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Synthesis and Highly Stereoselective Hydrogenation of the Statin Precursor Ethyl (5*S*)-5,6-Isopropylidenedioxy-3-oxohexanoate[1]

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Abstract: A search for the large-scale preparation of (5*S*)-5,6-(isopropylidenedioxy)-3-oxohexanoates (**2**) – a key intermediate in the synthesis of pharmacologially important statins – starting from (*S*)-malic acid is described. The synthesis of the required initial compound methyl (3*S*)-3,4-(isopropylidenedioxy)butanoate (**1**) by Moriwake's reduction of dimethyl (*S*)-malate (**3**) has been improved. Direct 2-C chain elongation of ester **1** using the lithium enolate of *tert*-butyl acetate has been shown to be successful at a 3- to 5-fold excess of the enolate. Unfortunately, the product, *tert*-butyl (5*S*)-5,6-(isopropylidenedioxy)-3-oxohexanoate (**2a**) is unstable during distillation. Ethyl (5*S*)-5,6-(isopropylidenedioxy)-3-oxohexanoate (**2b**) was prepared alternatively on a multigram scale from (3*S*)-3,4-(isopropylidenedioxy)butanoic acid (**7**) by activation with *N,N′*-carbonyldiimidazole and subsequent reaction with $Mg(OOCCH_2COOEt)_2$. A convenient pathway for the *in situ* preparation of the latter is also described. Ethyl ester (**2b**) can be advantageously purified by distillation. The stereochemistry of the catalytic hydrogenation of β-keto ester (**2b**) to ethyl (5*S*)-5,6-(isopropylidenedioxy)-3-hydrohyhexanoate (*syn*-**6** and *anti*-**6**) has been studied using a number of homogeneous achiral and chiral Rh(I) and Ru(II) complexes with phosphine ligands. A comparison of Rh(I) and Ru(II) catalysts with (*S*)- and (*R*)-BINAP as chiral ligands revealed opposite activity in dependence on the polarity of the solvent. No influence of the chiral backbone of substrate **2b** on the enantioselectivity was noted. A ratio of *syn*-**6**/*anti*-**6** = 2.3 was observed with an achiral $(Ph_3P)_3RuCl_2$ catalyst. 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*)-5,6-isopropylidenedioxy-3-hydroxyhexanoate (*syn*-**6**) at a preparative substrate/catalyst ratio of 1000:1.

Keywords: asymmetric catalysis; hydrogenation; β-keto esters; rhodium; stereoselectivity

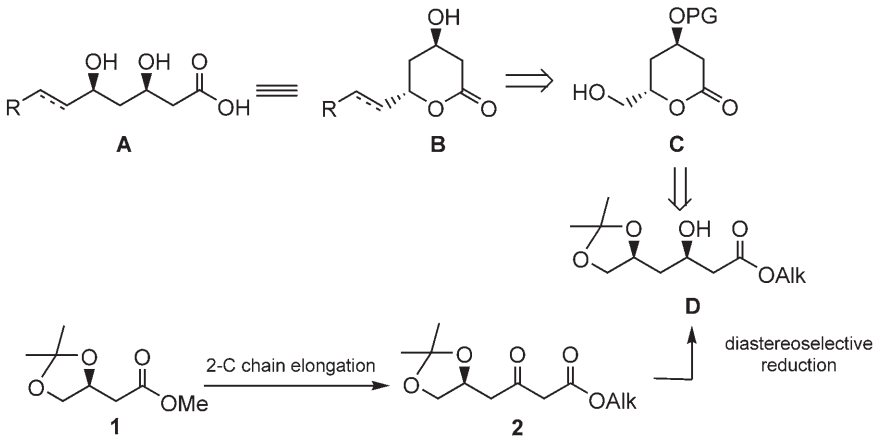
Introduction

Inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme reductase (HMG-CoA reductase) commercialized under the general trade name statins have become the standard of care for treatment of hypercholesterolemia due to the efficacy, safety and long-term benefits.[2] Atorvastatin calcium was the first totally synthetic HMG-CoA-reductase inhibitor developed and marketed as a single enantiomer. Currently, it ranks at the top of the drugs best sold in the world.

Biotechnologically produced or fully synthetic statins[3] used in medical practice comply with general structures **A** and **B** (Scheme 1), where R is a hydrophobic heterocyclic or a carbocyclic moiety. Stereogenic centers at C-3 and C-5 atoms must have the indicated configurations. Structures **A** and **B** are equivalent for retrosynthetic considerations. Protected hydroxy lactones **C** were formulated as possible building blocks[4,5] as soon as the free hydroxy group could be transformed into a variety of reactive leaving groups by functional group transformations and subsequent coupling with appropriate building blocks.

A straightforward avenue to lactones **C** consists in the cyclization of the protected hydroxy ester **D**.[4,6] The latter was prepared in low to reasonable diastereoselectivity with diastereomers that differ only in the configuration at C-3 (0% *de*,[4] 60% *de*,[6] 84% *de*[7]).

Our strategy is likewise shown in Scheme 1. It includes two-carbon atom elongation of the acetonide **1** to afford 3-keto esters **2** followed by catalytic hydrogenation of the prochiral keto group to afford hydroxy esters **D**. To the best of our knowledge the catalytic diastereoselective hydrogenation using molecular hydrogen of compounds **2** has never been studied



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

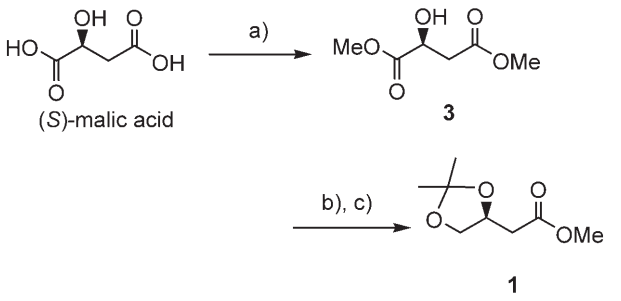
before. This transformation could open an economically and ecologically benign avenue to a series of statins. Besides the preparation of optically pure hydroxy esters **D**, we were also interested to elaborate a simple and efficient approach to 3-keto esters **2** which may be easily scaled up for industrial applications.

Results and Discussions

Preparation of the Substrate for Hydrogenation

Preparation of the Intermediate Acetonide 1

The acetonide **1** is commercially available at a rather high price. Alternatively, it can be prepared from (*S*)-malic acid by a known sequence (Scheme 2). The intermediate dimethyl (*S*)-malate (**3**) is also commercially available but for our purpose we improved the protocol of the literature[8] by adding dimethyl orthoformate during the esterification with methanol. Due to this modification full conversion of (*S*)-malic acid was achieved and dimethyl ester **3** could be obtained in one step with 93% yield.

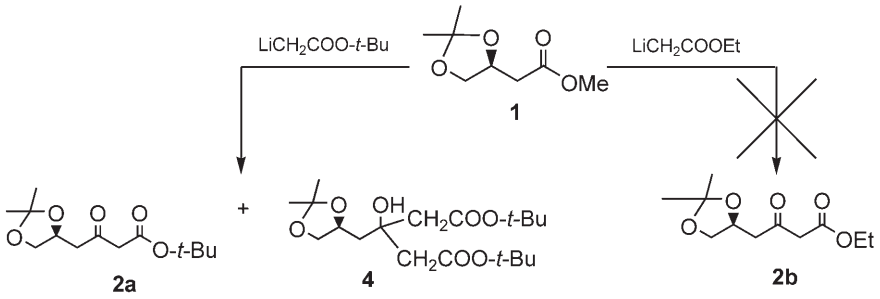


Scheme 2. Preparation of the initial compound **1**. a) MeOH, $HC(OMe)_3$, cat. HCl, room temperature, 93%; b) $BH_3{\cdot}SMe_2$, THF, cat. $NaBH_4$ (1 mol%), room temperature; c) $Me_2C(OMe)_2$, Me_2CO, cat. *p*-TsOH, room temperature, 74%.

