# A New and Efficient Synthesis of the HMG-CoA Reductase Inhibitor Pitavastatin

by **Murat Acemoglu***, **Andre Brodbeck**, **Angel Garcia**, **Dominique Grimler**, **Marc Hassel**, **Bernhard Riss**, and **Robert Schreiber**

*Novartis Pharma AG*, Chemical & Analytical Development, Process Research & Development, CH-4002 Basel
(phone: +41 613245929; fax: +41 613249536; e-mail: murat.acemoglu@novartis.com)

Dedicated to Professor Dr. *Conrad Hans Eugster*

A new synthetic method for the preparation of pitavastatin is described. The approach circumvents various synthetic problems associated with the buildup of the 3,5-dihydroxy-$C_7$ acid side chain of HMG-CoA reductase inhibitors (statins). The use of the $C_6$-amide derivative **5** instead of ester derivatives in the coupling reaction with carboxaldehyde **8** (*Scheme 3*) prevents undesired side reactions, such as eliminations and *retro*-aldol reactions. The method provides synthetic statins, such as pitavastatin, in >99% ee and exceptionally high overall yield. The enantiomerically pure starting material, (3*S*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-5-oxo-5-{[(1*S*)-1-phenylethyl]amino}pentanoic acid (**3c**), is prepared by an improved procedure from 3-{[(*tert*-butyl)dimethylsilyl]oxy}glutaric anhydride (**1**) and (1*S*)-1-phenylethylamine (**2c**; *Scheme 1*).

**Introduction.** – The low-density lipoprotein (LDL) cholesterol-lowering drugs (statins) act by inhibition of the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity, resulting in the inhibition of cholesterol biosynthesis. Their physiological activity is attributed to the presence of the 3,5-dihydroxyheptanoic acid substructure, which resembles the HMG moiety of HMG-CoA. (*R*)-Configuration at C(3) and '*syn*'-configuration of the OH groups were shown to be essential for obtaining high affinities [1]. Since the discovery of the HMG-CoA reductase inhibitory activity of the fungal metabolites compactin [2][3] and mevinolin [4] (=monacolin K, [5]), a series of analogous compounds have been synthesized and introduced into the market. *Fig. 1* shows a selection of compounds marketed as HMG-CoA reductase inhibitors for the treatment of hypercholesterolemia.

In recent years, a large number of enzymatic and microbiological methods have been reported for the synthesis of the enantiomerically pure 3,5-dihydroxyheptanoic acid side chain of statins [6]. Nevertheless, there are also synthetic approaches for the construction of this moiety utilizing enantiomerically pure compounds from the chiral pool as starting materials, and applying highly diastereoselective reactions. One of these approaches is based on desymmetrization of the prochiral 3-{[(*tert*-butyl)dimethylsilyl]oxy}pentanedioic anhydride (**1**) with various, chiral nucleophiles. In their pioneering work, *Heathcock* and co-workers have reported two methods for the diastereoselective ring-opening reaction of anhydride **1** (*Scheme 1*): with (1*R*)-1-phenylethanol (**2a**) as nucleophile in the presence of $Et_3N$ and *N*,*N*-dimethylpyridine-4-

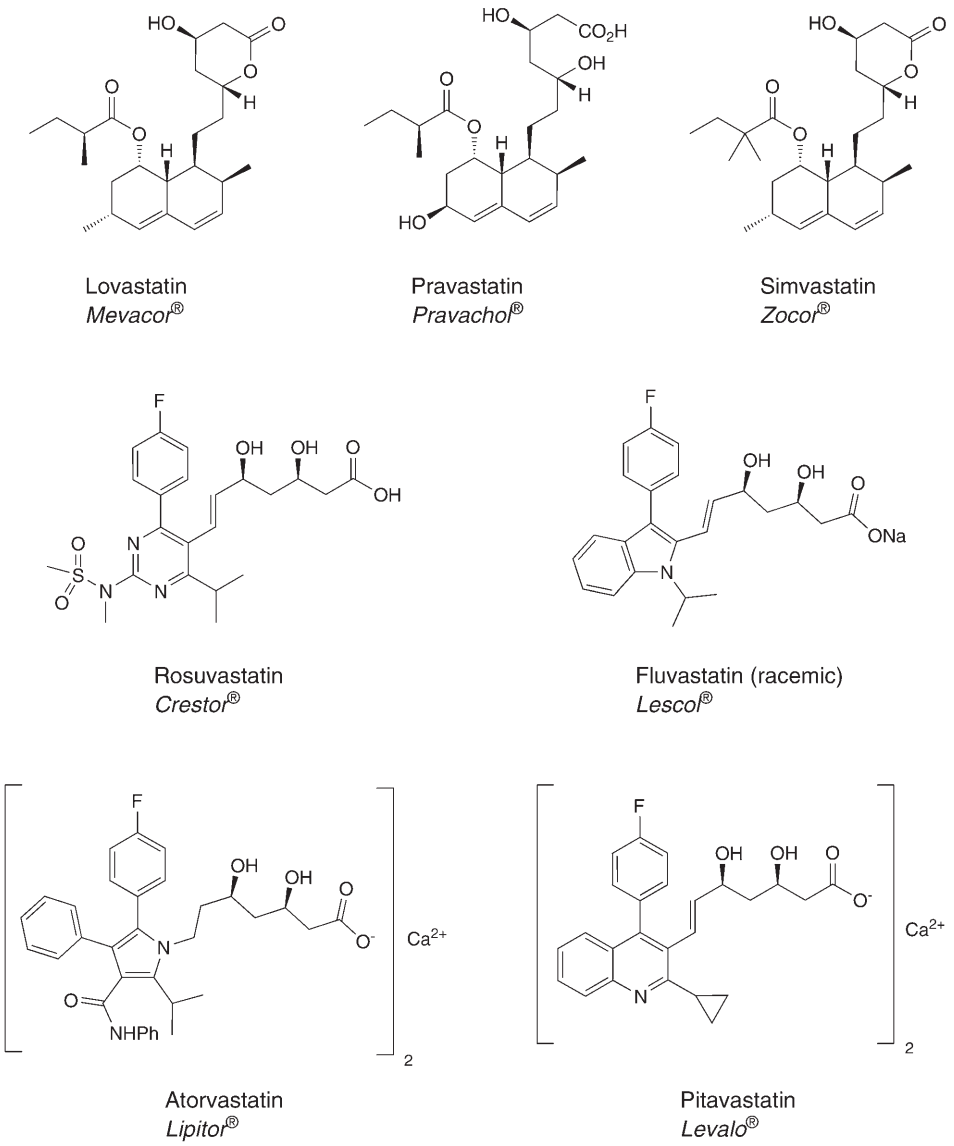



Fig. 1. *A selection of marketed HMG-CoA reductase inhibitors*

amine (DMAP) at $-30°$, a ratio of 8:1 was obtained for **3a**/epi-**3a** in 70% yield [7]. The ratio of diastereoisomers was improved to 15:1 by using only DMAP as base at $-40°$. With (1*R*)-1-(1′-naphthyl)ethanol as nucleophile in the presence of DMAP in $CH_2Cl_2$ as solvent, a mixture of epimers **3b**/epi-**3b** in a ratio of up to 50:1 was obtained in 92% yield [8] (*Scheme 1*). These compounds have been demonstrated to be useful intermediates for the synthesis of stereoisomeric HMG-CoA reductase inhibitors in

