DOI: 10.1002/ejoc.200600849

Synthesis of the Chiral Side Chain of Statins – Lactone versus Lactol Pathway[‡]

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Keywords: Drug design / Lactones / Alcohols / Synthetic methods

4-*O*-Protected (4*R*,6*S*)-4-hydroxy-6-(hydroxymethyl)tetrahydropyran-2-ones (**3**) derived from enantiomerically pure (3*R*,5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)hexanoates (**2**) are frequently considered as pivotal intermediates for the synthesis of pharmacologically important statins. Remarkably, up to now no proof for this assumption can be derived from the literature. Our study revealed that only silyl-type protecting groups can be successfully employed for 3-*O*-protection of initial ethyl (3*R*,5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)hexanoate (**1**). After cyclization, hydroxy lactone **3b** was transformed into tosylate **5b** and successively into iodide **6b**. The latter was converted into phosphonate **9b**. All stereochemical assignments and the diastereomerical purity of the intermediates were confirmed by an X-ray structural analysis of tosylate **5b**. Surprisingly, neither tosylate **5b** nor iodide **6b** could be converted into corresponding nitrile **7b** which is the key intermediate on the way to atorvastatin. Phosphonate **9b** and aldehyde **4b** are nearest intermediates to fluvastatin and rosuvastatin lactones. Unfortunately, Wittig–Horner-reaction of phosphonate **9b** under basic conditions was unsuccessful. Finally, it was not possible to oxidize hydroxy tetrahydropyranone **3b** to related aldehyde **4b**. Apparently the main reason for this unexpected behaviour of these compounds consists in the acidity of the hydrogen atoms in the 3-position of the tetrahydropyranone-2-one ring which facilitates the fast elimination of tBuPh$_2$SiOH and further decomposition of the pyranone core. In contrast, the desired transformations could be performed with related lactol **13** in hand. Thus, a successful alternative for the preparation of the side chain of statins was discovered.

Introduction

Statins like atorvastatin, fluvastatin or rosuvastatin (Scheme 1) are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) and became the standard of care for treatment of hypercholesterolemia because of its efficacy, safety and long-term benefits.[1] For instance, atorvastatin calcium was the first totally synthetic HMG-CoA-reductase inhibitor developed and marketed as a single enantiomer. Currently, it ranks as one of the top ten drugs sold in the world. Different pathways exist for the preparation of these compounds.[2]

In a preceding publication we reported the efficient preparation of optically pure ethyl (3*R*,5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)hexanoate (**1**) on a multi gram scale.[3] The potential use of this compound lies in the preparation of precursors of several statins. One crucial problem in the synthetic approach depicted in Scheme 1 is the choice of the protecting group (PG). It must be stable under acidic conditions since lactonization of **2**, which gives rise to **3**, is known to be assisted by acids.[4] Attempts to introduce a benzyl protecting group failed. Only silyl protection was proven to be successful. It can be easily achieved by using commercially available tBuMe$_2$SiCl or tBuPh$_2$SiCl.

Some intermediate compounds represented in Scheme 1 can be found in relevant databases. Thus, cyclization of linear compound **2a** as a ca. 1:1 mixture of C-3 epimers into a diastereomeric mixture of lactones **3a** (60% yield) was for the first time described in ref.[4] Diastereomerically pure crystalline tosylate **5a** was isolated in an overall 28% yield by column chromatography. Later on, the synthesis of compound **2a** with a diastereoselectivity of 60% was achieved in a four step synthesis (ca. 25% yield).[5] Interestingly, the Me- and tBu-esters parent to **2a** failed to give lactone **3a**.[5] Approaches detailed in ref.[4,5] utilize (3*S*)-3,4-(isopropylidenedioxy)butanal as the initial compound which can be prepared from (*S*)-malic acid.[6] Recently, a five step chemo–enzymatic procedure for the preparation of **3a** starting from phloroglucitol (*cis*-1,3,5-cyclohexantriol) with an overall 13% yield was reported.[7] Iodide **6a** was synthesized independently with 50% *de* by iodolactonization of the protected enantioenriched (76% *ee*[8] and 88% *ee*[9]) (*R*)-3-hy-

[‡] Part II of a series of manuscripts dedicated to the synthesis of statins. For part 1, see ref.[3]

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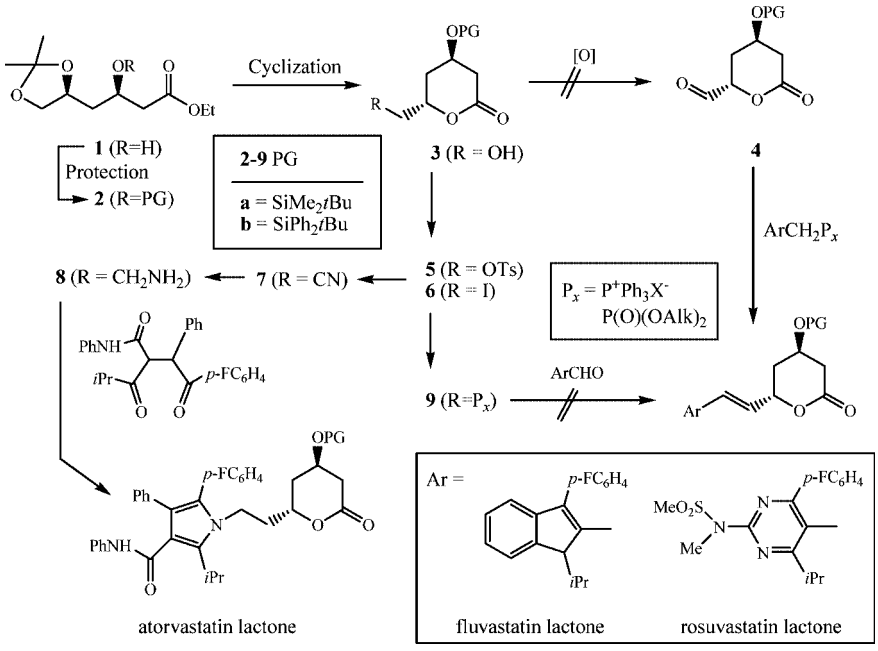


Scheme 1. Possible pathways to the most important statin lactons.

droxy-5-hexenoic acid. The latter was prepared by a chemo–enzymatic approach. It is noteworthy to mention that the chloro analogue of iodide **6a** could be synthesized in a six step sequence (34% overall yield) starting from (*S*)-β-trichloromethyl-β-propiolactone.[10] Protected hydroxy lactone **3b** was synthesized by a 15-step sequence starting from D-glucose and transformed via tosylate **5b** into iodide **6b** with a 17% overall yield.[11] Alternatively, **6b** was prepared with 60% *de* by iodolactonization of protected enantioenriched (*R*)-3-hydroxy-5-hexenoic acid (76% *ee*)[7] which was prepared on the basis of a chemo–enzymatic approach.[12]

While much synthetic work has been focused on the preparation of lactones **3**, **5** and **6**, we were not able to find in the chemical and patent literature the requisite subsequent transformations to targeted statins.[13] In order to clarify this matter, we devised a synthetic program with the aim to test whether the lactone methodology depicted in Scheme 1 could be employed for the synthesis of statins.