Moriwake's reduction ($BH_3{\cdot}SMe_2$, THF, cat. $NaBH_4$)[9] allows the regioselective transformation of one ester group of diester **3**. Originally this transformation was carried out by slow addition of a small excess of the $Me_2S{\cdot}$borane complex to a THF solution of the diester **3** followed by the addition of 5 mol% of $NaBH_4$ in one portion. At this point we were faced by some difficulties. In one trial, addition of $NaBH_4$ resulted in a gentle reaction with slow gas evolution. In another trial, after the addition of $NaBH_4$ a very vigorous and uncontrolled reaction occurred with part of the reaction mixture being splashed out. We noticed also that not the whole amount of $NaBH_4$ was dissolved in the reaction mixture. This gave us the chance to reduce the amount of $NaBH_4$ to 1 mol%. We have found also that the reduction of diester **3** could be achieved under controlled conditions when 1 mol% of $NaBH_4$ was added to the solution of **3** in THF followed by addition of $BH_3{\cdot}SMe_2$. In this case the rate of the reaction (gas evolution) could be controlled by the rate of the addition of the $Me_2S{\cdot}$borane complex. After the work-up the intermediate crude product was transformed without additional chromatographic purification directly into the acetonide **1** with a yield of 74% after distillation.

2-C Elongation of Acetonide 1

An elongation of acetonide **1** by a 2-carbon unit affording keto ester **2a** can be achieved according to Scheme 3 using an excess of the lithium enolate of *tert*-butyl acetate. The reagent could be generated with LDA. This approach was broadly used for the 2-C elongation of 3-hydroxy esters in the preparation of several 5-hydroxy-3-keto esters related to statins.[10] It is also possible to elongate under these conditions esters which lack a 3-hydroxy group,[11] but this is less exploited. For the successful application of this mixed ester condensation in the literature the use of a 3–4



Scheme 3. Attempts for the synthesis of β-keto esters **2a,b** by means of lithium enolates (other conditions: THF, −78 °C→ room temperature).

fold excess of $LiCH_2COO$-*t*-Bu was recommended. Interestingly, we were unable to find any reason for this in literature.

In order to clarify this matter, we undertook a detailed study of the reaction of acetonide **1** with $LiCH_2COO$-*t*-Bu. We found that this reaction is complicated by the formation of the bis-alkylated side-product **4**. It was isolated by chromatography and characterized by NMR. Our study revealed furthermore that the ratio **2a**/**4** is strongly dependent on the ratio Li/**1** (where Li corresponds to $LiCH_2COO$-*t*-Bu). The data obtained are collected in Table 1. The ratios of products **2a**:**4** were determined by ^{1}H NMR.

Table 1. The influence of Li/**1**[a] ratio on the product ratio **2a**/**4**.

Run	Ratio Li/**1**	Ratio **2a**/**4**
1	1:1	2.5:1[b]
2	2:1	1:1
3	3:1	3.5:1
4	4:1	8:1

[a] Li corresponds to the portion of $LiCH_2COO$-*t*-Bu.
[b] Formation of unsaturated products was observed.

At a ratio of Li/**1** = 1:1 (run 1) the keto ester **4** was an important side-product. But in this trial not all initial ester **1** was consumed and some additional unsaturated compounds of unidentified structure were observed in the NMR spectrum. When the ratio of Li/1 was ≥2 (runs 2–4) then complete conversion of ester **1** was achieved. Only two products could be observed in the NMR spectrum derived from run 3. An increase of the Li/**1** ratio resulted in an improvement of the yield of keto ester **2a** (compare runs 3 and 4). In run 4 additionally *ca.* 10% of MeCOCOO-*t*-Bu was identified in the raw reaction mixture. In the best runs 78–89% yield of keto ester **2a** could be achieved using ratios of Li/**1** in the range of 3:1 to 4:1 (runs 3 and 4). The formation of the tertiary alcohol **4** is kinetically controlled since by employment of an excess of $LiCH_2COO$-*t*-Bu no formation of keto ester **2a** has been observed. Obviously the exclusive formation of the lithium enolate of **2a** in the presence of an excess of $LiCH_2COO$-*t*-Bu prevents the second alkylation and the formation of the tertiary alcohol **4**.

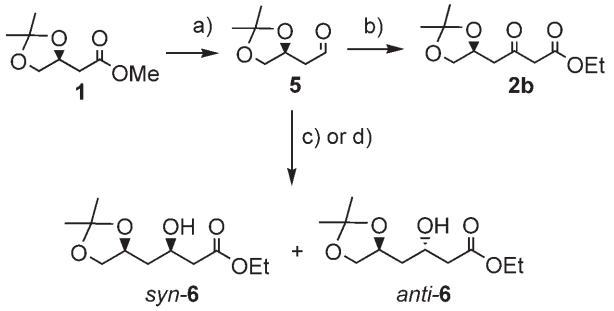
The data presented in Table 1 were obtained using an LDA solution prepared *in situ* from $(i\text{-Pr})_2NH$ and commercial BuLi (2.5 M solution in hexane) for the generation of $LiCH_2COO$-*t*-Bu. A commercial LDA solution (*ca.* 2 M solution in THF-heptane-EtPh) could be used as well without significant differences in the **2a**/**4** ratio. Unfortunately on the preparative scale it was not possible to purify keto ester **2a** by distillation. Significant decomposition with tar formation was observed and the yield of the pure material was low (22%). The thermal instability of **2a** is probably due to the presence of the *t*-Bu ester group.

Attempts to synthesize the corresponding ethyl ester **2b** from acetonide **1** by application of the same methodology using $LiCH_2COOEt$ resulted in a complex mixture of unidentified products, probably due to the easy oligomerization or polycondensation which are hindered in the case of the *t*-Bu ester. Although this mixture could be distilled in vacuum we were not able to isolate pure **2b**.

Finally attempts of transesterification of **2a** to **2b** under acidic conditions were not successful since **2b** is prone to rearrange to (2-furyl)acetate[12] in acidic medium.

2-C Elongation *via* Aldehyde 5

Acetonide **1** could be reduced selectively to the aldehyde **5** using diisobutylaluminium hydride (DIBALH) at −78 °C according to a published protocol (Scheme 4).[13] The reduction proceeded cleanly and gave the desired aldehyde **5** with reproducible yields of 71–75% after distillation. The aldehyde **5** can be elongated by insertion of the carbene generated from $N_2CHCOOEt$ catalyzed by $SnCl_2$.[14] In general, this reaction worked well, but we were faced by some purification problems. Neither chromatography on SiO_2 nor successive distillation gave the pure product **2b**.

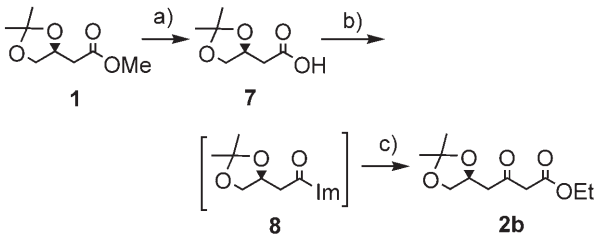


Scheme 4. Synthetic pathways *via* aldehyde **5**. a) DIBALH, Et_2O, −78 C, 75%; b) $N_2CHCOOEt$, CH_2Cl_2, cat. $SnCl_2$, room temperature; c) $BrCH_2COOEt$, benzene, Zn, reflux, 71%; d) $BrCH_2COOEt$, THF, Sn, room temperature, 41%.

In another attempt the addition reaction of carbanions to aldehyde **5** affording alcohol **D** was studied. Having aldehyde **5** in hand we achieved a hitherto undeclared Reformatskii reaction. Thus, the reaction of aldehyde **5** with $BrCH_2COOEt$ promoted by activated Zn dust in boiling benzene[15] afforded a mixture of alcohols **6** in 71% yield. No diastereoselection was observed as found earlier for the addition of $LiCH_2COOEt$ (generated from AcOEt and LDA).[4] The reaction promoted by activated Sn (generated from $SnCl_2$ and $LiAlH_4$)[16] in THF at room temperature gave a 41% yield of **6** with a diastereomeric ratio of 2:1 in favour of the undesired *anti*-isomer. The ratio of isomers **6** was established on the basis of ^{13}C NMR spectroscopy (*anti*-isomer, $\delta = 73.5$; *syn*-isomer, $\delta = 74.6$) and related to the reported data[7] for the corresponding methyl ester (*anti*-isomer, $\delta = 73.2$; *syn*-isomer, $\delta = 74.4$).

2-C Elongation *via* Acid 7

As an alternative a two-step sequence has been envisaged for the 2-C elongation of ester **1** (Scheme 5).