*Scheme 1*

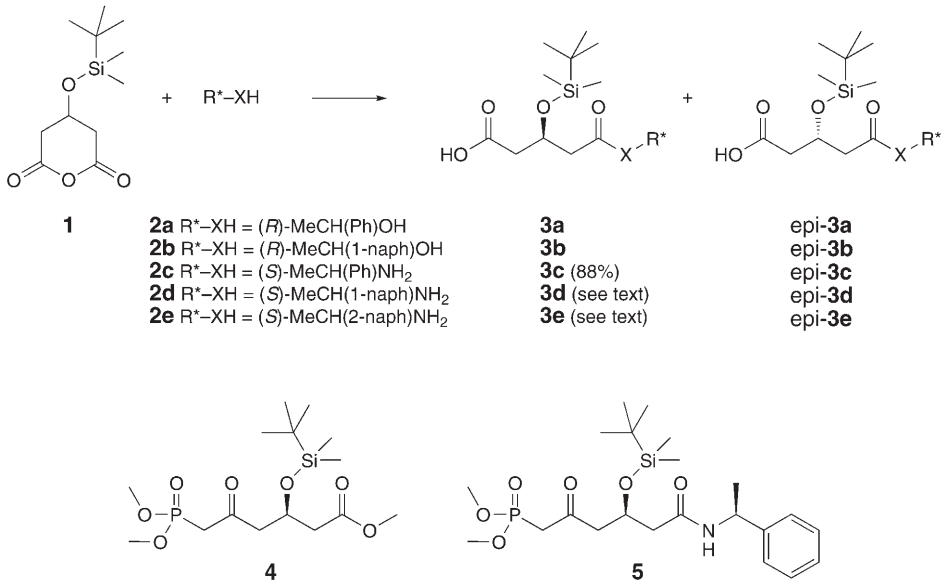



Fig. 2. *β-Keto phosphonate intermediates used in the published synthesis* [9] (compound **4**) *and in this work* (compound **5**)

multigram quantities [7][8]. However, for large scale synthesis, these methods turned out to have several disadvantages: the enantiomerically pure alcohols were both expensive and not readily available in bulk quantities. In addition, *retro*-aldol reactions and *β*-elimination of the silyloxy group were observed as side reactions during functionalization of these intermediates, *e.g.*, during formation of phosphonic acid ester derivatives, such as compound **4** (*Fig. 2*) [8]. From a practical point of view, these methods remained to be expensive and very sensitive to reaction conditions. Diastereoselective opening of anhydride **1** with enantiomerically pure (1*S*)-1-phenylethylamine (**2c**) was introduced by *Karanewsky* and co-workers [9] as a practical alternative (*Scheme 1*). The corresponding product **3c** was isolated as enantiomerically pure, crystalline diastereoisomer in 72% yield, although the differentiation of the enantiotopic CO groups in the ring-opening step was moderate, and the epimers **3c**/epi-**3c** were formed in a ratio of 79:21. Since both (1*R*)- and (1*S*)-enantiomers of 1-phenylethylamine are commercially available on large scale at reasonable prices, the method of *Karanewsky* and co-workers [9] represents an interesting approach towards an industrial-scale synthesis of the enantiomerically pure side chains of statins. Among other methods reported for the asymmetric synthesis of the side-chain moieties of statins were the application of a highly diastereoselective hetero-*Diels–Alder* reaction [10], of diastereoselective aldol reactions with (–)-(1*S*)-2-hydroxy-1,2,2-triphenylethyl acetate ((*S*)-HYTRA) [11], and of the *Blaise* reaction [12]. Finally, the synthesis of fluorinated analogues have recently been reported by *Ramachandran* and co-workers [13].

Pitavastatin is a powerful statin comprising a 3,5-dihydroxyhept-6-enoic acid substructure instead of the 3,5-dihydroxyheptanoic acid moiety [14] (*Fig. 1*). The double bond of the heptenoic acid substructure has (*E*)-configuration. Various syntheses for pitavastatin and its lactone NK-104[1]) have been published: utilization of *Taber*'s alcohol as chiral auxiliary [15], use of enantiomerically pure epichlorohydrin as starting material [16], and resolution [17][18]. The different epimers of NK-104, the corresponding lactone of pitavastatin[1]), were also synthesized by asymmetric aldol reaction with (*S*)-HYTRA as chiral auxiliary [17]. In this report, a new, short, and efficient synthesis of pitavastatin and NK-104 will be described.

**Results and Discussion.** – The method of *Karanewsky* and co-workers [9] for the preparation of the enantiomerically pure compound **3c** was the starting point of our investigations. In addition to (1*S*)-1-phenylethylamine (**2c**), which had been used by *Karanewsky* and co-workers in the presence of $Et_3N$, we investigated the use of (1*S*)-1-(1-naphthyl)ethylamine (**2d**) and (1*S*)-1-(2-naphthyl)ethylamine (**2e**) as chiral amines for the diastereoselective ring opening of anhydride **1** in the presence of $^{i}Pr_2EtN$: a mixture of epimers in a ratio of 79:21 was formed with **2d** as nucleophile. The major epimer was isolated by trituration in $Et_2O$ in 73% yield and with a diastereoisomer ratio (d.r.) of 97.5:2.5. With **2e** as nucleophile, a mixture of epimers in a ratio of 68:32 was obtained. Again, the major epimer was isolated by trituration in 57% yield and 99:1 d.r. In comparison, reaction of **2c** with anhydride **1**, under the same conditions, afforded compound **3c** as major epimer in 72% yield and $>99:1$ d.r. The epimers **3c**/epi-**3c** were formed in a ratio of 82:18 in this case. In conclusion, both **2d** and **2e** gave lower yields and diastereoselectivities as compared to **2c**. Based on these results, the reactions of the chiral amines **2d** and **2e** with anhydride **1** were not further investigated, and the absolute configurations of the major diastereoisomers isolated from these reactions were not determined.