Results and Discussions

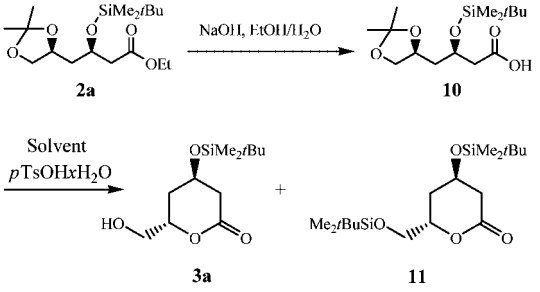
Testing of the Lactone Pathway

Protection of *syn*-β-hydroxy ester **1** with the use of *t*BuMe$_2$SiCl or *t*BuPh$_2$SiCl and imidazole proceeded smoothly and afforded protected compounds **2a**,**b** after chromatographic purification in high yield. Cyclization of compound **2a** (as ca. 1:1 mixture of C-3 epimers) in an 80% AcOH water solution at 100 °C was reported to give after recrystallization 60% of a mixture of diastereoisomers of **3a**.[4] Later on, 51% yield of lactone **3a** after recrystallization was reported starting from **2a** with a 60% *de*.[5] Unfortunately, we were unable to achieve, under these conditions, the transformation of diastereomerically pure **2a** into lactone **3a** with a reasonable yield. In our hands, this procedure gave only 22–35% of raw semi-crystalline lactone **3a**. Recrystallization from hexane according to the recommendations cited above afforded pure lactone **3a** in only ca. 10% yield. Careful control and modification, respectively, of the reaction conditions (preheated bath, concentration and time) did not improve the yield.

To find the reason for these negative results we envisaged a detailed study. Thus, samples of **2a** were heated in 80% AcOH at 100 °C in a preheated bath for 0.5 h, 1 h and 3 h. After subsequent immediate cooling, the volatile substances were evaporated in high vacuum at ambient temperature, and the residues were then analyzed by NMR spectroscopy. The following conclusions could be derived from these experiments: (1) the isopropylidene group is cleaved first, (2) the *t*BuMe$_2$Si group is not stable under these conditions since significant desilylation takes place even after 30 min, (3) the cyclization reaction does not reach completion. Even after 3 h, the signals of the EtO group were still present in the NMR spectrum; meanwhile, decomposition under the formation of unsaturated compounds started. At 60 °C and at 25 °C in 80% AcOH, we also observed desilylation; however, in general, the isopropylidene group was removed faster. Mixtures of AcOH/H$_2$O have also been recommended for the deprotection of *t*BuMe$_2$Si ethers.[14] However, on the basis of our experiments and literature data, we can conclude that it is impossible to achieve high or even moderate yields of lactone **3a** under these conditions.

One of the reasons for this failure might be comparable substitution rates of the ethoxy group by the primary hydroxy group and with the desilylation reaction proceeding in parallel.[15] We tried to remove the ethoxy group first and to then achieve lactonization of acid **10** as depicted

in Scheme 2. Hydrolysis of ester **2a** proceeded under mild conditions to afford acid **10** in a yield of 93%. The progress of lactonization of acid **10** could be followed by TLC. It is interesting to note that acid **10** is surprisingly stable in boiling toluene even after 9 h. Treatment of this acid with 2.5% (w/w) of *p*-TsOH in benzene at room temp. overnight resulted in the full conversion and gave, after aqueous work up, a solid material which after recrystallization afforded 35% of lactone **3a** contaminated with ca. 10% of unidentified material. From the mother liquors, a less polar solid compound with reasonable purity (ca. 90%) could be isolated. The structure of this dominant compound was assigned on the basis of its NMR spectra. Observed chemical shifts and integrals fit well with the structure of bis-silylated lactone **11**. In the more polar solvent Et_2O under similar conditions, transformation of **10** was significantly slower. Complete conversion of acid **10** required 3 d. After aqueous work up and chromatography, 20% of lactone **11** was isolated. Lactone **3a** (24% of crude product) contained ca. 30% of hitherto unidentified compounds.



Scheme 2. Synthesis of lactone **3a**.

Next, we tried to improve the yield of the lactonization of ester **2a** by using another acidic catalyst. We found that heating **2a** in a 90% aqueous dioxane solution in the presence of *p*TsOHxPy (10%w/w) at 100 °C for 30 min gave, after aqueous work up, column chromatography and recrystallization from hexane, an analytically pure sample of lactone **3a** in 47% yield. Interestingly, the properties of lactone **3a** prepared by this methodology differed strikingly with the values reported: compare m.p. 96–98 °C with reported [ref.[5b] 72–74 °C;[16] $[a]_D^{24}$ = +0.33 (*c* 1 or 10, $CDCl_3$); $[a]_D^{20}$ = –7.5 (*c* 1, $CDCl_3$)[5b]]. Surprisingly, for tosylate **5a** we observed a stronger coincidence: compare m.p. 107–109 °C with reported m.p. 106–108 °C[4,5b] and $[a]_D^{22}$ = +8.2 (*c* 1, $CDCl_3$) with reported $[a]_D^{20}$ = +5 (*c* 0.82, $CDCl_3$).[5b] Although we managed to obtain lactone **3a** in moderate yield, this quantity was not sufficient to test the other reactions outlined in Scheme 1.

In contrast to HO protection of the lactone with the *t*BuMe_2Si group, the related *t*BuPh_2Si protecting group was revealed to be much more stable under acidic conditions. Thus, heating of ester **2b** in 80% AcOH (100 °C, 1 h) afforded lactone **3b** in 81% yield after chromatographic purification. Also, *p*TsOHxPy (10%w/w) in 90% dioxane/water (100 °C, 1 h) mediated the cyclization of **2b** to lactone **3b** with 98% yield. Although tosylate **5b** was reported earlier, it was not characterized.[11] Now its structure could be confirmed by X-ray crystallography (Figure 1). The expected *trans* orientation of the substituents in the lactone ring has been established. Thus, the stereochemistry of alcohol **1** has been unambiguously proven.

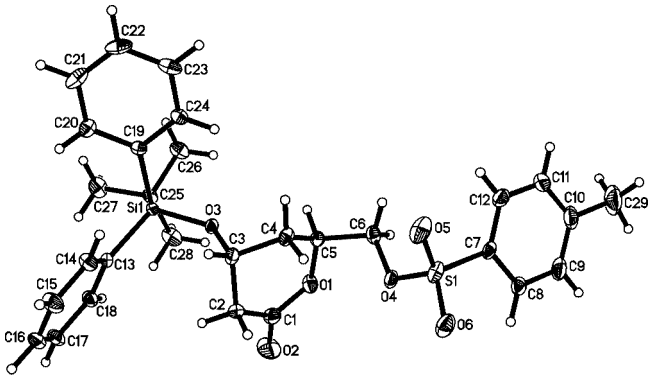


Figure 1. Crystal structure of tosylate **5b**. The thermal ellipsoids correspond to 30% probability.

We found that tosylate **5b** could be prepared from alcohol **1** without chromatographic separation of intermediates **2b** and **3b**. Final purification could be achieved by recrystallization of **5b** from a hexane/AcOEt mixture.