Scheme 5. Large scale preparation of substrate **2b** for the diastereoselective hydrogenation. a) 2 N NaOH, room temperature and neutralization with 2 N $NaHSO_4$, 78%; b) CDI (*N,N′*-carbonyldiimidazole), THF, room temperature; c) $Mg(MEMA)_2$ (MEMA = monoethyl malonate anion) THF, room temperature, 12 h, 90%.

Butyric acid derivative **7** could be easily prepared from ester **1** by saponification and subsequent neutralization. A known protocol utilized a 4-fold excess of 2 M LiOH water solution in THF.[17] We found that complete hydrolysis can be achieved employing an excess of 2 M aqueous NaOH solution. The chemical yield of the desired acid **7** was within a range 71–78%. The acid could be successfully elongated by applying a general protocol developed for the synthesis of β-keto esters.[18] Thus, imidazolide **8** was prepared *in situ* and subsequently the solid complex $Mg(MEMA)_2$ was added directly to the resultant solution. After work-up the raw keto ester **2b** was isolated in 84–94% yield. In contrast to the preparation of the *tert*-butyl ester **2a** the former could be distilled in vacuum without decomposition and could be isolated in 90% yield. The main advantage of this approach is that low temperatures or hazardous reagents are not required.

Originally the complex $Mg(MEMA)_2$ was prepared by reaction of $Mg(OEt)_2$ with a stoichiometric amount of $EtOCOCH_2COOH$ (MEMAH)[19] in THF and subsequent evaporation and lingering drying in vacuum with occasional crushing of the resultant amorphous solid. In order to avoid this tedious procedure and to find a more convenient way for triggering the reaction of **8** with MEMAH, we tested different derivatives of this acid and additives. Main results are compared in Table 2. *C*-Acylation of MEMA and its K salt did not take place in the presence of simple nitrogen bases (runs 1–4). K and Li salts were not acylated (runs 3 and 5). It was not even possible to achieve acylation of the Li dianion (runs 6 and 7). In contrast, Zn and Al salts proved to be suitable for the preparation of **2b** (runs 8–10).

With Al salts some difficulties were faced during the isolation of the product. With Zn salts the best yield was observed when the symmetrical salt, $(MEMA)_2Zn$, was formed (run 9, compare with run 8). Although the yield of the product is moderate the advantage consists in the *in situ* preparation of the salt which does not demand any additional manipulations. The usage of the unsymmetrical salt (MEMA)MgOAc, with the intention to reduce the quantity of MEMA, resulted in a significant drop of the yield (compare runs 12 and 11). Finally we found that the most convenient way for the *in situ* preparation of $(MEMA)_2Mg$ is heating a THF solution of MEMAH with a slight excess of commercially available Mg powder under reflux for 4 h. With this protocol keto ester **2b** was obtained after distillation in 82% yield (run 13). The compound had satisfactory elemental analysis and NMR spectra according to the data previously reported.[12] Unexpectedly, a striking contrast was observed in the specific rotation: compare our value $[\alpha]_D^{23}$: 6.6 (*c* 1.43, $CHCl_3$) and reported $[\alpha]_D^{23}$: −0.9 (*c* 1.43, $CHCl_3$).[12] The reason for this strong de-

Table 2. Comparison of procedures for *C*-acylation of MEMAH derivatives by imidazolide **8**.[a]

Run	Derivative[b]	Additive	Yield of raw **2b** [%][c]	Procedure
1	MEMAH	Et_3N	traces	5-fold molar excess of Et_3N
2	MEMAH	pyridine	traces	5-fold molar excess of pyridine
3	MEMAK		0	
4	MEMAK	Et_3N	0	
5	MEMALi		0	*in situ* addition of 1 mol equiv. of BuLi
6	(MEMA-H)Li_2		0	*in situ* addition of 2 mol equivs. of BuLi
7	(MEMA-H)Li_2		0	*in situ* addition of 2 mol equivs. of LDA
8	(MEMA-H)Zn		45	*in situ* addition of 1 mol equiv. of Et_2Zn
9	$(MEMA)_2Zn$		71	*in situ* addition of 0.5 mol equivs. of Et_2Zn
10	$(MEMA)_2AlCl$		61	*in situ* addition of 0.5 mol equivs. of Me_2AlCl
11	(MEMA)MgOAc		71	prepared by the reaction of stoichiometric amounts of $Mg(OEt)_2$, MEMAH and AcOH with subsequent evaporation and drying in vacuum
12	$(MEMA)_2Mg$		84-94	prepared by the reaction of stoichiometric amounts of $Mg(OEt)_2$, MEMAH with subsequent evaporation and drying in vacuum
13	$(MEMA)_2Mg$		82[d]	prepared *in situ* by refluxing of MEMAH with Mg in THF

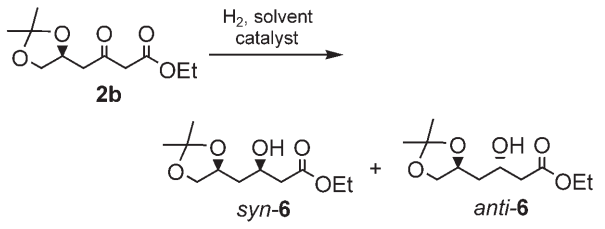
[a] *General conditions:* room temperature, THF, 16–20 h.
[b] MEMAH = acid form, MEMA = monoanion, MEMA-H = dianion of enol form.
[c] Yields of keto ester **2b** were calculated on the raw product which was characterized as pure compound due to NMR (^1H and ^{13}C) spectra.
[d] After distillation (see Experimental Section).

viation is unclear. Nevertheless, in the present work we observed the same sign and magnitude of rotation for structurally similar keto esters **2a** and **2b**, $[\alpha]_D^{23}$: 6.8 (*c* 1, EtOH) and $[\alpha]_D^{23}$: 7.8 (*c* 1, EtOH), correspondingly.

Stereoselective Hydrogenations of Keto Ester 2b

In order to elucidate principal conditions for the stereoselective hydrogenation of β-keto ester **2b** to the desired *syn*-diol **6** (Scheme 6) first we studied the performance of homogeneous achiral and chiral Rh and Ru catalysts.

The *syn*/*anti* ratio was determined on the basis of NMR data. The hydrogenation was performed under mild conditions (50 bar initial H_2 pressure, room temperature). The results of the hydrogenation of substrate **2b** with several homogeneous achiral catalysts are listed in Table 3. Hydrogenation of **2b** catalyzed with Rh(dppb) catalysts did not give significant diastereoselectivity [runs 1–5; dppb = 1,4-bis(diphenylphosphino)butane]. A change of the solvent resulted mainly in the change of the productivity while the diastereoselectivity was not affected. The Rh catalyst is more active in aprotic solvents than in MeOH. A quite opposite tendency was noted for the achiral complex $(Ph_3P)_3RuCl_2$ (runs 7 and 8). It was more active in MeOH than in aprotic solvents. In order to find the desired product alcohol in the reaction mixture it was necessary to neutralize this complex with Et_3N (runs 9–11). The complex $(Ph_3P)_3RuCl_2{\cdot}Et_3N$ displayed the same solvent feasibility. In MeOH (run 9) reasonable diastereoselectivity was observed. From these experiments based on achiral catalysts we could expect that chiral Ru complexes must exhibit a reasonable degree of diastereoselection in comparison with Rh complexes.



Scheme 6. Hydrogenation of keto ester **2b** under homogeneously catalyzed conditions.

In Table 4 relevant examples of the hydrogenation of **2b** with chiral Rh(I) catalysts are detailed. As observed with achiral analogues, chiral Rh(I) complexes gave higher activities in aprotic solvents (runs 1 and 2). The Rh catalyst with (*S*)-BINAP as ancillary ligand induced reasonable *syn*-selectivity while with (*R*)-BINAP as ligand a completely opposite result was noted. Remarkably no influence of the chiral backbone of the substrate on the *syn-anti* selectivity was observed. A minor influence was detected with pairs of (*S*,*S*)-(*R*,*R*)-Et-DUPHOS and corresponding Me-DUPHOS ligands (runs 4 and 5, 6 and 7). Good selectivity was observed also with catalysts based on TolBINAP (run 8) and (*R*,*S*)-JOSIPHOS (run 9).