The observed low diastereoselectivity of the ring-opening reaction of anhydride **1** with (1*S*)-1-phenylethylamine (**2c**) under the conditions similar or identical to those used by *Karanewsky* and co-workers might partially be attributed to the use of an achiral tertiary amine as base. The tertiary amine is supposed to promote the addition of the nucleophile by cleaving the anhydride and forming an acylammonium intermediate, which is then attacked by the nucleophile. In the case of (1*S*)-1-phenylethylamine (**2c**) as nucleophile, we questioned the necessity for a tertiary amine as catalyst: replacement of $^{i}Pr_2EtN$ by a second equivalent of (1*S*)-1-phenylethylamine under the same conditions improved the diastereoselectivity, and a ratio of 86:14 was observed for **3c**/epi-**3c**. Finally, by additional optimization of reaction conditions such as solvent change and crystallization, a final ratio of 93:7 was achieved for the formation of **3c**/epi-**3c**, and the desired, crystalline diastereoisomer **3c** was isolated in 87.6% yield (with regard to the expensive anhydride **1**) and in $>99.8:0.2$ d.r.

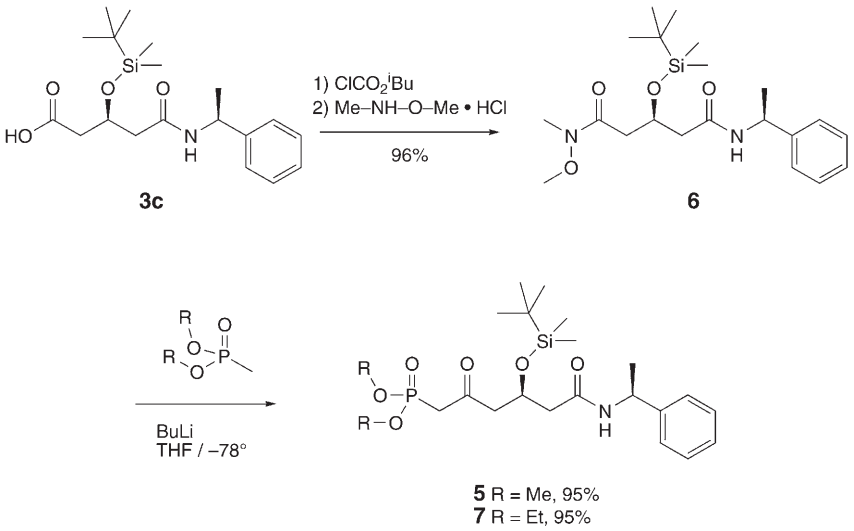
---

[1]) There seems to be some confusion in the literature with regard to the synonyms NK-104 and pitavastatin: In [15] and [16], the lactone derived from pitavastatin is named NK-104. In [17], NK-104 is used as synonym for the monocalcium salt of the acid. In this report, NK-104 will be used as synonym for the lactone and pitavastatin as synonym for the monocalcium salt.

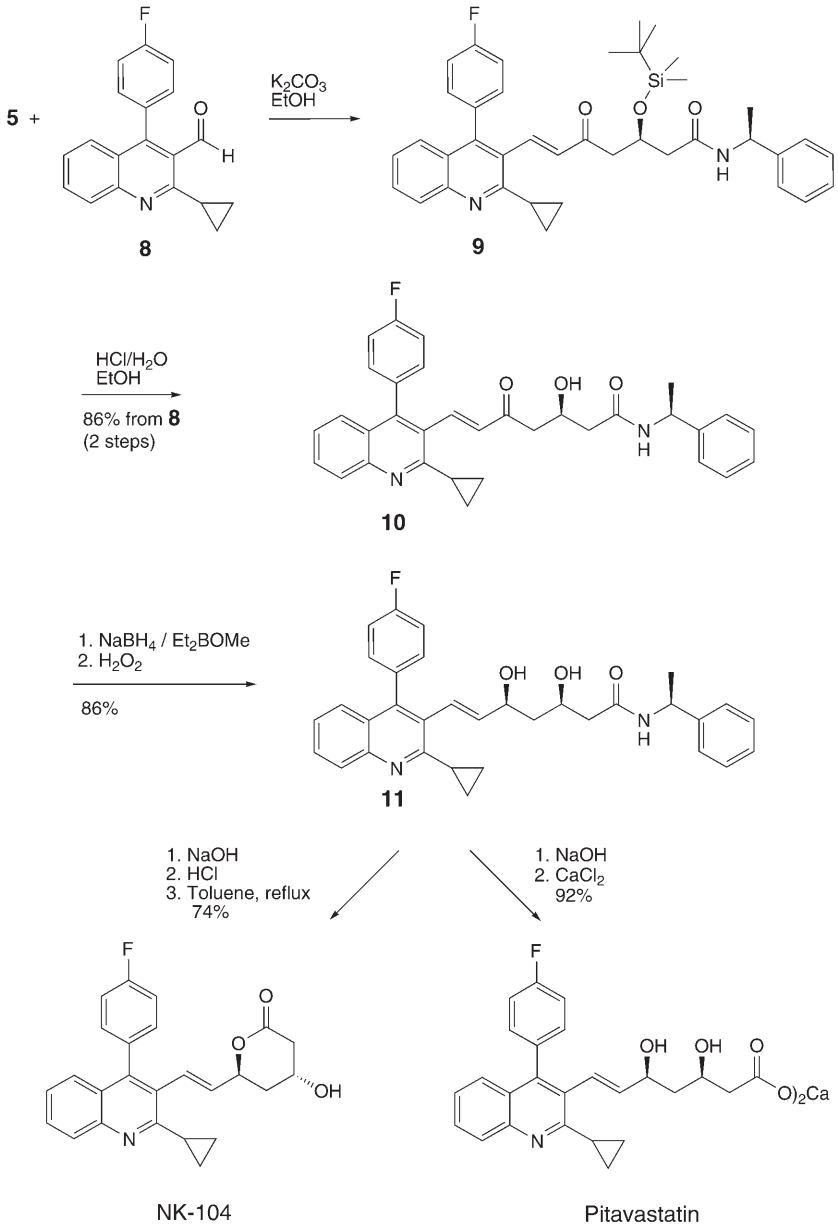
Having developed an efficient method for the preparation of **3c**, we turned our attention to the further functionalization and application of this chiral intermediate. According to [9], intermediate **3c** is converted to $\beta$-keto phosphonate **4** (*Fig. 2*) by a five-step sequence of reactions, involving cleavage of the amide by nitrosation with dinitrogen tetraoxide and *White* rearrangement of the resulting *N*-nitrosoamide, followed by treatment with excess dimethyl (lithiomethyl)phosphonate and esterification with diazomethane. In this strategy, the elimination of the (*tert*-butyl)dimethylsilyloxy group was prevented by using the salt form of glutaric monomethyl ester for the reaction with dimethyl (lithiomethyl)phosphonate. However, the elimination remained to be a potential problem for the subsequent *Horner–Wadsworth–Emmons* condensations with the $\beta$-keto phosphonate **4** (*Fig. 2*). In our design, we hypothesized that the tedious hydrolysis of the *N*-[(1*S*)-1-phenylethyl]amide function of **3c** was not necessary and that the amide function would rather be advantageous to prevent elimination during both preparation and subsequent *Horner–Wadsworth–Emmons* condensation of the corresponding $\beta$-keto phosphonate **5** (*Fig. 2*). In the presence of the amide function, excess base should lead to enolization of the amide instead of the elimination. This hypothesis proved to be correct and has lead to a very short and highly efficient synthesis of pitavastatin.