Unfortunately, it was not possible to achieve substitution of the tosyl group by cyanide under a variety of conditions. Thus, heating of **5b** with an excess of NaCN in DMSO (80 °C, 14 h) resulted in the formation of *t*BuPh_2SiOH, which was isolated after aqueous work up in 91% yield. Desilylation was also observed at room temperature in DMSO in the presence of an excess of NaCN. After 14 h, 63% of *t*BuPh_2SiOH was produced. Employment of alternative solvents, like THF or Me_2CO, as well as the usage of an excess of $Me_2C(OH)CN$ in THF in the presence of BuLi or *t*BuOLi under anaerobic conditions was likewise unsuccessful. A literature search revealed at least two other precedents where substitution of a *p*TsO group by cyanide failed.[17] Thus, the problem was overcome by utilization of *p*Cl$C_6H_4SO_2$ and *p*O_2N$C_6H_4SO_2$ as leaving groups and by performing the reaction in DMSO at room temperature.[17a] Unfortunately, for our purpose these methods did not work. Tosylate **2a** bearing the *t*BuMe_2Si protecting group also underwent decomposition in the presence of an excess of NaCN in DMSO at room temperature.

Attempts to introduce phosphorus-containing groups via tosylate **5b** were likewise unsuccessful. Decomposition was observed when $HP(O)(OEt)_2$ was employed in the presence of a base, by refluxing with $P(OMe)_3$ or $P(OEt)_3$ and by heating with PPh_3 at 160 °C.

Nevertheless nucleophilic substitution of the *p*TsO group in compound **5b** is possible. For example, it can be easily transformed into iodide **6b**.[11] In our preparation, iodide **6b** had a melting point equal to the reported value but its specific rotation differed significantly from the reported one: compare $[a]_D^{23}$ = –9.5 (*c* 1, Me_2CO) and reported $[a]_D^{24}$ = –0.89 (*c* 1.08, Me_2CO).[11]

Unfortunately, this transformation also did not open up access to the preparation of desired cyanide **7b**. Thus, reaction of **6b** with an excess of NaCN in DMSO at room temperature resulted in quantitative desilylation. Reaction with neat PPh_3 afforded a complex mixture. Interestingly, we found that iodide **6b** could be transformed into phosphonate **9b** [P_x = $P(O)(OEt)_2$] by refluxing in $P(OEt)_3$ for 4 h with a 59% yield after isolation by column chromatography. No product was formed in boiling $P(OMe)_3$.

As a model reaction for the synthesis of statins, we tested the reaction of phosphonate **9b** with benzaldehyde. Unfortunately, in the presence of bases (DABCO in MeCN heated at 82 °C or BuLi in THF cooled to –78 °C) this reaction resulted in decomposition. The only product isolated after aqueous work up was tBuPh$_2$SiOH.

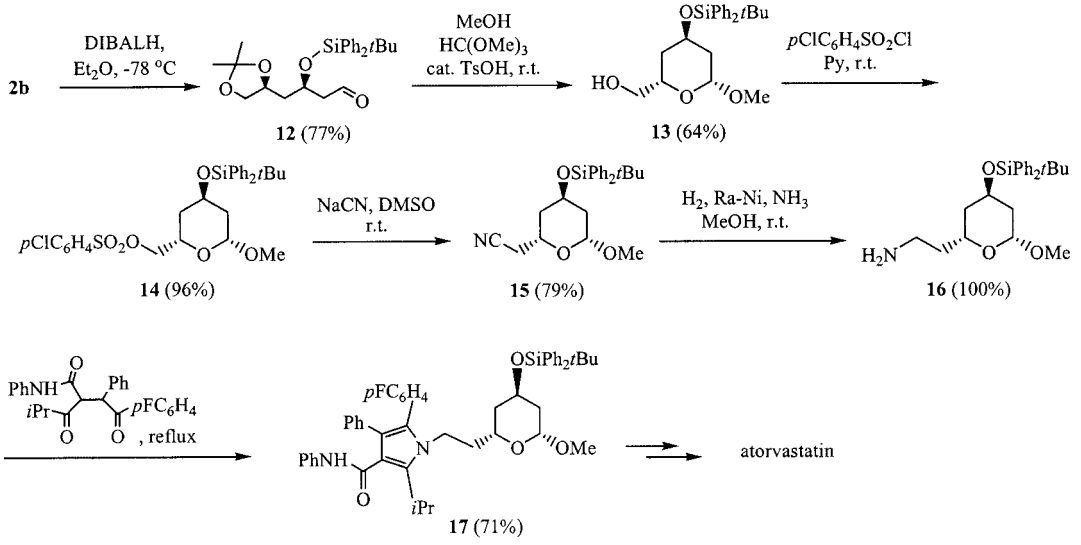
Finally, we tried to oxidize hydroxy lactone **3b** into aldehyde **4b**. Swern oxidation[18] gave a complex mixture of products (6 different CHO signals were observed in the final product). Pfitzner–Moffat[19] oxidation and usage of Cr^{VI} reagents, for example PCC,[20] PDC,[21] CrO_3·2Py,[22] only resulted in the decomposition of the starting material.

In further trials we employed 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in the presence of NaClO as an oxidant. Usually, the TEMPO oxidation is mild and efficient and has been demonstrated on a variety of primary alcohols. In most cases the products were shown to be enantiomerically pure, which demonstrates the absence of any appreciable racemization during the formation of aldehydes.[23] The oxidation of hydroxy lactone **3b** was tested in a two-phase CH_2Cl_2/H_2O mixture, efficient stirring, with 1.1 equiv. of 1.26 M aqueous NaClO in the presence of 0.1 mol-% of TEMPO at 15 °C. After only a 3 min reaction time, a complex mixture of aldehydes, impurities and starting compound **3b** were observed. The stirring of the reaction mixture overnight at 20 °C under the same conditions also resulted in the formation of a complex mixture of aldehydes and gave the corresponding acid in only 7% yield after purification by column chromatography. At temperatures below 10 °C, no conversion was observed. Homogenization of the reaction mixture by exchange of CH_2Cl_2 with acetonitrile gave a mixture of aldehydes and corresponding acid (detected by ^{1}H NMR spectroscopy).

Alternatively, the oxidation of alcohol **3b** was tested in the two-phase system CH_2Cl_2/H_2O with the addition of 2 equiv. of iodine in the presence of a catalytic amount of TEMPO (10 mol-%) and 3 equiv. of a 10% aqueous solution of $NaHCO_3$.[24] Usually, iodine acts as a superior chemoselective reoxidant of TEMPO compared to NaOCl. The reaction mixture was stirred overnight at 20 °C, followed by work up with 10% aq. HCl and 10% aq. $Na_2S_2O_3$. After investigation of the reaction mixture, only traces of desired aldehyde **4b** together with the corresponding acid were observed.