Table 3. Table 3 Hydrogenation of keto ester **2b** with achiral homogeneous precatalysts.[a]

Run No	Precatalyst	Solvent	Time [min][b]	Conversion [%]	Ratio *syn-/anti*-**6**
1	$[Rh(dppb)COD]BF_4$	MeOH	200	100	1.1
2	$[Rh(dppb)COD]BF_4$	THF	120	100	1.1
3	$[Rh(dppb)COD]BF_4$	Et_2O	120	100	1.3
4	$[Rh(dppb)COD]BF_4$	AcOEt	50	100	1.1
5	$[Rh(dppb)COD]BF_4$	CH_2Cl_2	30	100	0.7
6	$(Ph_3P)_3RuCl_2$	MeOH	420	100	complex mixture
7	$(Ph_3P)_3RuCl_2$	CH_2Cl_2	300	<10	n.d.
8	$(Ph_3P)_3RuCl_2$	THF	300	<10	n.d.
9	$(Ph_3P)_3RuCl_2{\cdot}Et_3N$[c]	MeOH	420	100	2.3
10	$(Ph_3P)_3RuCl_2{\cdot}Et_3N$[c]	CH_2Cl_2	1200	44	1.3
11	$(Ph_3P)_3RuCl_2{\cdot}Et_3N$[c]	THF	1200	<10	nd

[a] *Conditions:* 2.5 mmol of substrate, 0.01 mmol of a precatalyst, 10 mL of solvent, room temperature, 50 bar initial H_2 pressure.
[b] Indicated time corresponds to the end of H_2 consumption.
[c] The complex was prepared by treating commercial $(Ph_3P)_3RuCl_2$ with an excess of Et_3N in CH_2Cl_2 and subsequent evaporation of the volatiles in vacuum (the real composition was not studied).

Table 4. Hydrogenation of keto ester **2b** with chiral Rh precatalysts.[a]

Run	Precatalyst	Solvent	Time [min]	Conversion[%]	Ratio *syn/anti*
1	$\{Rh[(S)\text{-BINAP}](COD)\}BF_4$	MeOH	1000	100	3.3
2	$\{Rh[(S)\text{-BINAP}](COD)\}BF_4$	AcOEt	120	100	3.1 (76/24)
3	$\{Rh[(R)\text{-BINAP}](COD)\}BF_4$	AcOEt	120	100	0.34 (25/75)
4	$\{Rh[(S,S)\text{-Et-DUPHOS}](COD)\}BF_4$	AcOEt	70	100	2.1 (68/32)
5	$\{Rh[(R,R)\text{-Et-DUPHOS}](COD)\}BF_4$	AcOEt	70	100	0.7 (41/59)
6	$\{Rh[(S,S)\text{-Me-DUPHOS}](COD)\}BF_4$	AcOEt	120	100	2.3 (70/30)
7	$\{Rh[(R,R)\text{-Me-DUPHOS}](COD)\}BF_4$	AcOEt	150	100	0.78 (44/56)
8	$Rh[(R)\text{-Tol-BINAP}](COD)]BF_4$	AcOEt	80	100	0.34
9	$\{Rh[(R,S)\text{-JOSIPHOS}](COD)\}BF_4$	AcOEt	50	100	2.3

[a] *Conditions:*2.5 mmol of substrate, 0.01 mmol of a precatalyst, 10 mL of solvent, room temperature, 50 bar initial H_2 pressure.

In parallel we studied the catalytic performance of Ru(II) catalysts based on the diphosphine ligands BINAP and Tol-BINAP, respectively. These catalysts were introduced into chemical practice as highly enantioselective catalysts for the hydrogenation of β-keto esters.[20] But significant improvement was necessary to apply these catalytic systems for hydrogenation of keto ester **2b** considered herein. Results are detailed in Table 5.

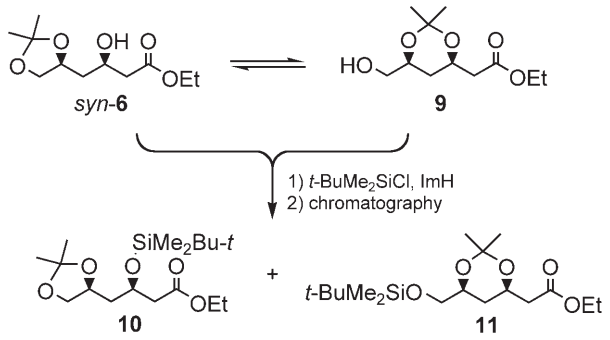
First, we found that application of commercially available or prepared in-house[21] $Ru[(R)\text{-BINAP}]Cl_2$ afforded a complex mixture of products although the conversion of keto ester **2b** was complete (run 1). In comparison with the related Rh(I) complex (Table 4 runs 1 and 2) the latter catalyst did not work in AcOEt (run 2). Along with the desired alcohol *syn*-**6** ($\delta = 109.9$) a side product characterized in the ^{13}C NMR spectrum at $\delta = 99.4$ was formed in MeOH. It is well established that the chemical shift of the tertiary isopropylidene carbon atom $\delta = ca.$ 99, corresponds to a 6-membered ring while 5-membered rings are characterized by $\delta = ca.$ 110.[22] On the basis of these data we assumed that a thermodynamic equilibrium is established between *syn*-**6** and the rearranged product **9** during the hydrogenation reaction (Scheme 7). This assumption was confirmed by a standard *O*-silylation procedure[4] of the mixture of alcohols *syn*-**6** and **9** followed by chromatographic separation of products **10** and **11**. Compound **11** is less polar than **10** and it was eluted first. Both isomers **10** and **11** had the same element analysis and displayed the same peak pattern in the mass-spectrum ($m/z = 331$ $[M^+ - Me]$ and $m/z = 231$ $[M^+ - t\text{-}BuMe_2Si]$). The chemical shift of the tertiary isopropylidene carbon atom of compound **10** was found to be $\delta = 109$ and for compound **11** $\delta = 99.1$. It is remarkable that 1,3-dioxolane **10** as well as 1,3-dioxane **11** showed only one set of signals in the NMR spectrum. This gives clear evidence that the hydrogenation reaction produced alcohols *syn*-**6** and **9** with excellent diastereomeric purity.

The same rearrangement was also observed when $Ru[(R)\text{-Tol-BINAP}]Cl_2$ was used as a catalyst. It

Table 5. Hydrogenation of keto ester **2b** with chiral Ru catalysts.[a]

Run	Precatalyst	Solvent	Time [min]	Conversion [%]	Ratio *syn/anti*
1	Ru[(*R*)-BINAP]Cl_2	MeOH	80	100	*syn*-**6** and **9**
2	Ru[(*R*)-BINAP]Cl_2	AcOEt	940	<10	nd
3	Ru[(*R*)-BINAP]Cl_2 + 0.5 Et_3N	MeOH	100	100	>99% *syn*
4	Ru[(*R*)-BINAP]Cl_2 + 1.0 Et_3N	MeOH	200	100	98.2% *syn*
5	Ru[(*R*)-BINAP]Cl_2 + 2.0 Et_3N	MeOH	1310	0	
6	Ru[(*S*)-BINAP]Cl_2 + 1.0 Et_3N	MeOH	380	100	2.3% *syn*
7	Ru[(*R*)-BINAP]Cl_2·Et_3N	MeOH	120	100	>99% *syn*
8	Ru[(*R*)-BINAP]Cl_2·Et_3N	EtOH	300	100	>99% *syn*
9	Ru[(*R*)-BINAP]Cl_2·Et_3N	*i*-PrOH	340	0	
10	Ru[(*R*)-BINAP]Cl_2·Et_3N	96% aqueous EtOH	340	0	
11	Ru[(*R*)-BINAP]Cl_2 + 1.0 AcONa	MeOH	140	100	>99% *syn*
12	Ru[(*R*)-BINAP]Cl_2 + 1.5 AcONa	MeOH	750	100	>98.1% *syn*
13	Ru[(*R*)-BINAP]Cl_2 + 2.0 AcONa	MeOH	1000	0	
14	Ru[(*R*)-BINAP]$(OAc)_2$	MeOH	20 h	0	
15	Ru((*R*)-BINAP)$(OAc)_2$	MeOH	20 h	0	
16	Ru[(*R*)-TolBINAP]Cl_2·Et_3N	MeOH	100	100	>99% *syn*
17	Ru[(*R*)-TolBINAP]Cl_2·AcONa	MeOH	130	100	>99% *syn*

[a] *Conditions:* 2.5 mmol of substrate, 0.01 mmol of a precatalyst, 10 mL of solvent, room temperature, 50 bar initial H_2 pressure.