Activation of the carboxylic acid function of **3c** with isobutyl carbonochloridate and *in situ* treatment of the formed mixed anhydride with *N*-methoxymethanamine gave the *Weinreb* intermediate **6** in 96% yield (*Scheme 2*). Reaction of this compound with a fourfold excess of dimethyl (lithiomethyl)phosphonate in THF at $-78°$ afforded the $\beta$-keto phosphonate **5** in 95% yield. Similarly, phosphonate **7** was obtained in 95% yield from the reaction of **6** with an excess of diethyl (lithiomethyl)phosphonate. Because of the bulk availability and low price of methylphosphonic acid dimethyl ester, the $\beta$-keto phosphonate **5** was used for the following steps.

*Scheme 2*



*Scheme 3*




The *Horner–Wadsworth–Emmons* reaction of the $\beta$-keto phosphonate **5** with aldehyde **8** (*Scheme 3*) was investigated in some detail: different bases (NaH, KOH, $K_2CO_3$, $Cs_2CO_3$) in different solvents (THF, MeCN, $^i$PrOH, EtOH, MeOH, and mixtures with $H_2O$) were screened for the best yield and conversion. With NaH as base

in THF as solvent, no reasonable conversion was observed. With $K_2CO_3$ as base and EtOH as solvent, the condensation was a very clean reaction with peak-to-peak conversion to **9** without formation of any by-products. However, the reaction rate decreased substantially with increasing reaction time, and an excess of 5–10 mol-% of the phosphonate **5** had to be added to achieve >95% conversion of the aldehyde. It is noteworthy to mention that no elimination occurred under these conditions, regardless of the very long reaction time at 40°. With $Cs_2CO_3$ instead of $K_2CO_3$, the reaction could be accelerated substantially, reducing the reaction time from 48 h to 16 h. However, the formation of a by-product (3–5 area-% by HPLC) was observed in this case. With KOH as base in EtOH, the reaction was much faster (completion after 2–3 h) but by-product formation was observed also in this case (2–3 area-% by HPLC). Based on these results, the *Horner–Wadsworth–Emmons* condensation was performed in EtOH as solvent with $K_2CO_3$ as base.

After workup, the crude **9** (quant. yield) was used for the next step without purification. The $^t$BuMe$_2$Si protecting group was cleaved with either $H_3PO_4$ in MeCN or HCl in EtOH. The conversion of **9** to **10** with HCl in EtOH was faster and cleaner. After crystallization from toluene/hexane, pure **10** was isolated in 78% yield over two steps with regard to **5** and in 86% yield with regard to aldehyde **8**.

The stereoselective reduction of hydroxy ketone derivative **10** to the '*syn*'-diol **11** ((3*R*,5*S*)) was accomplished with $Et_2BOMe/NaBH_4$ according to the method described by *Prasad* and co-workers [19]. We investigated the effect of the amount of $Et_2BOMe$ on the formation of the '*syn*'/'*anti*' diastereoisomers (*Table*): even in the presence of only 0.5 equiv. of $Et_2BOMe$, a ratio of 97.4 : 2.6 was observed. Obviously, the reduction of the hydroxy ketone/$Et_2BOMe$ complex was much faster than the reduction of the free hydroxy ketone moiety. In all cases, the reaction proceeded very smoothly as a peak-to-peak conversion according to HPLC analysis. The crude product **11** was recrystallized from $^t$BuOMe to obtain crystalline **11** in 99.9 : 0.1 d.r. and 86% yield as a 1 : 1 solvate with $^t$BuOMe.

Table. *Dependency of the* 'syn'-*Selectivity on the Amount of Diethylborinic Acid Methyl Ester* ($Et_2BOMe$) *for the Reduction of* **10**

| Mol-equiv. of **10** | Mol-equiv. of $Et_2BOMe$ | '*syn*'/'*anti*' (crude) [area-% by HPLC] |
|---|---|---|
| 1.00 | 1.12 | 99.57 : 0.43 |
| 1.00 | 1.00 | 98.70 : 1.30 |
| 1.00 | 0.50 | 97.40 : 2.60 |

The hydrolysis of compound **11** with NaOH in EtOH/$H_2O$ was a clean reaction under mild conditions. Participation of OH–C(5) in a neighboring-group effect can be assumed to facilitate the hydrolysis in this case although no lactone intermediate was observed during the hydrolysis. After hydrolysis, the sodium salt was not isolated but was converted to NK-104 by protonation with HCl and subsequent lacton formation in toluene. Crystallization from $^t$BuOMe/hexane afforded pure NK-104. Alternatively, the calcium salt pitavastatin was obtained upon treatment of the sodium salt with $CaCl_2$. In both cases, the by-product of hydrolysis, (1*S*)-1-phenylethylamine, had to be removed from the solution to obtain pure products. Pitavastatin precipitated in high

purity and was isolated as a hydrate, comprising 10.6% (*w*/*w*) of $H_2O$. According to electrophoresis on a chiral column, the product had >99.9% e.e. The (3*S*,5*R*)-enantiomer ('*anti*') of pitavastatin was not detectable in the product at a detection limit of 0.05%. In the HPLC, MS, NMR, and IR spectra, pitavastatin was identical to the drug substance of *Livalo*®, a drug marketed by *Kowa Pharmaceuticals*. The overall yield of pitavastatin was 55% starting from **3c** and 67% with regard to the aldehyde **8**.

In summary, a new, short, and highly efficient method for the synthesis of statins was devised. The new strategy afforded synthetic statins, such as pitavastatin, in >99.9% ee and in exceptionally high overall yield.