Testing of the Lactol Pathway

As an alternative for the preparation of the functionalized C7 side chain, we investigated whether an intermediate lactole would be more suitable. The sequence starting with ethyl (3*R*,5*S*)-3-hydroxy-5,6-(isopropylidenedioxy)hexanoate (**2b**) is represented in Scheme 3. First, reduction of ester **2b** gave aldehyde **12** in good yield. Upon subsequent cleavage of the acetal, lactol **13** was obtained. Esterification of the primary hydroxy group with 4-chlorotoluenesulfonyl chloride afforded sulfonate **14**, which in turn was transformed with NaCN into nitrile **15**. Raney nickel catalyzed hydrogenation of the latter gave rise to desired amine **16**. In order to show the usefulness of this material for the Paal–Knorr reaction, the amine was condensed with the appropriate functionalized diketone to give atorvastatin lactole **17** in 71% yield. Oxidation and desilylation in order to obtain the free acid of atorvastatin can be conveniently performed as recently suggested.[25]



Scheme 3. Successful synthesis of atovastatin by the lactol pathway.

Conclusions

Although lactones **3**, **5** and **6** were announced in the literature several times to be useful intermediates for the synthesis of statins, our study clearly shows that they are not stable under the conditions required for producing pivotal precursors. Apparently, the main reason is associated with the acidity of the hydrogen atoms in the 3-position of the lactone ring which cause fast elimination of silanols and the formation of unsaturated compounds.

As a more successful alternative, the employment of the related lactol was shown. Relevant intermediates are stable under the conditions of the incorporation of an exocyclic amine group. Even under the conditions of the Paal–Knorr reaction, the protected lactol was not affected. Thus, by this methodology, atorvastatin lactol was obtained in good overall yield which can be converted by known methods into atorvastatin.[25]

Experimental Section

General: Commercial reagents were used without additional purification. NMR spectra were recorded with a Bruker ARX 400 spectrometer. For the description of the NMR spectra of lactones pyran-2-one, numeration of carbon atoms was used. Chemical shifts 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 = 77.36 ppm).[26] Note that in some instances the aromatic carbon atoms are not listed as part of the ^{13}C NMR spectroscopic data. This is due to a poor signal-to-noise ratio and extensive overlapping of peaks. Optical rotations were measured with a "gyromat-HP" instrument (Fa. Dr. Kernchen).

Ethyl (3*R*,5*S*)-3-Hydroxy-5,6-(isopropylidenedioxy)hexanoate (1): Preparation of this compound by hydrogenation of ethyl (5*S*)-5,6-(isopropylidenedioxy)-3-oxohexanoate has been described in ref.[3]

Ethyl (3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5,6-(isopropylidenedioxy)hexanoate (2a): To a stirred solution of alcohol **1** (2.26 g, 9.73 mmol) in DMF (4.5 mL) was added imidazole (1.5 g, 22.0 mmol) followed by *t*BuMe$_2$SiCl (1.7 g, 11.3 mmol). The mixture was stirred at 50 °C for 2 h. After cooling, the mixture was diluted with water, and the product was extracted with AcOEt. The extract was washed thoroughly with brine, dried with Na_2SO_4 and the solvents evaporated. Product **2a** (2.77 g, 82.2%) was isolated by column chromatography on SiO_2 with hexane/AcOEt (9:1).

Ethyl (3*R*,5*S*)-3-*tert*-Butyldiphenylsilyloxy-5,6-(isopropylidenedioxy)hexanoate (2b): A solution of alcohol **1** (4.0 g, 17.2 mmol) and imidazole (2.5 g, 36.70 mmol) in DMF (8 mL) was cooled with water, (10–15 °C) and *t*BuPh$_2$SiCl (5.2 mL, 5.5 g, 20 mmol) was added with stirring. The reaction mixture was stirred at room temp. overnight. The mixture was diluted with water and AcOEt with stirring. The organic layer was separated. The water phase was extracted additionally with AcOEt. The combined organic extracts were washed with brine, dried with Na_2SO_4 and the solvents evaporated. The residue was chromatographed on SiO_2 (35 × 8 cm column, hexane/AcOEt 9:1) to give **2b** (7.63 g, 94.1%) as a very viscous colourless oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 0.92 (t, *J* = 7.1 Hz, 3 H, OCH$_2$*CH$_3$*), 1.15 (s, 9 H, CMe$_3$), 1.23 (s, 3 H, Me), 1.24 (s, 3 H, Me), 1.63–1.74 (m, 1 H, 4-C*H$_a$*H$_b$), 1.77–1.87 (m, 1 H, 4-CH$_a$*H$_b$*), 2.60 (dd, *J* = 15.3 and 5.9 Hz, 1 H, 2-C*H$_a$*H$_b$), 2.66 (dd, *J* = 15.3 and 6.5 Hz, 1 H, 2-CH$_a$*H$_b$*), 3.15 (dd, *J* = 7.7 and 7.7 Hz, 1 H, 6-C*H$_a$*H$_b$), 3.60 (dd, *J* = 7.7 and 6.1 Hz, 1 H, 6-CH$_a$*H$_b$*), 3.84–3.96 (m, 2 H, OC*H$_2$*CH$_3$), 4.11–4.22 (m, 1 H, 3-CH), 4.52–4.62 (m, 1 H, 5-CH), 7.15–7.25 (m, 6 H, ArH), 7.72–7.83 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 14.78 (OCH$_2$*CH$_3$*), 20.12 (*C*Me$_3$), 26.60 (Me), 27.70 (Me), 27.78 (C*Me$_3$*), 41.28 (4-CH$_2$), 42.50 (2-CH$_2$), 60.75 (OC*H$_2$*CH$_3$), 69.31 (3-CH), 70.24 (6-CH$_2$), 73.22 (5-CH), 109.50 (*C*Me$_2$), 128.55 (CH), 128.60 (CH), 130.61 (CH), 130, 64 (CH), 134.81 (C), 134.93 (C), 136.89 (CH), 171.53 (COO) ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, CMe$_3$), 1.19 (t, *J* = 7 Hz, 3 H, OCH$_2$*CH$_3$*), 1.25 (s, 3 H, Me), 1.26 (s, 3 H, Me), 1.65–1.75 (m, 1 H, 4-C*H$_a$*H$_b$), 1.76–1.86 (m, 1 H, 4-CH$_a$*H$_b$*), 2.55 (dd, *J* = 15.2 and 6.3 Hz, 1 H, 2-C*H$_a$*H$_b$), 2.59 (dd, *J* = 15.2 and 6.2 Hz, 1 H, 2-CH$_a$*H$_b$*), 3.26 (dd, *J* = 8 and 8 Hz, 1 H, 6-C*H$_a$*H$_b$), 3.71 (dd, *J* = 8 and 5.9 Hz, 1 H, 6-CH$_a$*H$_b$*), 3.96–4.09 (m, 2 H, OC*H$_2$*CH$_3$), 4.13–4.23 (m, 1 H, 3-CH), 4.26–4.37 (m, 1 H, 5-CH), 7.33–7.47 (m, 6 H, ArH), 7.61–7.73 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.43 (OCH$_2$*CH$_3$*), 19.57 (*C*Me$_3$), 26.03 (Me), 27.11 (Me), 27.23 (C*Me$_3$*), 40.54 (4-CH$_2$), 42.07 (2-CH$_2$), 60.59 (OC*H$_2$*CH$_3$), 68.23 (3-CH), 69.71 (6-CH$_2$), 72.66 (5-CH), 108.92 (*C*Me$_2$), 127.89 (CH), 127.97 (CH), 130.04 (CH), 130,10 (CH), 133.99 (C), 134.03 (C), 136.18 (CH), 171.54 (COO) ppm.