Scheme 7. Transacetalization reaction in acidic medium.

became obvious that these complexes have acidic properties and it is necessary to neutralize them before use. For this reason, we tested several nitrogen bases (Et_3N, $BnNH_2$, imidazole, piperazine). These bases had an equal influence on the activity of the catalysts. In Table 5 only examples with Et_3N are listed (runs 3–5). The addition of Et_3N inhibited completely the formation of the transacetalization product **9**. An increase in the concentration of Et_3N affected the activity of the catalyst. At an Ru/Et_3N ratio equal to 2 complete inhibition of hydrogenation took place. It is interesting to note that imidazole and piperazine possessing two basic centers behaved similarly to Et_3N. The (*R*)-configuration of the BINAP ligand induced exclusively (within the analytical error) the *syn*-configuration in the product **6** while (*S*)-BINAP (run 6) had the opposite effect and *anti*-**6** alcohol was the predominant product. No significant influence of the chiral backbone of the substrate has been observed.

Partial neutralization of Ru[(*R*)-BINAP]Cl_2 could also be achieved by treating the complex 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·Et_3N {possible composition might be $Ru_2Cl_4[((R)\text{-BINAP})]_2$·$Et_3N$[23]}, was tested in the hydrogenation of keto ester **2b**. Run 7 illustrates that the activity of this complex is comparable to the activity of the catalytic system arising after neutralization in solution (compare with runs 3 and 4). The activity of the complex is strongly dependent upon the polarity of the alcohol and follows the order: MeOH > EtOH ⩾ *i*-PrOH (compare runs 7–9). Surprisingly no activity was observed in 96% aqueous EtOH (run 10). 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 11–13). It was interesting to see that AcONa acted in the same way as Et_3N, e.g., lowering the activity with the increase in the AcONa:Ru ratio and complete inhibition of the hydrogenation at a ratio of 2 (runs 11–13). In the literature Ru(BINAP)-$(OAc)_2$ was claimed to be efficient in the hydrogenation of β-keto esters.[20a] Surprisingly, in our investigations this complex prepared according to a known protocol[24] was completely ineffective in MeOH and AcOEt (runs 14 and 15).

The parent Ru[(*R*)-TolBINAP]Cl_2·Et_3N complex exhibited a similar activity and *syn*-selectivity (run 16, compare with run 7). The solubility of this precatalyst in MeOH was better than the analogous BINAP complex. Finally, we found that addition of 1 mol equiv. of AcONa during the preparation (see above) gave a

solid mixture of Ru[(*R*)-Tol-BINAP]Cl_2·AcONa (the real composition was not determined) which performed well (run 17).

Some complications were observed during our attempts to increase the substrate to catalyst ratio. Thus, additional products of unidentified structure were observed when the hydrogenation was carried in MeOH. Best results were obtained with Ru[(*R*)-Tol-BINAP]Cl_2·AcONa as a catalyst in EtOH. At 50 °C and 100 bar H_2 initial pressure it was possible to run the hydrogenation procedure at a substrate to catalyst ratio of 1000:1 with complete conversion within 4 h. The product **2b** was obtained with at least 99% *de* and *ca*. 98% chemical purity.

Conclusions

We have developed a convenient method for the preparation of ethyl (5*S*)-5,6-isopropylidenedioxy-3-oxohexanoate, a key intermediate in the synthesis of pharmaceutically statins. Its catalytic hydrogenation has been studied for the first time using a broad array of achiral and chiral Rh(I) and Ru(II) complexes with diphosphines as ancillary ligands. Interestingly, the influence of the chiral side chain in the β-keto ester on the stereochemical course of the hydrogenation is rather small. The activity of Rh(I) and Ru(II) complexes with BINAP as ligand was opposite in dependence on the polarity of the solvent. Moreover, the ligand of a certain chirality induces opposite chirality in the newly formed centre when coordinated to Rh or Ru. The same effect was found earlier with α-acylamino acrylic acids as substrates.[23] No diastereoselection was observed with Rh or Ru catalysts based on BINAP. We found that Ru[(*R*)-Tol-BINAP]-Cl_2·AcONa is a highly efficient catalysts for the production of *syn*-(5*S*)-5,6-isopropylidenedioxy-3-hydroxyhexanoate at a preparative substrate/catalyst ratio of 1000:1. In a subsequent publication we will describe the application of *syn*-**2b** for the synthesis of statins.[25]

Experimental Section

General Methods

MeOH and AcOEt (packed under N_2) for hydrogenation were purchased from Aldrich. CH_2Cl_2 was distilled over CaH_2, THF and Et_2O were distilled over Na-Ph_2CO under Ar. Other commercial reagents were used without additional purification. NMR spectra were recorded with a Bruker ARX 400 spectrometer in $CDCl_3$. Chemical shifts (δ, in ppm) are given for ^1H relative to TMS as internal standard and for ^{13}C relative to the residual $CDCl_3$ peak (77.36 ppm). Spin-spin coupling constants (*J*) are given in Hz. The optical rotation was measured on a "gyromat-HP" instrument (Fa. Dr. Kernchen).

Dimethyl (*S*)-Malate (3)

Acetyl chloride (10 mL) was added to MeOH (100 mL). After 30 min (*S*)-malic acid (50 g, 0.373 mol) followed by $HC(OMe)_3$ (80 mL, 77.6 g, 0.73 mol) were added to this solution. The resultant solution was stirred at room temperature overnight. The volatiles were evaporated and the residue was distilled in vacuum to afford **3**; yield: 56.2 g (92.9%); bp 66–68 °C/0.03 mbar. NMR spectra were in accordance to those recorded with a commercial sample.

Methyl (3*S*)-3,4-(Isopropylidenedioxy)butanoate (1)

To a solution of dimethyl (*S*)-malate (**3**) (113.4 g, 0.70 mol) in THF (300 mL) $NaBH_4$ (0.28 g, 0.0074 mol) was added in one portion followed by slow addition of BH_3·Me_2S complex (68 mL, 54.5 g, 0.72 mol) at room temperature with stirring. During the addition the evolution of gaseous products took place. The rate of gas evolution could be controlled by the rate of the addition of the BH_3·Me_2S complex. When the addition was finished the reaction mixture was kept at ambient temperature for 3 h. Then MeOH (285 mL) was added and the resultant solution was left overnight at room temperature. The volatiles were evaporated and the viscous residue was dried for 6 h in high vacuum. The residue was mixed with acetone (300 mL), $Me_2C(OMe)_2$ (96.3 mL, 81.6 g, 0.78 mol) and *p*-TsOH·H_2O (4 g, 0.021 mol). The reaction mixture was left overnight at room temperature with stirring. It was neutralized with solid Na_2CO_3 (4 g). The mixture was stirred for additional 1 h, filtered off and evaporated. The residue was distilled in vacuum (bp 74 °C/6 mbar) affording compound **1**; yield: 90.6 g (74.4%). NMR spectra were in accordance to those obtained with a commercial sample.

General Procedure for Ester Condensation of Acetonide 1 with MeCOO-*t*-Bu

All manipulations before work-up were done under Ar. A 2.5 M hexane solution of BuLi (4.6×n mL, 11.5×n mmol) was added to a solution of $(i\text{-Pr})_2NH$ (1.7×n mL, 12.0×n mmol) in 10 mL of THF at 0 °C with stirring. After 5–10 min the resulted solution was cooled down to −70 °C (EtOH/CO_2 bath) and CH_3COO-*t*-Bu (1.6×n mL, 11.9×n mmol) was added. The mixture was stirred at this temperature for additional 30 min. Then neat acetonide **1** (2.0 g, 11.5 mmol) was added dropwise (5–10 min). When addition was complete the mixture was removed from the bath and stirred at ambient environment for 1 h. The reaction was quenched by addition of saturated NH_4Cl solution (5×n mL) and the product was extracted with AcOEt. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was analyzed by NMR. The results of runs 1–4 are presented in Table 1. Analytical samples of **2a** and **4** were isolated from run 2 by column chromatography on SiO_2 (AcOEt-hexane, 1:4), compound **4** being the less polar compound.

