by column chromatography (silica gel, eluent *n*-hexane/EtOAc, 10:1) afforded aldehyde (*R*)-**11** (1.05 g, 98% yield) as a colorless, viscous oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 0.88 (t, *J* = 7.17 Hz, 3 H, OCH_2CH_3), 1.11 [s, 9 H, $C(CH_3)_3$], 2.30–2.34 (m, 2 H, CH_2CHO), 2.39 (d, *J* = 6.07 Hz, 1 H, $CH^aH^bCO_2Et$), 2.46 (d, *J* = 6.07 Hz, 1 H, $CH^aH^bCO_2Et$), 3.82

(q, J = 7.17 Hz, 2 H, OCH_2CH$_3$), 4.67 (quintet, J = 6.0 Hz, 1 H, CHOSi), 7.17–7.23 (m, 6 H, Ar), 7.67–7.80 (m, 4 H, Ar), 9.24 (t, J = 1.88 Hz, 1 H, CHO) ppm.

(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-ethoxy-5-oxopentanoic Acid (12): Jones' oxidizing reagent was added dropwise (over ca. 30 min) at 0 °C to a solution of alcohol (*R*)-**10** (1.2 g, 2.7 mmol) in an acetone/water mixture (5:1, 10.6 mL). The addition was continued until the characteristic orange color of the reagent persisted for about 20 min. The stirrer was removed, and the mixture was decanted. The residual green salts were rinsed with acetone (2 × 10 mL). The washings were added to the main acetone solution and additional oxidizing agent was added, if necessary, to ensure complete reaction. The stirrer was replaced and propan-2-ol was added dropwise until excess Jones' reagent was destroyed. In small portions and with caution, a solution of $NaHCO_3$ was added and the suspension was stirred vigorously until the pH of the reaction mixture became neutral. The suspension was filtered, and the filter cake was washed with acetone (2 × 25 mL). The filtrate was concentrated and additionally purified by column chromatography (silica gel, eluent *n*-hexane/EtOAc, 1:1). Yield of (*R*)-**12**: 761 mg (68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 [s, 9 H, SiC(CH_3)$_3$], 1.08 (t, J = 7.17 Hz, 3 H, OCH$_2$CH_3), 2.38–2.60 (m, 4 H, CH_2CO$_2$H and CH_2CO$_2$Et), 3.92 (q, J = 7.17 Hz, 2 H, OCH_2CH$_3$), 4.67 (quintet, J = 6.04 Hz, 1 H, CHOSi), 7.23–7.36 (m, 6 H, Ar), 7.54–7.60 (m, 4 H, Ar), 12.9 (br. 1 H, CO$_2$$H$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.12 (OCH$_2$$CH_3$), 19.25 ($CMe_3$), 26.83 [C($CH_3$)$_3$], 41.43 ($CH_2CO_2$Et), 41.68 ($CH_2CO_2$H), 60.55 (OCH$_2$Me), 66.98 ($C$HOSi), 127.69 ($C$H, Ar), 129.89 ($C$H, Ar), 133.24 ($C$, Ar), 133.36 ($C$, Ar), 135.89 ($C$H, Ar), 170.78 ($CO_2$Et), 176.78 ($CO_2$H) ppm.

(*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-ethoxy-5-oxopentanoic (Ethyl Carbonic) Anhydride (13b): A solution of acid (*R*)-**12** (4.97 g, 11.99 mmol) and triethylamine (1.81 g, 17.89 mmol) in dry toluene (40 mL) was cooled to –40 °C, and ethyl chlorocarbonate (1.95 g, 17.97 mmol) was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was then stirred overnight at room temp. and diluted with ethyl acetate (150 mL). The solution was washed successively with saturated $NaHCO_3$ (2 × 80 mL) and brine (2 × 80 mL) and was then dried with $MgSO_4$. The solvent was evaporated, and the residue was dried in high vacuum to give the anhydride (*R*)-**13b** (5.54 g, 95% yield) as a clear, colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.87 (t, J = 7.17 Hz, 3 H, OCH$_2$CH_3), 0.90 (t, J = 7.17 Hz, 3 H, OCH$_2$CH_3), 1.14 [s, 9 H, SiC(CH_3)$_3$], 2.49–2.72 (m, 4H CH_2CO$_2$CO$_2$Et and CH_2CO$_2$Et), 3.82 (q, J = 7.17 Hz, 2 H, OCH_2CH$_3$), 3.89 (q, J = 7.17 Hz, 2 H, OCH_2CH$_3$), 4.69 (quintet, J = 6.02 Hz, 1 H, CHOSi), 7.17–7.26 (m, 6 H, Ar), 7.74–7.85 (m, 4 H, Ar) ppm.