(4*R*,6*S*)-4-*tert*-Butyldimethylsilyloxy-6-(hydroxymethyl)tetrahydropyran-2-one (3a): A mixture of compound **2a** (1.7 g, 4.91 mmol), *p*TsOH*x*H$_2$O (0.17 g), dioxane (6.8 mL) and water (0.68 mL) was heated at 100 °C (preheated bath) for 30 min with stirring. The resulted solution was cooled with water and diluted with AcOEt. The mixture was washed successively with brine, saturated $NaHCO_3$ solution and brine. It was then dried with Na_2SO_4. The solution was concentrated and the residue was chromatographed on a SiO_2 column (AcOEt/hexane 2:1). Fractions containing lactone **3a** were collected, and the solvents were evaporated. The residue was recrystallized from hexane to afford lactone **3a** (0.60 g, 47.0%). M.p. 96–98 °C (Ref.[5b] 72–74 °C). $[\alpha]_D^{24}$ = +0.33 (*c* 1 or 10, $CDCl_3$) {ref.[5b] $[\alpha]_D^{20}$ = –7.5 (*c* 1, $CDCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.064 (s, 3 H, SiMe), 0.071 (s, 3 H, SiMe), 0.87 (s, 9 H, CMe$_3$), 1.73–1.82 (m, 1 H, 5-C*H$_a$*H$_b$), 1.86–1.97 (m, 1 H, 5-CH$_a$*H$_b$*), 2.30 (br. s, 1 H, OH), 2.55–2.61 (m, 2 H, 3-CH$_2$), 3.64 (dd, *J* = 12.5 and 4.8 Hz, 1 H, HOC*H$_a$*H$_b$), 3.89 (dd, *J* = 12.5 and 4.8 Hz, 1 H, HOCH$_a$*H$_b$*), 4.32–4.39 (m, 1 H, 4-CH), 4.73–4.82 (m, 1 H, 6-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.61 (SiMe), –4.57 (SiMe), 18.25 (*C*Me$_3$), 25.98 (C*Me$_3$*), 32.21 (5-CH$_2$), 39.50 (3-CH$_2$), 63.78 (4-CH), 64.98 (HOCH$_2$), 77.15 (6-CH),170.5 (COO) ppm. $C_{12}H_{24}O_4Si$ (260.402): calcd. C 55.35, H 9.29; found C 55.44, H 9.90.

(4*R*,6*S*)-4-*tert*-Butyldiphenylsilyloxy-6-(hydroxymethyl)tetrahydropyran-2-one (3b): *Method A:* A mixture of compound **2b** (7.63 g, 16.6 mmol) and AcOH (80%, 17 mL) was stirred at 100 °C (preheated oil bath) for 1 h. After cooling with cold water, the mixture was diluted with water, and the product was extracted with AcOEt. The extracts were washed thoroughly with saturated $NaHCO_3$ and brine, dried with Na_2SO_4 and the solvents evaporated. The residue was subjected to column chromatography (AcOEt/hexane, 2:1) to give lactone **3b** (5.17 g, 81.1%) as a viscous oil. It was not possible to remove traces of AcOEt even in high vacuum. *Method B:* A mixture of **2b** (1.23 g, 2.6 mmol), *p*TsOHxPy (0.12 g), dioxane (5 mL) and water (0.5 mL) was stirred at 100 °C (preheated oil bath) for 1 h. After cooling with water, the mixture was diluted with AcOEt and washed successively with brine, saturated $NaHCO_3$ and brine. The solution was dried with Na_2SO_4, and the solvents evaporated. The residue was dried in high vacuum to give lactone **3b** (0.98 g, 98%) containing only traces of dioxane and AcOEt. The sample did not require additional chromatographic purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, CMe$_3$), 1.69–1.82 (m,

2 H, 5-CH_2), 2.42 (dd, J = 17.7 and 4.1 Hz, 1 H, 3-CH_aH_b), 2.49–2.62 (m, 2 H, 3-CH_aH_b+OH), 3.60 (dd, J = 12.3 and 4.8 Hz, 1 H, HOCH_aH_b), 3.87 (dd, J = 12.3 and 3.0 Hz, 1 H, HOCH_aH_b), 4.31–4.39 (m, 1 H, 4-CH), 4.86–4.94 (m, 1 H, 6-CH), 7.34–7.49 (m, 6 H, ArH), 7.59–7.66 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.39 (CMe_3), 27.16 (CMe_3), 31.67 (5-CH_2), 39.09 (3-CH_2), 64.72 (4-CH), 64.88 ($HOCH_2$), 77.29 (6-CH), 128.20 (CH), 130.41 (CH), 133.25 (C), 133.38 (C), 135.87 (CH), 135.91 (CH), 170.45 (COO) ppm.

(4*R*,6*S*)-4-*tert*-Butyldimethylsilyloxy-6-(*p*-tosyloxymethyl)tetrahydropyran-2-one (5a): To a cold (ice-water bath) and stirred solution of lactone **3a** (0.27 g, 1.04 mmol) in pyridine (1 mL) was added *p*TsCl (0.23 g, 1.2 mmol) in one portion. After 1 h the bath was removed, and the mixture was stirred overnight at ambient temperature. The mixture was diluted with Et_2O and washed successively with brine, HCl (5%), saturated $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4 and evaporated to give a solid material. The solid was triturated under hexane/Et_2O. The mixture was stored overnight in a refrigerator. The solid material was filtered and dried to give tosylate **5a** (0.31 g, 72.1%). M.p. 107–109 °C (ref.[4,5b] 106–108 °C). $[\alpha]_D^{22}$ = +8.2 (c 1, $CDCl_3$) {ref.[5b] $[\alpha]_D^{20}$ = +5 (c 0.82, $CDCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.047 (s, 3 H, SiMe), 0.054 (s, 3 H, SiMe), 0.84 (s, 9 H, CMe_3), 1.78–1.96 (m, 2 H, 5-CH_2), 2.44 (s, 3 H, MeAr), 2.51–2.56 (m, 2 H, 3-CH_2), 4.14 (dd, J = 11 and 3.9 Hz, 1 H, OCH_aH_b), 4.19 (dd, J = 11 and 3.6 Hz, 1 H, OCH_aH_b), 4.31–4.37 (m, 1 H, 4-CH), 4.80–4.88 (m, 1 H, 6-CH), 7.35 (d, J = 8.1, 2 H, ArH), 7.78 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.67 (SiMe), –4.63 (SiMe), 18.19 (CMe_3), 21.98 (MeAr), 25.92 (CMe_3), 32.34 (5-CH_2), 39.33 (3-CH_2), 63.48 (4-CH), 70.80 (OCH_2), 73.29 (6-CH), 128.31 (CH), 130.31 (CH), 132.62 (C), 145.58 (C), 169.1 (COO) ppm.