## Experimental Part

*General.* Reagents and solvents were obtained from commercial sources and were used as received. All reactions were carried out under $N_2$ unless otherwise stated. Temp. were internally measured unless otherwise stated. Column chromatography (CC): silica gel (*E. Merck*, grade *60*, particle size 0.040–0.063 mm, 230–400 mesh ASTM). Capillary zone electrophoresis (CE): *Agilent-3D* CE apparatus, fused silica capillary at 20°; UV detection (248 nm). Melting points: *Leitz-Kofler* hot-stage apparatus; uncorrected. Specific optical rotations: *Perkin-Elmer 341* polarimeter. IR Spectra: *Bruker IFS66* or *Bruker IFS88* instrument; in $cm^{-1}$. NMR Spectra: *Bruker DPX400*, *DMX-500*, or *DRX-500* spectrometer; $\delta$ in ppm, *J* in Hz. Mass spectra: *Fisons-VG Quattro-II* (ESI), *Finnigan TSQ-7000* (ApCI), or *Finnigan 8430* (EI) instrument; in *m*/*z*.

*(3*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-oxo-5-{[(1*S*)-1-phenylethyl]amino}pentanoic Acid* (**3c**). The clear soln. of **1** (30 g, 0.123 mol), in $^t$BuOMe (210 ml), and heptane (120 ml) was cooled to −78° to obtain a slurry. A soln. of (−)-(1*S*)-1-phenylethylamine (**2c**; 31.3 g, 0.258 mol; 99.6% e.e.) in heptane (120 ml) was added slowly under mechanical stirring over 60–90 min at −78 to −75°. The clear viscous soln. was stirred for 2 h at −78 to −75° and then allowed to warm up to 20–25°. $H_2O$ (100 ml) was added followed by the addition of 20% aq. $H_3PO_4$ soln. (100 ml) until a pH of 2.5–3.5 was reached, whilst keeping the temp. at 30–35°. The mixture was then heated to reflux and stirred for 30 min under reflux. Finally, the mixture was cooled to 0–5° and the product isolated by filtration. The filter cake was washed with heptane/$H_2O$ 1:1 (80 ml) followed by 20% EtOH/$H_2O$ (100 ml). The product was dried at 50–60°/10–20 mbar: 39.4 g (87.7%) of **3c**. White crystals. M.p. 170–172°. $[\alpha]_D^{20} = -70.8$ ($c = 1.10$, MeOH) ([9]: $[\alpha]_D^{20} = -69.2$ ($c = 1.12$, MeOH)). HPLC: >99.8% of **3c** and <0.2% of epi-**3c** ((3*R*)). Spectroscopic data: identical to those published in [9]. Anal. calc. for $C_{19}H_{31}NO_4Si$: C 62.43, H 8.55, N 3.83, Si 7.68; found: C 62.32, H 8.55, N 3.74, Si 7.73.

*3-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-{[(1*S*)-(naphthalen-1-yl)ethyl]amino}-5-oxopentanoic Acid* (**3d** or epi-**3d**, *i.e.*, major epimer). A soln. of **1** (1.428 g, 5.84 mmol) in toluene (25 ml) was cooled to −78°, and $^i$Pr$_2$EtN (0.755 g, 5.84 mmol) was added, followed by (−)-(1*S*)-1-(1-naphthyl)ethylamine (**2d**; 1.082 g, 6.32 mmol). The mixture was mechanically stirred for 4.5 h at −78°, then allowed to warm up to 25°, and stirred for an additional hour at 25°. The reaction was quenched by pouring onto a 5% aq. $KHSO_4$ soln. (35 ml), and the product was extracted with AcOEt/THF 2:1 (30 ml). The org. layer was washed with 5% aq. $KHSO_4$ soln. (20 ml) and brine (20 ml) and dried ($MgSO_4$), the solvent evaporated at 55°, and the crude solid epimer mixture analyzed by HPLC: epimer ratio 79:21. The mixture was triturated in $Et_2O$ (10 ml), the formed suspension stirred for 3.5 h at 0–5°, and the precipitate isolated by filtration and dried for 16 h at 45° under reduced pressure: 1.776 g (73%) of **3d** or epi-**3d** (major epimer). White, crystalline solid. HPLC: 97.5% of major epimer and 2.5% of minor epimer. M.p. 169.5–172°. $[\alpha]_D^{20} = -8.54$ ($c = 1.0$, $CHCl_3$). IR: 3334, 2950, 2928, 2856, 1696, 1618, 1552, 1299, 1258, 1209, 1152, 1096, 843, 831, 777. $^1$H-NMR ((D$_6$)DMSO, 400 MHz): 0.061 (*s*, 3 H); 0.076 (*s*, 3 H); 0.85 (*s*, 9 H); 1.49 (*d*, $J = 7$, 3 H); 2.25–2.31 (*m*, 2 H); 2.38–2.48 (*m*, 2 H); 4.45–4.55 (*m*, 1 H); 5.67–5.77 (*m*, 1 H); 7.47–7.60 (*m*, 4 H); 7.82 (*d*, $J = 8$, 1 H); 7.94 (*d*, $J = 7.3$, 1 H); 8.1 (*d*, $J = 7.9$, 1 H); 12.22 (*s*, 1 H). $^{13}$C-NMR ((D$_6$)DMSO, 125 MHz): −4.5; −4.3; 18.2; 22.0; 26.2 (3C); 43.0; 44.0; 44.3; 67.4; 122.8; 123.5; 125.9; 126.0; 126.6;

127.7; 129.1; 130.8; 133.8; 140.7; 169.0; 172.7. ESI-MS: 414 ($[M-H]^-$). Anal. calc. for $C_{23}H_{33}NO_4Si$: C 66.47, H 8.00, N 3.37, Si 6.76; found: C 66.09, H 8.06, N 3.22, Si 6.96.

*3-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-{[(1*S*)-(naphthalen-2-yl)ethyl]amino}-5-oxopentanoic Acid* (**3e** or epi-**3e**, *i.e.*, major epimer). As described for **3d** or epi-**3d**, from (1*S*)-1-(2-naphthyl)ethylamine (**2e**) and **1**: crude epimer mixture, ratio 68:32. The major isomer **3e** or epi-**3e** was isolated in 57% yield and 99.1% purity, comprising 0.9% of the minor isomer (by HPLC). M.p. 146–148°. $[\alpha]_D^{20} = -58.36$ ($c = 1.0$, $CHCl_3$). IR: 3329, 2927, 2855, 1700, 1623, 1559, 1305, 1257, 1209, 1154, 1098, 831, 814, 779, 748. $^1$H-NMR ($(D_6)$DMSO, 400 MHz): 0.057 (*s*, 6 H); 0.844 (*s*, 9 H); 1.43 (*d*, $J = 7.1$, 3 H); 2.28–2.38 (*m*, 2 H); 2.39–2.48 (*m*, 2 H); 4.45–4.54 (*m*, 1 H); 5.04–5.14 (*m*, 1 H); 7.45–7.53 (*m*, 3 H); 7.77 (*s*, 1 H), 7.85–7.93 (*m*, 3 H); 8.46 (*d*, $J = 8.1$, 1 H); 12.25 (*s*, 1 H). $^{13}$C-NMR ($(D_6)$DMSO, 125 MHz): −4.55; −4.36; 18.2; 22.7; 26.2 (3 C); 43.0; 44.1; 48.3; 67.4; 124.3; 125.3; 126.0; 126.5; 127.9; 128.0; 128.3; 132.5; 133.3; 142.8; 169.2; 172.7. ESI-MS: 414 ($[M-H]^-$). Anal. calc. for $C_{23}H_{33}NO_4Si$: C 66.47, H 8.00, N 3.37, Si 6.76; found: C 66.24, H 8.09, N 3.21, Si 6.74.