(5*S*)-*tert*-Butyl 5,6-(isopropylidenedioxy)-3-oxohexanoate (2a): Colourless liquid; bp 102–103 °C/0.06 mbar. During distillation significant decomposition was observed. An analytical sample was obtained by column chromatography on SiO_2 (hexane-AcOEt, 9:1). $[\alpha]_D^{23}$: 6.8 (*c* 1, EtOH). The optical purity was confirmed by GC on a 25 m Lipodex column (65 °C) with a racemic sample as reference.

About 10% of the relevant enol form was present in $CDCl_3$. *Keto form:* ^{1}H NMR: δ = 1.35 (s, 3H, Me), 1.41 (s, 3H, Me), 1.47 (s, 9H, CMe_3), 2.74 (dd, 1H, *J* = 17.1 and 7.0 Hz, 4-C*Ha*H_b), 2.99 (dd, 1H, *J* = 17.1 and 5.9 Hz, 4-CH_a*Hb*), 3.38 (d, 1H, *J* = 15.5 Hz, 2-C*Ha*H_b), 3.42 (d, 1H, *J* = 15.5 Hz, 2-CH_a*Hb*), 3.57 (dd, 1H, *J* = 8.3 and 6.6 Hz, 6-C*Ha*H_b), 4.19 (dd, 1H, *J* = 8.3 and 6.1 Hz, 6-CH_a*Hb*), 4.43–4.51 (m, 1H, 5-CH); ^{13}C NMR: δ = 25.72 (Me), 27.15 (Me), 28.24 (C*Me3*), 47.38 (4-CH_2), 51.29 (2-CH_2), 69.60 (6-CH_2), 71.73 (5-CH), 82.47 (*C*Me_3), 109.24 (O*C*Me_2O), 166.39 (COO), 201.46 (C=O). *Enol form:* ^{1}H NMR: δ = 1.36 (s, 3H, Me), 1.43 (s, 3H, Me), 1.49 (s, 9H, CMe_3), 2.36 (dd, 1H, *J* = 14.2 and 6.4 Hz, 4-C*Ha*H_b), 2.51 (dd, 1H, *J* = 14.2 and 6.6 Hz, 4-CH_a*Hb*), 3.66 (dd, 1H, *J* = 8.3 and 6.5 Hz, 6-C*Ha*H_b), 4.10 (dd, 1H, *J* = 8.3 and 5.9 Hz, 6-CH_a*Hb*), 4.34–4.42 (m, 1H, 5-CH), 4.96 (s, 1H, C=CH), 12.26 (s, 1H, OH); ^{13}C NMR: δ = 25.88 (Me), 27.24 (Me), 28.56 (C*Me3*), 39.99 (4-CH_2), 69.44 (6-CH_2), 73.23 (5-CH), 81.32 (*C*Me_3), 92.57 (C=*CH*), 109.51 (O*C*Me_2O), 172.68 (COO), 173.63 (HOC=); anal. calcd. for $C_{13}H_{22}O_5$: C 60.45, H 8.58; found: C 60.35, H 8.64.

Di-*tert*-butyl 3-hydroxy-3-(2,3-isopropylidenedioxypropyl)glutarate (4): Very viscous colourless oil contaminated with AcOEt which was not possible to remove in vacuum. ^{1}H NMR: δ = 1.35 (s, 3H, Me), 1.38 (s, 3H, Me), 1.46 (s, 9H, C*Me3*), 1.47 (s, 9H, C*Me3*), 1.87 (dd, 1H, *J* = 14.5 and 4.4 Hz, 4-C*Ha*H_b), 2.02 (dd, 1H, *J* = 14.5 and 7.9 Hz, 4-CH_a*Hb*), 2.64 (s, 2H, 2-CH_2), 2.65 (s, 2H, 3′-CH_2), 3.51 (dd, 1H, *J* = 8.1 and 8.1 Hz, 6-C*Ha*H_b), 4.10 (dd, 1H, *J* = 8.1 and 5.9 Hz, 6-CH_a*Hb*), 4.32–4.40 (m, 1H, 5-CH), position of OH is not indicated; ^{13}C NMR ($CDCl_3$): δ = 26.14 ((Me), 27.09 (Me), 28.31 (C*Me3*), 42.80 (4-CH_2), 43.82 (2-CH_2), 45.42 (3′-CH_2), 70.38 (6-CH_2), 71.22 (3-C), 72.51 (5-CH), 81.23 (*C*Me_3), 81.37 (*C*Me_3), 108.91 (*C*Me_2), 171.32 (COO), 171.35 (COO).

(3*S*)-3,4-(Isopropylidenedioxy)butanal (5)[13]

All manipulations before work-up were done under Ar. A solution of acetonide **1** (10 g, 0.057 mol) in Et_2O (100 mL) was cooled down to −70 °C and a 1.5 M solution of DIBALH in toluene (8.4 mL, 0.0126 mol) was added over a period of 5 min with stirring. The resultant clear solution was stirred at this temperature for additional 10 min, then it was quenched with MeOH (5 mL). The cooling bath was removed and the solution was stirred at ambient conditions for 2–3 h. The precipitate formed was filtered off and washed with Et_2O. The filtrate was concentrated and the residue was distilled in vacuum to afford aldehyde **5**; yield: 6.48 g (78.3%); bp 73–74 °C/15 mbar. NMR spectra were similar to those reported in the literature.

Reaction of Aldehyde 5 with N_2CH_2COOEt[14]

To a mixture of $SnCl_2$ (0.13 g, 0.67 mmol) and N_2CH_2COOEt (0.8 g, 7.0 mmol) in CH_2Cl_2 (15 mL) the aldehyde **5** (1.0 g, 6.94 mmol) was slowly added. When the addition was completed the reaction mixture was stirred at room temperature for 2 h and concentrated under vacuum. The residue was diluted with AcOEt. The resultant mixture was filtered through a pad of SiO_2. The SiO_2 was washed with AcOEt. The volatiles were evaporated and the residue was purified by column chromatography on SiO_2 (hexane-AcOEt, 4:1) affording keto ester **2b**; yield: 0.76 g (47.6%), contaminated with side products of undetermined structure. vacuum distillation did not give complete purification. Characterization of pure keto ester **2b** is given below.

Reformatski Reaction of Aldehyde 5

Zn promotion: Zinc dust was activated by washing with dilute HCl solution (conc. HCl-H_2O, 9:1). The resultant powder was washed successively with water (till neutral washings), acetone, Et_2O and finally dried under high vacuum. A solution of aldehyde **5** (1.0 g, 6.94 mmol) and $BrCH_2COOEt$ (0.8 mL, 1.21 g, 7.23 mmol) in benzene (5 mL) was added to a stirred and vigorously refluxed mixture of benzene (5 mL), activated Zn dust (0.55 g, 8.41 mmol) and several crystals of I_2 at such a rate as to maintain the boiling of benzene. After the addition was complete the resultant mixture was refluxed for additional 10 min. After cooling saturated NH_4Cl solution and water were added. The organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated to afford a transparent liquid; yield: 1.15 g (71.4%). Analysis of the NMR spectra revealed a *ca.* 1:1 ratio of *syn*-**6** and *anti*-**6** alcohols. Characterization of these products is given below.

Sn promotion.[16] Commercial $SnCl_2$ was dried under vacuum at 120 °C for 4 h. To a solution of $SnCl_2$ (1.37 g, 7.23 mmol) in THF (5 mL) was added by portions LiALH (0.14 g, 3.69 mmol) at 0 °C with stirring. When the addition was complete the mixture was stirred for additional 10 min at room temperature. To this mixture a solution of aldehyde **5** (1 g, 6.94 mmol) and $BrCH_2COOEt$ (0.8 mL, 1.21 g, 7.23 mmol) in THF (5 mL) was added with stirring. The resultant mixture was stirred at room temperature for 4 h and quenched by the addition of concentrated NH_4Cl solution followed by water. The product was extracted with AcOEt. The thick precipitate caused difficulties during extraction. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated affording a liquid; yield: 0.66 g (41%). Analysis of NMR spectra revealed a *ca.* 1:2 ratio of *syn*-**6** and *anti*-**6** alcohol. Characterization of these products is given below.