(4*R*,6*S*)-4-*tert*-Butyldiphenylsilyloxy-6-(*p*-tosyloxymethyl)tetrahydropyran-2-one (5b): The compound was prepared as described for the preparation of **5a** starting with lactone **3b** (3.82 g, 9.93 mmol), *p*TsCl (2.5 g, 13.1 mmol) and pyridine (10 mL). Aqueous work up and recrystallization of the raw product from hexane/AcOEt (2:1) afforded tosylate **5b** (3.81 g, 71.2%). An additional crop of **5b** (0.39 g, 7.3%) was isolated from the mother liquors. M.p. 124–126 °C. $[\alpha]_D^{24}$ = +11.7 (c 1, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H, CMe_3), 1.66–1.84 (m, 2 H, 5-CH_2), 2.36 (dd, J = 17.6 and 4.0 Hz, 1 H, 3-CH_aH_b), 2.44 (s, 3 H, CH_3), 2.54 (dt, J = 17.6 and 2.2 Hz, 1 H, 3-CH_aH_b), 4.12 (dd, J = 10.9 and 4.0 Hz, 1 H, O-CH_aH_b), 4.18 (dd, J = 10.9 and 3.8 Hz, 1 H, O-CH_aH_b), 4.33 (s, 1 H, 4-CH), 4.94–5.03 (m, 1 H, 6-CH), 7.30–7.50 (m, 8 H, ArH), 7.56–7.63 (m, 4 H, ArH), 7.78 (d, J = 8.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.37 (MeAr), 21.97 (CH_3), 27.14 (CMe_3), 31.87 (5-CH_2), 38.94 (3-CH_2), 64.43 (4-CH), 70.72 ($HOCH_2$), 73.39 (6-CH), 128.27 (CH), 128.29 (CH), 130.29 (CH), 130.52 (CH), 132.60 (C), 132.99 (C), 133.11 (C), 135.81 (CH), 135.87 (CH), 145.55 (C), 168.95 (COO) ppm. $C_{29}H_{34}O_6SSi$ (538.727): calcd. C 64.65, H 6.36, S 5.95; found C 64.78, H 6.38, S 5.84.

X-ray Crystallographic Study of Tosylate 5b: Data were collected with a STOE-IPDS-diffractometer with the use of graphite-monochromated Mo-K_α radiation. The structure was solved by direct methods (SHELXS-86)[27] and refined by full-matrix least-squares techniques against F^2 (SHELXL-93).[28] XP (BRUKER AXS) was used for structure representation. Space group $P2_1$; monoclinic; a = 9.625(2), b = 10.660(2), c = 13.965(3) Å; β = 93.17(3)°; V = 1430.7(5) Å^3; Z = 2; $\rho_{calcd.}$ = 1.251 g cm^{-3}; 7677 reflections measured; 4441 were independent of symmetry and 3865 were observed [$I > 2\sigma(I)$]; R_1 = 0.030; wR_2 (all data) = 0.062, 334 parameters. CCDC-622927 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(4*R*,6*S*)-4-*tert*-Butyldiphenylsilyloxy-6-(iodomethyl)tetrahydropyran-2-one (6b): Tosylate **5b** (3.44 g, 6.39 mmol) and NaI (9.6 g, 64 mmol) were refluxed in acetone (30 mL) overnight. Acetone was evaporated and the residue was diluted with water. The product was extracted with AcOEt. The combined extracts were washed with brine, dried with Na_2SO_4 and the solvents evaporated. The yellow–brown residue was subjected to column chromatography (SiO_2, hexane/AcOEt 2:1). The isolated material was triturated under hexane to cause crystallization and was left in a refrigerator overnight. The solid product was filtered, washed with cold hexane and dried to give the colourless iodide **6b** (2.51 g, 79.5%). M.p. 77–79 °C (ref.[11] 78–79 °C). $[\alpha]_D^{23}$ = –9.5 (c 1, Me_2CO) {ref.[11] $[\alpha]_D^{24}$ = –0.89 (c 1.08, Me_2CO)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 1.60 (ddd, J = 14, 11.5 and 2.2 Hz, 1 H, 5-CH_aH_b), 2.05 (ddd, J = 14, 6 and 3.4 Hz, 1 H, 5-CH_aH_b), 2.42 (dd, J = 17.7 and 4.1 Hz, 1 H, 3-CH_aH_b), 2.60 (ddd, J = 17.7, 2.4 and 2.4 Hz, 1 H, 3-CH_aH_b), 3.35 (dd, J = 10.7 and 6.1 Hz, 1 H, ICH_aH_b), 3.38 (dd, 10.7 and 5.1 Hz, 1 H, ICH_aH_b), 4.28–4.36 (m, 1 H, 4-CH), 4.69–4.78 (m, 1 H, 6-CH), 7.36–7.50 (m, 6 H, ArH), 7.58–7.67 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.76 (ICH_2), 19.41 (CMe_3), 27.18 (CMe_3), 36.25 (5-CH_2), 38.82 (3-CH_2), 64.52 (4-CH), 74.64 (6-CH), 128.27 (CH), 130.48 (CH), 133.08 (C), 133.21 (C), 135.90 (CH), 169.37 (COO) ppm. $C_{22}H_{27}IO_3Si$ (494.438): calcd. C 53.44, H 5.50, I 26.01; found C 53.94, H 5.22, I 25.67.

(4*R*,6*S*)-4-*tert*-Butyldiphenylsilyloxy-6-(diethoxyphosphonomethyl)-tetrahydropyran-2-one (9b): Iodide **6b** (1.0 g, 2.02 mmol) was refluxed in $P(OEt)_3$ (2.5 mL) for 4 h. After this period no starting compound could be detected by TLC. The mixture was subjected to column chromatography on SiO_2 in AcOEt. The crude product (1.02 g) was purified additionally by column chromatography to afford **9b** (0.6 g, 58.9%) as a colourless viscous material contaminated with AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 9 H, CMe_3), 1.32 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.33 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.61–1.72 (m, 1 H) and 2.03–2.63 (m, 5 H, CH_2 groups of lactone moiety), 4.05–4.21 (m, OCH_2CH$_3$), 4.24–4.32 (m, 1 H, 4-CH), 5.13–5.26 (m, 1 H, 6-CH), 7.35–7.49 (m, 6 H, ArH), 7.59–7.67 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.65 (OCH_2Me), 16.70 (OCH_2Me), 19.37 (CMe_3), 27. 11 (CMe_3), 33.02 (d, $J_{P,C}$ = 140, PCH_2) 36.78 (d, $J_{P,C}$ = 4.8, 5-CH_2), 39.0 (3-CH_2), 62.23 (d, $J_{P,C}$ = 1.9, $POCH_2$), 62.30 (d, $J_{P,C}$ = 1.9, $POCH_2$), 64.56 (4-CH), 71.97 (6-CH), 128.18 (CH), 130.36 (CH), 130.38 (CH), 133.15 (C), 133.27 (C), 135.87 (CH), 135.92 (CH), 169.69 (COO) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.85ppm.