*{(4*R*)-4-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,6-dioxo-6-{[(1*S*)-1-phenylethyl]amino}hexyl}phosphonic Acid Dimethyl Ester* (**5**). A soln. of methylphosphonic acid dimethyl ester (140.83 g, 1.101 mol) in THF (390 ml) was cooled to −78°, and 1.6M BuLi in hexane (374.4 g, 881 mmol) was added under mechanical stirring within 3 h. After stirring for additional 60 min at −78°, a soln. of **6** (see below; 90 g, 220.2 mmol) in THF (360 ml) was added while maintaining the temp. at −78°. Stirring was continued for 2.5 h at −78°, and the reaction was quenched by slow addition of a soln. of AcOH (66.1 g, 1.100 mol) in THF (46 ml) at −78°. The mixture was then allowed to warm up to r.t. and poured onto *t*BuOMe (1300 ml) and brine (1300 ml). The biphasic mixture was stirred for 15 min. Then the $H_2O$ layer was extracted again with *t*BuOMe (1300 ml), the combined org. phase washed with $H_2O$ ($4 \times 1300$ ml) and dried ($MgSO_4$ (75 g)), and the solvent evaporated. The viscous oil (107.2 g) solidified by storage in the refrigerator: **5** (104.0 g, 95%). $[\alpha]_D^{20} = -37.7$ ($c = 1.0$, $CHCl_3$). IR (film): 3299, 2955, 2929, 2855, 1717, 1651, 1542, 1376, 1256, 1186, 1035, 838, 813, 779, 701. $^1$H-NMR ($(D_6)$DMSO, 500 MHz): 0.02 (*s*, 3 H); 0.03 (*s*, 3 H); 0.82 (*s*, 9 H); 1.315 (*d*, $J = 7$, 3 H); 2.21 (*dd*, $J = 14$, 4.5, 1 H); 2.295 (*dd*, $J = 14$, 7.9, 1 H); 2.70–2.85 (*m*, 2 H); 3.21–3.31 (*m*, 2 H); 3.64 (*d*, $J$(H,P) = 11.2, 6 H); 4.40–4.50 (*m*, 1 H); 4.85–4.94 (*m*, 1 H); 7.15–7.25 (*m*, 1 H); 7.25–7.35 (*m*, 4 H); 8.33 (*d*, $J = 8.0$, 1 H). $^{13}$C-NMR ($CDCl_3$, 125 MHz): −4.87; −4.82; 17.98; 22.22; 25.85 (3 C); 42.32 (*d*, $J$(C,P) = 128); 43.58; 48.81; 49.74; 53.05 (*d*, $J$(C,P) = 6.5); 53.16 (*d*, $J$(C,P) = 6.5); 65.98; 126.30 (2 C); 127.41; 128.76 (2 C); 143.66; 169.32; 200.22 (*d*, $J$(C,P) = 6.5). ESI-MS: 494 ($[M+Na]^+$). Anal. calc. for $C_{22}H_{38}NO_6PSi$: C 56.03, H 8.12, N 2.97, P 6.57, Si 5.96; found: C 56.32, H 8.29, N 2.74, P 6.37, Si 6.09.

*(3*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-N$^1$-methoxy-N$^1$-methyl-N$^5$-[(1*S*)-1-phenylethyl]pentanediamide* (**6**). To **3c** (150 g, 410.3 mmol) and $CH_2Cl_2$ (1400 ml), 4-methylmorpholine (84.70 g, 820.7 mmol) was added under mechanical stirring at r.t. The clear soln. was cooled to −20°, and isobutyl carbonochloridate (57.19 g, *ca.* 98% (*w*/*w*) purity, 410.3 mmol) was added to the mixture at −15 to −20°. The mixture was stirred for 15 min at −15 to −20° and then treated with *N*-methoxymethanamine hydrochloride (40.43 g, 410.3 mmol). Stirring was continued for an additional hour at −15 to −20°, and the mixture was allowed to warm to r.t. After stirring for additional 4 h at r.t., the reaction was quenched by addition of $H_2O$ (1400 ml). The biphasic mixture was stirred. Then the $H_2O$ layer was extracted with $CH_2Cl_2$ ($2 \times 1000$ ml), the combined org. phase washed with brine (1400 ml), dried ($MgSO_4$ (40 g)), and concentrated. The crude, wet product **6** (177.2 g) recrystallized from hexanes (670 ml), and the crystalline product was dried at 40° under reduced pressure: 160.23 g (96%) of **6**. HPLC: purity of 100 area-%. M.p. 69.6–70.1°. $[\alpha]_D^{20} = -27$ ($c = 1.0$, $CHCl_3$). IR: 3304, 2933, 1666, 1630, 1541, 1493, 1454, 1380, 1257, 1107, 1083, 940, 831, 779, 698. $^1$H-NMR ($(D_6)$DMSO, 400 MHz): 0.033 (*s*, 3 H); 0.059 (*s*, 3 H); 0.842 (*s*, 9 H); 1.353 (*d*, $J = 7$, 3 H); 2.25–2.45 (*m*, 3 H); 2.64–2.74 (*m*, 1 H); 3.08 (*s*, 3 H); 3.64 (*s*, 3 H); 4.49–4.59 (*m*, 1 H); 4.89-4.98 (*m*, 1 H); 7.18–7.27 (*m*, 1 H); 7.28–7.35 (*m*, 4 H); 8.33 (*d*, $J = 8.3$, 1 H). $^{13}$C-NMR ($(D_6)$DMSO, 100 MHz): −4.09; −4.05; 18.58; 23.31; 26.61 (3 C); 32.38; 44.74; 48.55 (2 C); 61.87; 67.69; 126.78 (2 C); 127.39; 129.04 (2 C); 145.72; 169.54; 171.67. ESI-MS: 431 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{36}N_2O_4Si$: C 61.73, H 8.88, N 6.86, Si 6.87; found: C 61.90, H 9.04, N 6.66, Si 6.84.