(3*S*)-3,4-(Isopropylidenedioxy)butanoic acid (7)

Methyl (3*S*)-3,4-(isopropylidenedioxy)butanoate (**1**) (50 g, 0.287 mol) was added to an ice-cooled aqueous 2 M NaOH solution (287 mL, 0.574 mol) with stirring . The bath was removed and the resultant mixture was stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the organic extracts were discarded. The water layer was mixed with Et_2O (100 mL) and cooled in an ice bath. To this mixture an aqueous $NaHSO_4$ solution (2 N, 300 mL) was added. The mixture was vigorously stirred for 15 min. The organic layer was separated and the water layer was additionally extracted with AcOEt (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was dried under high vacuum to afford the liquid acid **7**; yield: 36 g (78.3%). According to its NMR spectra the product **7** had *ca.* 95% purity. It was used further without additional purification. ^{1}H NMR: δ = 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.58 (1H, dd, *J* = 16.2 and 6.7 Hz, 2-C*Ha*H_b), 2.75 (1H, dd, *J* = 16.2 and 6.7 Hz, 2-CH_a*Hb*), 3.68 (1H, dd, *J* = 8.5 and 6 Hz, 4-C*Ha*H_b), 4.17 (dd, *J* = 8.5 and 6 Hz, 4-CH_a*Hb*), 4.45–4.53 (1H, m, 3-CH), 11 (1H, br. s, COOH); ^{13}C NMR: δ = 25.8 (CH_3), 27.2

(CH_3), 39.2 (CH_2), 69.4 (CH_2), 72.1 (CH), 109.9 (C), 176.7 (COO).

General Procedure for Reaction of Imidazolide 8 with MEMAH Derivatives

The acid **7** (0.9 g, 5.62 mmol) was reacted with *N,N'*-carbonyldiimidazole (CDI) (1 g, 6.17 mmol) in THF (5 mL) at room temperature for 2 h with stirring. To the resultant solution the corresponding MEMAH derivative was added. Solids were added directly and solutions (in 5 mL THF) were introduced by syringe. The resultant reaction mixture was stirred at room temperature overnight, evaporated and the residue dissolved in AcOEt. The organic layer was separated and washed successively with aqueous $NaHSO_4$ solution (2 M), saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated. The residue was analyzed by NMR. Other conditions and results are presented in Table 2.

Preparative Synthesis of Ethyl (5*S*)-5,6-(Isopropylidenedioxy)-3-oxohexanoate (2b)

A mixture of monoethyl malonate (49.0 g, 0.371 mol) and commercial Mg powder with particle size <0.1 mm (6.0 g, 0.248 mol) in THF (200 mL) was refluxed with stirring for 4 h to produce *in situ* $Mg(OOCCH_2COOEt)_2$. In another flask, to a solution of the acid **7** (25.8 g, 0.161 mol) in THF (100 mL) was added by portions solid CDI (28.8 g, 0.177 mol). The addition was accompanied by gas evolution. After the addition was completed (5–10 min) the mixture was stirred at room temperature for 2 h to produce *in situ* imidazolide **8**. The resulted solution was mixed with the solution of the Mg complex. The residual Mg powder was rinsed with THF (50 mL) and the washings were added to the reaction mixture. The reaction mixture was left with stirring overnight at room temperature. The mixture was evaporated, the residue was dissolved in AcOEt (200 mL) and acidified with aqueous $NaHSO_4$ solution (2 M, 430 mL) with vigorous stirring. The organic layer was separated, washed successively with aqueous $NaHSO_4$ solution (2 N, 2×200 mL), saturated aqueous $NaHCO_3$ solution (3×200 mL), dried over Na_2SO_4 and evaporated. The residue was distilled in vacuum (bp 90–93 °C/0.07 mbar) affording product **2b**; yield: 30.5 g (82.3 %); bp 97–100 °C/0.067 mbar; $[\alpha]_D^{23}$: 6.6 (*c* 1.43, $CHCl_3$), 7.8 (*c* 1 in EtOH), {Ref.[12] $[\alpha]_D^{23}$: −0.9 (*c* 1.43, $CHCl_3$)}.

About 10 % of the relevant enol-form was present in $CDCl_3$. *Keto-form:* ^{1}H NMR: δ = 1.29 (t, 3H, *J* = 7.1 Hz, OCH_2CH3), 1.35 (s, 3H, Me), 1.40 (s, 3H, Me), 2.75 (dd, 1H, *J* = 17.0 and 6.7 Hz, 4-C*Ha*H_b), 2.99 (dd, 1H, *J* = 17.0 and 6.3 Hz, 4-CH_a*Hb*), 3.47 (d, 1H, *J* = 15.9 Hz, 2-C*Ha*H_b), 3.51 (d, 1H, *J* = 15.9 Hz, 2-CH_a*Hb*), 3.57 (dd, 1H, *J* = 8.4 and 6.6 Hz, 6-C*Ha*H_b), 4.15–4.24 (m, 3H, 6-CH_a*Hb* + O*CH2*CH_3), 4.43–4.51 (m, 1H, 5-CH); ^{13}C NMR: δ = 14.31 (CH_2CH_3), 25.65 (Me), 27.07 (Me), 47.36 (4-CH_2), 49.95 (2-CH_2), 61.66 (*CH2*CH_3), 69.48 (6-CH_2), 71.67 (5-CH), 109.22 (*C*Me_2), 167.10 (COO), 200.97 (C=O). *Enol-form:* ^{1}H NMR: δ = 1.29 (t, 3H, *J* = 7.2 Hz, OCH_2CH3), 1.36 (s, 3H, Me), 1.42 (s, 3H, Me), 2.40 (dd, 1H, *J* = 14.3 and 6.4 Hz, 4-C*Ha*H_b), 2.53 (dd, 1H, *J* = 14.3 and 6.9 Hz, 4-CH_a*Hb*), 3.67 (dd, 1H, *J* = 8.3 and 6.3 Hz, 6-C*Ha*H_b), 4.10 (dd, 1H, *J* = 8.3 and 5.9 Hz, 6-CH_a*Hb*), 4.15–4.24 (m, 2H, O*CH2*CH_3), 5.06 (s, 1H, C=CH), 12.11 (s, 1H, OH); ^{13}C NMR: δ = 14.45 (CH_2CH_3), 25.79 (Me), 27.17 (Me), 39.89 (4-CH_2), 60.35 (*C*H_2CH_3), 69.30 (6-CH_2), 73.12 (5-CH), 91.16 (C=*CH*), 109.50 (*C*Me_2), 172.70 (COO), 174.33 (HOC=); anal. calcd. for $C_{11}H_{18}O_5$: C 57.38, H 7.88; found: C 56.85, H 7.87.

General Procedure for Hydrogenation of β-Keto Ester 2b (Catalysts Screening)

A detailed procedure is given in ref.[26] The screening was performed in a 25-mL autoclave charged with β-keto ester **2b** (0.58 g, 2.52 mmol), a precatalyst (0.01 mmol) and a solvent (10 mL). The reaction was monitored by the pressure decrease. When the reaction was completed the solvent was evaporated and the residue was analyzed by NMR. The data are listed in Table 4 and Table 5.

Ethyl (3*R*,5*S*)-5,6-(isopropylidenedioxy)-3-hydroxyhexanoate (*syn*-6): Prepared by hydrogenation with Ru[(*R*)-BINAP]Cl_2 catalyst with the addition of 1.0 mol equiv. of Et_3N (Table 5, run 4). The compound was not additionally purified. ^{1}H NMR: δ = 1.28 (t, 3H, *J* = 7.1 Hz, OCH_2CH3), 1.36 (s, 3H, Me), 1.42 (s, 3H, Me), 1.70–1.84 (m, 2H, 4-CH_2), 2.49 (dd, 1H, *J* = 16.0 and 4.8 Hz, 2-C*Ha*H_b), 2.55 (dd, 1H, *J* = 16.0 and 7.8 Hz, 2-CH_a*Hb*), 3.58 (dd, 1H, *J* = 8.1 and 7.3 Hz, 6-C*Ha*H_b), 4.10 (dd, 1H, *J* = 8.1 and 5.9 Hz, 6-CH_a*Hb*), 4.17 (q, 2H, *J* = 7.1 Hz, O*CH2*CH_3), 4.19–4.27 (m, 1H, 3-CH), 4.27–4.35 (m, 1H, 5-CH), position of OH is not indicated; ^{13}C NMR: δ = 14.38 (OCH_2CH3), 25.92 (Me), 25.09 (Me), 39.95 (4-CH_2), 41.77 (2-CH_2), 60.84 (O*CH2*CH_3), 67.00 (3-CH), 69.72 (6-CH_2), 74.63 (5-CH), 109.43 (*C*Me_2), 172.39 (COO).