(3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5,6-(isopropylidenedioxy)hexanoic Acid (10): A mixture of compound **2a** (1.84 g, 5.31 mmol), aqueous NaOH (2 N, 5.5 mL, 11 mmol) and EtOH (5 mL) was stirred at ambient temperature overnight. It was diluted with water and extracted with $CHCl_3$. The water solution was mixed with Et_2O, cooled in an ice bath and acidified with aqueous $NaHSO_4$ (2 N, 6 mL) with vigorous stirring. The organic layer was separated and the water layer was additionally extracted with AcOEt. Combined extracts were washed with brine, dried with Na_2SO_4 and the solvents evaporated. The residue was dried in high vacuum to give acid **9** (1.58 g, 93.4%) containing traces of AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.036 (s, 3 H, SiMe), 0.045 (s, 3 H, SiMe), 0.84 (s, 9 H, CMe_3), 1.32 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.72 (ddd, J = 14, 6.3 and 5.2 Hz, 1 H, 4-CH_aH_b), 1.87 (ddd, J = 14, 7.8 and 4.5 Hz, 1 H, 4-CH_aH_b), 2.53 (dd, J = 15.4 and 7 Hz, 1 H, 2-

CH_aH$_b$), 2.59 (dd, J = 15.4 and 5.7 Hz, 1 H, 4-CH$_a$$H_b$), 3.50 (dd, J = 7.9 and 7.4 Hz, 1 H, 6-CH_aH$_b$), 4.04 (dd, J = 7.9 and 5.9 Hz, 1 H, 6-CH$_a$$H_b$), 4.13–4.25 (m, 1 H, 3-CH), 4.22–4.32 (m, 1 H, 5-CH), 11.1 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.64 (SiMe), –4.34 (SiMe), 18.21 (*C*Me$_3$), 26.01 (C*Me$_3$*), 27.22 (Me), 41.14 (4-CH$_2$), 42.10 (6-CH$_2$), 67.04 (3-CH), 70.0 (6-CH$_2$), 72.60 (5-CH), 109.19 (*C*Me$_2$), 177.6 (COO) ppm.

Cyclization of Acid 10: A mixture of acid **10** (0.6 g, 1.88 mmol), *p*TsOHxH$_2$O (15 mg) and benzene (3 mL) was stirred overnight at ambient temperature. An excess of saturated $NaHCO_3$ was added followed by AcOEt. The organic layer was separated and washed with brine and dried with Na_2SO_4. The solvent was evaporated to dryness leaving a solid material which was dissolved in boiling hexane. The solution was cooled and kept in a refrigerator. The precipitate was filtered, washed with hexane and dried to yield lactone **3a** (0.17 g, 34.7%) having ca. 90% purity. Mother liquors were evaporated and the residue was fractionated by column chromatography on SiO_2 with hexane/acetone (4:1). First fraction was collected. Evaporation of the solvents gave a solid material (0.8 g, 11.9%). Main compound (ca. 90% content) was identified as (4*R*,6*S*)-4-*tert*-butyldimethylsilyloxy-6-(*tert*-butyldimethylsilyloxymethyl)tetrahydropyran-2-one (**11**) on the basis of NMR spectra which are given below. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.071 (s, 3 H, SiMe), 0.073 (s, 3 H, SiMe), 0.078 (s, 3 H, SiMe), 0.078 (s, 3 H, SiMe), 0.88 (s, 9 H, CMe$_3$), 0.89 (s, 9 H, CMe$_3$), 1.83–1.96 (m, 2 H, 5-CH$_2$), 2.51–2.63 (m, 2 H, 3-CH$_2$), 3.74 (dd, J = 11 and 3.5 Hz, 1 H, OCH_aH$_b$), 3.83 (dd, J = 11 and 4.7 Hz, 1 H, OCH$_a$$H_b$), 4.34–4.40 (m, 1 H, 4-CH), 4.65–4.73 (m, 1 H, 6-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.10 (SiMe), –5.04 (SiMe), –4.60 (SiMe), –4.56 (SiMe), 18.27 (*C*Me$_3$), 18.56 (*C*Me$_3$), 25.99 (C*Me$_3$*), 26.13 (C*Me$_3$*), 32.99 (5CH$_2$), 39.74 (3-CH$_2$), 63.84 (4-CH), 65.23 (OCH$_2$), 76.53 (6-CH), 170.38 (COO) ppm.

(3*R*,5*S*)-3-*tert*-Butyldiphenylsilyloxy-5,6-(isopropylidenedioxy)hexanal (12): A solution of ester **2b** (3.34 g, 0.0071 mol) in Et$_2$O (15 mL) was cooled to –78 °C and DIBALH in toluene (1.5 M, 5.1 mL, 0.0077 mol) was added within 5 min. The reaction mixture was kept under the same conditions for an additional 10 min. MeOH (10 mL) was then added. The cooling bath was removed and the mixture was stirred at room temp. for 2 h. The precipitate formed was filtered off and washed with Et$_2$O. Combined washings were evaporated and the product (thick oil) was isolated by column chromatography on SiO_2 (hexane/AcOEt 9:1) to give 2.34 g (77.2%) of aldehyde **12**. ^{13}C NMR (100 MHz, C_6D_6): δ = 20.04 (*C*Me$_3$), 26.57 (Me), 27.66 (Me), 27.75 (C*Me$_3$*), 41.45 (4-CH$_2$), 50.81 (2-CH$_2$), 67.94 (3-CH), 70.22 (6-CH$_2$), 72.98 (5-CH), 109.61 (*C*Me$_2$), aromatic C are omitted, 200.60 (CHO) ppm.

(2*R*,4*R*,6*S*)-4-*tert*-Butyldiphenylsilyloxy-2-hydroxymethyl-6-methoxytetrahydropyran (13): Aldehyde **12** (2.12 g, 0.00497 mol) was dissolved in MeOH (5 mL) and HC(OMe)$_3$ (2 mL) were added followed by *p*TsOHxPy (0.2 g). The resultant solution was placed in a hot bath (70–80 °C) and refluxed for 1 h. After cooling, water and a saturated aqueous solution of $NaHCO_3$ were added and the product was extracted with AcOEt. Combined extracts were dried with Na_2SO_4 and the solvents evaporated to dryness. The residue was triturated under hexane to cause crystallization. The mixture was kept in a refrigerator overnight. The solid product was filtered off and dried to give **13** (1.0 g, 50.2%). An additional amount of **13** could be isolated from the mother liquors. These were evaporated, and the residue was dissolved in MeOH (5 mL). *p*TsOH (0.05 g) was added, and the solution was left at room temp. overnight. The product (0.27 g, 13.5%) was isolated after aqueous work up as given above. Analytical sample was prepared by recrystallization from hexane. M.p. 94–95 °C [Ref.[29] 97–98 °C]. $[\alpha]_D^{22}$ = –21.2 (c 4.03, $CHCl_3$) {ref.[29] $[\alpha]_D^{24}$ = –11.2 (c 4.03, $CHCl_3$)} {ref.[30] $[\alpha]_D^{24}$ = –11.3 (c 0.195, $CHCl_3$)}. ^{1}H NMR (400 MHz, C_6D_6): δ = 1.13 (s, 9 H, CMe$_3$), 1.15–1.25 (m, 1 H, H of CH$_2$), 1.29–1.38 (m, 1 H, H of CH$_2$), 1.39–1.48 (m, 1 H, H of CH$_2$), 1.87–1.97 (m, 1 H, H of CH$_2$), 2.18 (br. s, 1 H, OH), 3.35 (s, 3 H, OMe), 3.39 (m, 1 H, OCH_aH$_b$), 3.52–3.62 (m, 1 H, OCH$_a$$H_b$), 4.11–4.22 (m, 2 H, 2-CH, 4-CH), 5.02 (dd, J = 9.5 and 2.2 Hz, 1 H, 6-CH), 7.13–7.25 (m, 6 H, ArH), 7.62–7.70 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = (C_6D_6): 20.01 (*C*Me$_3$), 27.81 (C*Me$_3$*), 35.02 (CH$_2$), 39.75 (CH$_2$), 56.52 (OMe), 66.44 (OCH$_2$), 68.00 (CH), 72.26 (CH), 100.6 (OCHO) ppm, aromatic C are omitted. $C_{23}H_{32}O_4Si$ (400.583): calcd. C 68.96, H 8.05; found C 69.43, H 8.10.