*{(4*R*)-4-{[(*tert*-Butyl)dimethylsilyl]oxy}-2,6-dioxo-6-{[(1*S*)-1-phenylethyl]amino}hexyl}phosphonic Acid Diethyl Ester* (**7**) As described for **5**, from **6** and methylphosphonic acid diethyl ester: **7**. Viscous oil.

$[\alpha]_D^{20} = -40.1$ ($c = 1.0$, $CHCl_3$). IR (film): 3297, 2956, 2930, 2856, 1717, 1652, 1542, 1374, 1254, 1163, 1026, 966, 837, 779, 700. $^1$H-NMR ($(D_6)$DMSO, 400 MHz): 0.033 (*s*, 3 H); 0.044 (*s*, 3 H); 0.83 (*s*, 9 H); 1.22 (*td*, *J*(H,H) = 7.1, *J*(H,P) = 1.0, 6 H); 1.32 (*d*, *J* = 7.1, 3 H); 2.22 (*dd*, *J* = 14.2, 4.6, 1 H); 2.31 (*dd*, *J* = 14.2, 7.8, 1 H); 2.78 (*dd*, *J* = 17.1, 6.1, 2 H); 3.21 (*d*, *J*(H,P) = 22, 2 H); 3.98–4.08 (*m*, 4 H); 4.45–4.52 (*m*, 1 H); 4.87–4.96 (*m*, 1 H); 7.20–7.27 (*m*, 1 H); 7.26–7.36 (*m*, 4 H); 8.32 (*d*, *J* = 8.1, 1 H). $^{13}$C-NMR ($D_6$)DMSO, 125 MHz): −4.48 (2 C); 16.52; 16.57; 18.13; 22.92; 26.19 (3 C); 42.7 (*d*, *J*(C,P) = 124); 43.87; 48.09; 51.30; 62.15; 62.20; 66.04; 126.33 (2 C); 126.95; 128.62 (2 C); 145.24; 169.05; 200.95 (*d*, *J*(C,P) = 5.9). ESI-MS: 522 ($[M + Na]^+$). Anal. calc. for $C_{24}H_{42}NO_6PSi$: C 57.69, H 8.47, N 2.80, P 6.20, Si 5.62; found: C 56.76, H 8.48, N 2.51, P 6.16, Si 5.50.

*(3*R,*6*E*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-5-oxo-[(1*S*)-1-phenylethyl]hept-6-enamide* (**9**). A soln. of **5** (424.92 g, 901 mmol) in EtOH (950 ml) was cooled to 0–5°, and fine powdered anh. $K_2CO_3$ (119.8 g, *ca.* 850 mmol) was added, followed by aldehyde **8** (250 g, 858.1 mmol). The mixture was diluted with EtOH (950 ml) and allowed to warm to r.t. After mechanical stirring for additional 30 min at r.t., the mixture was heated to 40° and stirred for 24 h at 40°. As HPLC revealed the presence of more than 10% of **8** in the mixture, **5** (21.17 g, 44.9 mmol) and $K_2CO_3$ (6 g, 43 mmol) were added, and the mixture was stirred for additional 24 h at 40° and 3 h at 45°. The reaction was quenched by addition of 5% aq. citric acid soln. (1800 ml), and the mixture was extracted with *t*BuOMe (1 × 3500 ml, 2 × 2500 ml). The org. layer was washed with $H_2O$ (3500 ml) and brine (3500 ml) and dried ($MgSO_4$ (70 g)), and the solvent was evaporated at 40°: crude **9** (660.1 g, quant.) as highly viscous oil, used directly for the next step without purification. An anal. sample was purified by CC (silica gel, hexane/AcOEt). $[\alpha]_D^{20} = -28.8$ ($c = 1.0$, $CHCl_3$). IR: 3300 (br.), 2954, 2928, 2840, 1647 (br.), 1605, 1540, 1513, 1489, 1253, 1223, 1094, 1066, 837, 778, 763, 699. $^1$H-NMR ($(D_6)$DMSO, 400 MHz): −0.07 (*s*, 3 H); 0.05 (*s*, 3 H); 0.77 (*s*, 9 H); 1.04–1.10 (*m*, 2 H); 1.22–1.32 (*m*, 2 H); 1.33 (*d*, *J* = 7.1, 3 H); 2.21 (*dd*, *J* = 14.2, 4.9, 1 H); 2.30–2.43 (*m*, 2 H); 2.60–2.73 (*m*, 2 H); 4.47–4.57 (*m*, 1 H); 4.87–4.97 (*m*, 1 H); 6.25 (*d*, *J* = 16.6, 1 H); 7.18–7.24 (*m*, 1 H); 7.25–7.42 (*m*, 9 H); 7.45 (*t*, *J* = 7.3, 1 H); 7.60 (*d*, *J* = 16.6, 1 H); 7.72 (*t*, *J* = 7.0, 1 H); 7.91 (*d*, *J* = 8.6, 1 H); 8.33 (*d*, *J* = 8.1, 1 H). $^{13}$C-NMR ($D_6$)DMSO, 125 MHz): −4.58; −4.40; 11.09; 11.20; 16.30; 18.10; 22.87; 26.13 (3 C); 44.06; 48.11; 48.21; 66.78; 115.94 (*d*, *J*(C,F) = 21, 2 C); 125.69; 126.33 (2 C); 126.41; 126.62; 126.95; 127.78; 128.59 (2 C); 128.93; 130.40; 132.29; 132.35; 132.53; 135.11; 139.69; 145.25; 145.9; 147.03; 160.07; 162.34 (*d*, *J*(C,F) = 246); 169.05; 197.66. ESI-MS: 659 ($[M + Na]^+$). Anal. calc. for $C_{39}H_{45}FN_2O_3Si$: C 73.55, H 7.12, N 4.40, F 2.98, Si 4.41; found: C 73.32, H 7.16, N 4.21, F 3.03, Si 4.30.