Ethyl (3*S*,5*S*)-5,6-(isopropylidenedioxy)-3-hydroxyhexanoate (*anti*-6): Prepared by the hydrogenation with Ru[(*S*)-BINAP]Cl_2 catalyst with the addition of 1.0 mol equiv. of Et_3N (Table 5, run 2). The compound was not additionally purified. ^{1}H NMR: δ = 1.28 (t, 3H, *J* = 7.1 Hz, OCH_2CH3), 1.34 (s, 3H, Me), 1.41 (s, 3H, Me), 1.70–1.75 (m, 2H, 4-CH_2), 2.47 (dd, 1H, *J* = 16.2 and 8.5 Hz, 2-C*Ha*H_b), 2.55 (dd, 1H, *J* = 16.2 and 3.9 Hz, 2-CH_a*Hb*), 3.57 (dd, 1H, *J* = 8.1 and 7.5 Hz, 6-C*Ha*H_b), 4.10 (dd, 1H, *J* = 8.1 and 5.9 Hz, 6-CH_a*Hb*), 4.17 (q, 2H, *J* = 7.1 Hz, O*CH2*CH_3), 4.19–4.28 (m, 1H, 3-CH), 4.28–4.37 (m, 1H, 5-CH) position of OH is not indicated; ^{13}C NMR: δ = 14.37 (OCH_2CH3), 25.90 (Me), 27.14 (Me), 40.95 (4-CH_2), 41.97 (2-CH_2), 60.90 (O*CH2*CH_3), 65.69 (3-CH), 69.83 (6-CH_2), 73.50 (5-CH), 108.96 (*C*Me_2), 172.74 (COO).

Characterization of Products Obtained by the Hydrogenation under Ru[(*R*)-BINAP]Cl_2 Catalysis without the Addition of a Base (Table 5, run 1)

The hydrogenation product was mixed several times with *n*-hexane and then evaporated. The residue was dried in high vacuum and reacted with *t*-BuMe_2SiCl under the same conditions as given in ref.[4] The resultant product was purified by chromatography on SiO_2 (hexane-AcOEt. 9:1). Compound **11** was eluted first. The raw compounds **10** and **11** were additionally purified under the same conditions.

Ethyl (3*R*,5*S*)-3-*tert*-butyldimethylsilyloxy-5,6-(isopropylidenedioxy)hexanoate (10): Colourless viscous liquid; $[\alpha]_D^{25}$: −22.8 (*c* 1, EtOH); ^{1}H NMR: δ = 0.015 (s, 3H, *Me*Si), 0.032 (s, 3H, *Me*Si), 0.83 (s, 9H, C*Me3*), 1.23 (t, 3H, *J* = 7.1 Hz,

OCH_2*CH3*), 1.31, (s, 3H, Me), 1.35 (s, 3H, Me), 1.69 (ddd, 1H, J=13.9, 5.8 and 5.8 Hz, 4-C*Ha*H_b), 1.85 (ddd, 1H, J= 13.9, 7.2 and 7.2 Hz, 4-CH_a*Hb*), 2.49 (d, 2H, J=6.5 Hz, 2-CH_2), 3.48 (dd, 1H, J=7.9 and 7.9 Hz, 6-C*Ha*H_b), 4.03 (dd, 1H, J=7.9 and 5.9 Hz, 6-CH_a*Hb*), 4.04–4.14 (m, 2H, O*CH2*CH_3), 4.14–4.21 (m, 1H, 3-CH), 4.21–4.31 (m, 1H, 5-CH); ^{13}C NMR: δ=−4.62 (*Me*Si), −4.32 (*Me*Si), 14.48 (OCH_2*CH3*), 18.20 (*C*Me_3), 26.01 (C*Me3*), 26.09 (Me), 27.25 (Me), 41.27 (4-CH_2), 42.46 (2-CH_2), 60.63 (O*CH2*CH_3), 67.23 (3-CH), 70.09 (6-CH_2), 72.72 (5-CH), 108.91 (*C*Me_2), 171.79 (COO); MS: m/z=331 [M^+−Me], 231 [M^+−(*t*-BuMe_2Si)]; anal. calcd. for $C_{17}H_{34}O_5Si$: C 58.92, H 9.89; found: C 59.95, H 10.03.

Ethyl (3*R*,5*S*)-6-*tert*-butyldimethylsilyloxy-3,5-(isopropylidenedioxy)hyhexanoate (11): Colourless viscous liquid; $[\alpha]_D^{23}$: −4.7 (*c* 1, EtOH); ^{1}H NMR: δ=0.012 (s, 3H, *Me*Si), 0.016 (s, 3H, *Me*Si), 0.85 (s, 9H, C*Me3*), 1.14 (ddd, 1H, J= 12.7, 11.7 and 11.7 Hz, 4-C*Ha*H_b), 1.21 (t, 3H, J=7.1 Hz, OCH_2*CH3*), 1.32, (s, 3H, Me), 1.41 (s, 3H, Me), 1.63 (ddd, 1H, J=12.7, 2.5 and 2.5 Hz, 4-CH_a*Hb*), 2.35 (dd, 1H, J= 15.3 and 5.8 Hz, 2-C*Ha*H_b), 2.49 (dd, 1H, J=15.3 and 7.2 Hz, 2-CH_a*Hb*), 3.44 (dd, 1H, J=10.3 and 5.9 Hz, 6-C*Ha*H_b), 3.62 (dd, 1H, J=10.3 and 5.2 Hz, 6-CH_a*Hb*), 3.85–3.94 (m, 1H, 3-CH), 4.04–4.17 (m, 2H, O*CH2*CH_3), 4.24–4.33 (m, 1H, 5-CH). ^{13}C NMR: δ=−5.02 (*Me*Si), −4.92 (*Me*Si), 14.48 (OCH_2*CH3*), 18.59 (*C*Me_3), 19.96 (Me), 26.15 (C*Me3*), 30.17 (Me), 33.61 (4-CH_2), 41.90 (2-CH_2), 60.66 (O*CH2*CH_3), 66.11 (3-CH), 67.08 (6-CH_2), 69.96 (5-CH), 98.95 (*C*Me_2), 171.15 (COO); MS: m/z=331 [M^+−Me], 231 [M^+−(*t*-BuMe_2Si)]; anal. calcd. for $C_{17}H_{34}O_5Si$: C 58.92, H 9.89; found: C 59.76, H 10.01.

Diastereoselective Hydrogenation of β-Keto Ester 2b to Hydroxy Ester *syn*-6 in a Preparative Scale

Catalyst preparation: A stirred mixure of (*R*)-Tol-BINAP (200 mg, 0.295 mmol), $[Ru(C_6H_6)Cl_2]_2$ (73.6 mg, 0.147 mmol), AcONa (24.2 mg, 0.295 mmol) and DMF (2 mL) was kept at 100 °C (in a preheated oil bath) for 15 min under Ar. The volatiles were evaporated and the residue was dried in high vacuum at 50 °C for 1 h. The solid material was used as a catalyst for the hydrogenation without further purification and characterization.

Hydrogenation: The catalyst (9.4 mg, ca. 0.01 mmol) and β-keto ester 2b (2.4 g, 10.4 mmol) were placed in a 50-mL autoclave. The autoclave was sealed and air was removed by three vacuum-Ar cycles. Absolute oxygen-free EtOH (20 mL) was added and the mixture was stirred under 100 bar initial H_2 pressure at 50 °C. The consumption of H_2 was followed by the decrease of the pressure. After *ca.* 4 h the consumption of H_2 ceased. The autoclave was opened, the mixture was evaporated and the residue dried in high vacuum. The conversion and the yield of *syn*-**6** were quantitative. NMR spectra were identical to the data reported above. The product was contaminated with *ca.* 2% of impurities of unknown structure.

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