Ethyl (*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-oxo-6-(triphenylphosphoranylidene)hexanoate (6): A suspension of methyltriphenylphosphonium bromide (8.85 g, 24.77 mmol) in dry THF (40 mL) was cooled to –78 °C, and *n*-BuLi in hexane (1.6 M, 15.4 mL, 24.66 mmol) was added dropwise over 20 min. The mixture was warmed to 0 °C and kept at this temperature for ca. 10 min (solution became yellow and the white powder dissolved). The mixture was again cooled to –78 °C, and a THF solution of the anhydride **13b** (6.0 g, 12.33 mmol) was added over 1 h. The resulting mixture was stirred overnight at –30 °C, warmed up to room temp., and additionally stirred for 1 h. The mixture was poured into water and extracted with EtOAc (2 × 100 mL). Combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Solvent was evaporated and residual material was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 1:10) to provide Wittig reagent **6** (3.7 g, 45%) as a viscous oil. $[\alpha]_D^{22}$ = –6.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 [s, 9 H, SiC(CH_3)$_3$], 1.19 (t, J = 7.12 Hz, 3 H, OCH$_2$CH_3), 2.33–2.83 (m, 4 H, CH_2COCH=PPh$_3$ and CH_2CO$_2$Et), 3.43 (br., 1 H, CH=P), 3.96–4.13 (m, 2 H, OCH_2CH$_3$), 4.57–4.65 (m, 1 H, CHOSi), 7.25–7.33 (m, 6 H, Ar), 7.37–7.44 (m, 6 H, Ar), 7.47–7.55 (m, 9 H, Ar) 7.69–7.74 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.11 (OCH$_2$$CH_3$), 19.23 ($CMe_3$), 26.83 [C($CH_3$)$_3$], 42.24 ($CH_2CO_2$Et), 49.44 (d, J_{CP} = 14.7 Hz, CH$_2$COCH=PPh$_3$), 53.3 (d, J_{CP} = 106.5 Hz, HC=PPh$_3$), 59.99 (OCH$_2$Me), 70.55 (CHOSi), 126.27 (C, Ar), 127.17 (CH, Ar), 127.34 (C, Ar), 127.44 (C, Ar), 127.46 (C, Ar), 128.51 (C, Ar), 128.62 (CH, Ar), 128.74 (CH, Ar), 129.34 (d, J_{CP} = 4.55 Hz, CH, Ar), 131.95 (d, J_{CP} = 2.89 Hz, CH, Ar), 132.93 (CH, Ar), 133.03 (CH, Ar), 133.91 (C, Ar), 134.36 (C, Ar), 135.92 (d, J_{CP} = 1.59 Hz, CH, Ar), 172.21 (CO$_2$Et), 189.58 (COCH=PPh$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 15.25 ppm.

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[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), vol. I–III, Springer-Verlag, Berlin, **1999**; *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.

[2] a) J. M. Brown, in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, **1999**, vol. I, pp. 121–182; b) T. Ohkuma, M. Kitamura, R. Noyori, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 1–110.

[3] T. Ohkuma, R. Noyori, in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, **1999**, vol. I, pp. 204–210.

[4] a) O. Labeeuw, D. Blanc, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genêt, *Eur. J. Org. Chem.* **2004**, 2352–2358; b) V. Ratovelomanana-Vidal, C. Girard, R. Touati, J. P. Tranchier, B. Ben Hassine, J.-P. Genêt, *Adv. Synth. Catal.* **2003**, *345*, 261–274; c) O. Poupardin, C. Greck, J.-P. Genêt, *Tetrahedron Lett.* **2000**, *41*, 8795–8797.

[5] a) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629–631; b) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858; c) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345–350.

[6] a) Z. Zhang, H. Qian, J. Longmire, X. Zhang, *J. Org. Chem.* **2000**, *65*, 6223–6226; b) A. Hu, H. L. Ngo, W. Lin, *Angew. Chem. Int. Ed.* **2004**, *43*, 2501–2504; c) Y.-G. Zhou, W. Tang, W.-B. Wang, W. Li, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953.