(2*R*,4*R*,6*R*)-4-*tert*-Butyldiphenylsilyloxy-2-cyanomethyl-6-methoxytetrahydropyran (14): A solution of hydroxylactol **8** (8.3 g, 0.0207 mol) in pyridine (15 mL) was cooled with ice water, and *p*ClC$_6$H$_4$SO$_2$Cl (5.51 g, 0.0261 mol) was added with stirring. After 1 h, the bath was removed and the mixture was stirred overnight at room temp. Water (5 mL) was added, and the mixture was stirred for an additional 1 h in order to destroy the excess sulfonyl chloride. The mixture was diluted with water and the product was extracted with AcOEt. The organic extract was washed successively with brine, ca. 2 N aqueous HCl (until the washing solution became acidic) and brine, dried with Na_2SO_4 and evaporated to give **14** (11.5 g, 96.4%) as a slightly yellow thick oil. This was dissolved in DMSO (30 mL). After addition of NaCN (4.1 g, 0.083 mol), the mixture was stirred at room temp. for 4 d. The mixture was diluted with water and was stirred for an additional 1 h to dissolve all of the inorganic material. The nonsoluble residue was filtered off, washed with water and dried in vacuo to give **15** as a brownish solid (8.13 g, 95.8%). For purification it was dissolved in a mixture of toluene/AcOEt (10:1) and filtered through a 2–3 cm layer of SiO_2 to remove coloured impurities. SiO_2 was washed with the same mixture and the combined washings were evaporated. The residue was recrystallized from hexane/EtOH. After keeping in a refrigerator overnight, the crystals were filtered off, washed with hexane and dried in air to give cyanolactole **15** (6.70 g, 78.9% based on starting hydroxylactole **8**) as colourless crystals. M.p. 129–30 °C. $[\alpha]_D^{22}$ = –23.0 (c 1, EtOH). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.80–0.90 (m, 1 H, H of CH$_2$), 1.11 (s, 9 H, CMe$_3$), 1.24–1.38 (m, 2 H, H, H of CH$_2$), 1.70 (dd, J = 16.6 and 5.9 Hz, 1 H, CH_aH$_b$CN), 1.77 (dd, J = 16.6 and 6.5 Hz, 1 H, CH$_a$$H_b$CN), 1.81–1.89 (m, 1 H, H of CH$_2$), 3.34 (s, 3 H, OMe), 3.94–4.04 (m, 2 H, 2-CH, 4-CH), 4.88 (dd, J = 9.4 and 2.1 Hz, 1 H, 6-CH), 7.12–7.27 (m, 6 H, ArH), 7.58–7.67 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 19.96 (*C*Me$_3$), 24.46 (*CH$_2$*CN), 27.77 (C*Me$_3$*), 38.02 (CH$_2$), 39.12 (CH$_2$), 56.56 (OMe), 67.15 (CH), 67.46 (CH), 100.59 (OCHO), 117.56 (CN) ppm, aromatic C are omitted. $C_{24}H_{31}NO_3Si$ (409.593): calcd. C 70.38, H 7.63, N 3.42; found C 70.79, H 7.42, N 3.36.

(2*R*,4*R*,6*R*)-2-(2-Aminoethyl)-4-*tert*-butyldiphenylsilyloxy-6-methoxytetrahydropyran (16): A 30-mL autoclave was charged with cyanolactol **15** (0.52 g, 0.00127 mol), Raney-Ni (0.25 g of wet catalyst washed 3 times with MeOH *prior* to hydrogenation), MeOH (8 mL) and methanolic NH$_3$ solution (7 N, 2 mL). Hydrogenation was carried out at 50 bar initial H_2 pressure and room temp. After 5 h, consumption of H_2 ceased. The catalyst was decanted and washed with MeOH. The methanol washings were evaporated. The residue was dissolved in MeOH, and the solution was filtered through a small pad of Celite to remove particles of the catalyst. Celite was washed with MeOH. The clear solution was evaporated and dried in vacuo to afford aminolactol as a colourless thick oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.089 (s, 9 H, CMe$_3$), 1.2–1.9 (complex multiplets, 8 H, four CH$_2$), 3.51 (s, 3 H, OMe),

4.01–4.15 (m, 1 H, CH), 4.22–4.32 (m, 1 H, CH), 4.83 (dd, J = 9.6 and 1.9 Hz, 1 H, OCHO), 7.33–7.47 (m, 6 H, ArH), 7.59–7.68 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.52 (CMe_3), 37.31 (CMe_3), 38.89 (CH_2), 38.96 (CH_2), 56.44 (OMe), 67.35 (CH), 69.53 (CH), 99.94 (OCHO) ppm, aromatic C are omitted.

Atorvastatin Lactol 17: A mixture of aminolactol **16** (0.48 g, 1.6 mmol), the relevant diketone (0.5 g, 0.00120 mol), pivalic acid (0.1 g, 0.979 mmol) and solvent (*n*-heptane-THF/MePh, 100:50:60, 5 mL) were heated at reflux for 30 h under a slow flow of Ar. After cooling, the mixture was diluted with AcOEt and washed successively with saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4 and the solvents evaporated. Flash chromatography of the solid residue on SiO_2 (hexane/AcOEt 5:1) afforded pyrrole **17** (0.66 g, 71.6%) as a yellowish solid. M.p. 169–171 °C. $[\alpha]_D^{22}$ = –24.4 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = (only characteristic signals): 1.11 (s, 9 H, CMe_3), 1.74 (d, J = 7.1 Hz, 3 H, $CHMe_a$), 1.75 (d, J = 7.1 Hz, 3 H, $CHMe_b$), 3.33 (s, 3 H, OMe), 3.71 (sept., J = 7.1 Hz, 1 H, $CHMe_2$), 3.83–3.98 (m, 2 H, CH_2N), 4.91 (dd, J = 9.6 and 1.9 Hz, 1 H, OCHO) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 19.94 (CMe_3), 22.53 ($CHMe_a$), 22.69 ($CHMe_b$), 27.36 ($CHMe_2$), 27.77 (CMe_3), 38.56 (CH_2), 38.60 (CH_2), 39.54 (CH_2), 42.15 (CH_2), 56.17 (OMe), 68.00 (CH), 68.47 (CH), 100.33 (OCHO) ppm, aromatic C are omitted. $C_{50}H_{55}FN_2O_4Si$ (795.067): calcd. C 75.53, H 6.97, N 3.52; found C 75.62, H 6.93, N 3.10.

Acknowledgments

The authors are grateful to Ratiopharm GmbH (Ulm) for financial support of this work. We appreciate skilled technical assistance by Mrs. K. Mevius.

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Received: June 19, 2006
Published Online: November 6, 2006