[7] M. J. Burk, T. G. P. Harper, C. S. Kalberg, *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.

[8] T. Yamano, N. Taya, M. Kawada, T. Huang, T. Imamoto, *Tetrahedron Lett.* **1999**, *40*, 2577–2580.

[9] K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069.

[10] T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843–852.

[11] P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 4441–4444.

[12] a) I. Karamé, E. Bellur, S. Rotzoll, P. Langer, C. Fischer, J. Holz, A. Börner, *Synth. Commun.* **2007**, *37*, 1067–1076; b) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan, W. T. Tong, *J. Am. Chem. Soc.* **2000**, *122*, 11513–11514; c) J. P. Genêt,

C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Cano de Andrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 675–690.
[13] V. I. Tararov, G. König, A. Börner, *Adv. Synth. Catal.* **2006**, *348*, 2633–2644.
[14] V. I. Tararov, N. Andrushko, V. Andrushko, G. König, A. Spannenberg, A. Börner, *Eur. J. Org. Chem.* **2006**, 5543–5550.
[15] Atorvastatin belongs to the class of statins that are very effective inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGR). Therefore statins are the most powerful lipid-lowering agents used for reducing cholesterol levels in people with or at risk of cardiovascular disease: *Statins, The HMG CoA Reductase Inhibitors in Perspective* (Eds: A. Gaw, C. J. Packard, J. Shepherd), Taylor & Francis, **2003**. For the application of statins for treatment of hypercholesterolemia and hyperlipidaemia see: a) *Contemporary Drug Synthesis* (Eds.: J.-J. Li, D. S. Johnson, D. R. Sliskovic, B. D. Roth), Wiley-Interscience, New York, **2004**, pp. 113–123; b) W. Insull Jr, *Nat. Clin. Pract. Cardiovasc. Med.* **2006**, *3*, 134–135; c) L. Calza, V. Colangeli, R. Manfredi, G. Legnani, L. Tampellini, D. Pocaterra, F. Chiodo, *AIDS* **2005**, *19*, 1103–1105. For a systematic review about application of statins in the treatment of chronic heart failure see: P. van der Harst, A. A. Voors, W. H. van Gilst, M. Böhm, D. J. van Veldhuisen, *PLoS Med.* **2006**, *3*, e333; and literature cited therein.
[16] T. Konoike, Y. Araki, *J. Org. Chem.* **1994**, *59*, 7849–7854.
[17] Rosuvastatin was approved as the cholesterol-lowering drug Crestor in August, 2003. More about the application of rosuvastatin see: N. S. Culhane, S. L. Lettieri, J. R. Skae, *Pharmacotherapy* **2005**, *25*, 990–1000 and literature cited therein.
[18] Rosuvastatin appears to reduce low-density lipoprotein (LDL) cholesterol to a greater degree than rivals in the class without additional adverse effects. Rosuvastatin is approved for the treatment of elevated LDL cholesterol (dyslipidemia), total cholesterol (hypercholesterolemia) and/or triglycerides (hypertriglyceridemia). The main competitor to rosuvastatin is atorvastatin, which is the first totally synthetic HMG-CoA-reductase inhibitor that is marketed as a single enantiomer.
[19] O. Poupardin, C. Greck, J.-P. Genêt, *Synlett* **1998**, 1279–1281.
[20] M. A. Ciufolini, N. Xi, *J. Chem. Soc. Chem. Commun.* **1994**, 1867–1868.
[21] D. W. Brooks, L. D.-L. Lu, S. Masamune, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72–74.
[22] If not otherwise indicated, reactions were performed at an initial H_2 pressure of 50 bar.
[23] J. M. Brown, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190–203.
[24] G. Beck, H. Jendralla, K. Kesseler, *Synthesis* **1995**, 1014–1018.
[25] M. Kitamura, T. Ohkuma, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1988**, *29*, 1555–1556.
[26] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.
[27] G. Franciò, C. G. Arena, F. Faraone, C. Graiff, M. Lanfranchi, A. Tiripicchio, *Eur. J. Inorg. Chem.* **1999**, *8*, 1219–1227.
[28] Unfortunately, it was not possible to increase the yield of (*R*)-**6** higher than noted above.
[29] N. Andrushko, V. Andrushko, G. König, A. Spannenberg, A. Börner, *Eur. J. Org. Chem.* **2008**, 847–853, following article.
[30] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512–7515.

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