*(3*R,*6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3-hydroxy-5-oxo-[(1*S*)-1-phenylethyl]-hept-6-enamide* (**10**). A soln. of crude **9** (660.1 g, theor. 858.1 mmol **9**) in EtOH (2400 ml) was cooled to 0–4°, and 2M aq. HCl (657.1 g of soln., 1276 mmol) was added dropwise at 0–4°. The mixture was allowed to warm to 25° and stirred for additional 4 h, until an in-process control (HPLC) indicated the completion of the reaction. The mixture was poured onto 2% aq. $NaHCO_3$ soln. (7400 ml) and extracted with AcOEt (5000 ml). The org. layer was washed with brine (1800 ml) and the combined aq. phase extracted with AcOEt (2000 ml). The combined org. phase was dried ($MgSO_4$) and the solvent evaporated: 561.2 g of a honey-like crude product. The crude product was dissolved in toluene (860 ml) and hexane (1075 ml) was added. The mixture was stirred at 60° for 2 h and at 50° for 1 h. Then, a second portion of hexane (1075 ml) was added at 50°, and the suspension was allowed to cool down to r.t. Stirring was continued overnight at r.t. and for additional 3 h at 0°. The product was isolated by filtration and the filter cake washed with cold hexane (500 ml) and dried *in vacuo* at 40°: 390.9 g of **10**, *i.e.*, 385.43 g after correction to 100% pure **10** (86% from **8** and 78% from **5** over 2 steps). Yellow powder. HPLC: purity of 98.6 area-%. M.p. 145–149° (crystallization from *t*BuOMe/hexane gave crystals of m.p. 150–151°). $[\alpha]_D^{20} = -26.9$ ($c = 1.0$, $CHCl_3$). IR: 3470 (br.), 3344, 1693, 1631, 1603, 1549, 1513, 1488, 1409, 1344, 1219, 1055, 1030, 995, 768, 697. $^1$H-NMR ($(D_6)$DMSO, 400 MHz): 1.02–1.13 (*m*, 2 H); 1.22–1.32 (*m*, 2 H); 1.33 (*d*, *J* = 7, 3 H); 2.21 (*dd*, *J* = 14.2, 5.6, 1 H); 2.28 (*dd*, *J* = 14.2, 7.4, 1 H); 2.37–2.48 (*m*, 1 H); 2.54–2.66 (*m*, 2 H); 4.22–4.32 (*m*, 1 H); 4.87 (*d*, *J* = 5.3, 1 H); 4.86–5.00 (*m*, 1 H); 6.29 (*d*, *J* = 16.6, 1 H); 7.16–7.26 (*m*, 1 H); 7.26–7.42 (*m*, 9 H); 7.44 (*t*, *J* = 7, 1 H); 7.55 (*d*, *J* = 16.6, 1 H); 7.71 (*t*, *J* = 7, 1 H); 7.91 (*d*, *J* = 8.2, 1 H); 8.26 (*d*, *J* = 8.2, 1 H). $^{13}$C-NMR ($(D_6)$DMSO, 125 MHz): 10.72; 10.77; 15.90; 22.46; 43.2; 47.64; 47.77; 64.69; 115.50 (*d*, *J*(C,F) = 21.3, 2 C); 125.205; 125.89 (2 C); 125.93; 126.13; 126.49; 127.32; 128.14 (2 C); 128.46; 129.90; 131.91 (*d*, *J*(C,F) = 7.4, 2 C); 132.04 (*d*, *J*(C,F) = 3.2); 134.45; 138.79;

144.72; 145.41; 146.55; 159.72; 161.88 (*d*, *J*(C,F) = 245.5); 169.28; 197.87. ESI-MS: 545 ($[M+Na]^+$), 523 ($[M+H]^+$). Anal. calc. for $C_{33}H_{31}FN_2O_3$: C 75.84, H 5.98, N 5.36, F 3.64; found: C 75.74, H 6.13, N 5.39, F 3.63.

*(3*R,*5*S,*6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-[(1*S*)-1-phenylethyl]-hept-6-enamide* (**11**). A suspension of $NaBH_4$ (30.26 g, *ca.* 96% (*w*/*w*), 768 mmol) in dry THF (1877 ml) was cooled to −78°. A soln. of diethylborinic acid methyl ester (54.85 g, 548.4 mmol) in THF (54.85 g) was added within 15 min at −78°, and the mixture was mechanically stirred for additional 5 min at −78°. A soln. of **10** (290.7 g, 556 mmol) in dry THF (488 ml) and MeOH (581 ml) was added slowly within 2.5 h to the mixture, maintaining the reaction temp. at −78°. After stirring for an additional hour at −78°, the mixture was poured onto an ice-cold soln. of $NaHCO_3$ (92.15 g) in $H_2O$ (4610 ml). Isopropyl acetate (7346 ml) was added, and the biphasic mixture was stirred, until two clear phases were formed. The aq. layer was extracted again with isopropyl acetate (2 × 3150 ml), the combined org. phase washed with brine (2 × 3150 ml), and the solvent evaporated at 40°. The obtained solid yellow foam was dissolved in isopropyl acetate (630 ml), and the soln. was warmed to 50°. A 35% aq. $H_2O_2$ soln. (174.02 g, corresponding to 60.907 g of $H_2O_2$, 1790 mmol) was added within 45 min at 50°, and the mixture was stirred for an additional hour at 50°. The reaction was quenched by addition of brine (3980 ml) at 45–50°, and the mixture was diluted with isopropyl acetate (2390 ml). The biphasic mixture was stirred for 20 min at 45–50°. The org. layer was treated with an aq. $Na_2SO_3$ soln. (118 g in 2850 ml of $H_2O$) at 45–50° and the mixture stirred for 5 min. Then the org. layer was washed with aq., half-sat. NaCl soln. (2 × 2390 ml) and dried ($MgSO_4$). The solvent was evaporated, the obtained crude, yellow, solid foam (349 g) dissolved in *t*BuOMe (706 ml), and the soln. cooled to 0°. After stirring for 30 min at 0°, the formed suspension was warmed to 30° and stirred for 15 min at 30°. The suspension was allowed to cool to 25° and stirred overnight at 25°. Finally, the suspension was stirred for 2 h at 0° and for 3 h at −20°. The product was isolated by filtration, and the filter cake was washed with heptane (2 × 75 ml) and dried at 40° under reduced pressure: 274.8 g (80.6%) of **11** as a 1:1 solvate with *t*BuOMe. HPLC: purity of 98.9 area-%. M.p. 59–75°. The crystalline product comprised 99.89% of the desired '*syn*'-(3*R*,5*S*)-diastereoisomer and 0.11% of its *anti*-(3*R*,5*R*)-epimer according to HPLC. Additional 18.08 g (5.3%) of **11** were obtained from the mother liquor by CC (silica gel) and subsequent crystallization. Total yield: 292.88 g (86%) of **11** · *t*BuOMe. $[\alpha]_D^{20} = -27$ (*c* = 1.0, $CHCl_3$). IR: 3479, 3296, 2977, 1642, 1557, 1513, 1490, 1411, 1365, 1215, 1158, 1116, 1068, 763, 698. $^1$H-NMR ((D$_6$)DMSO, 500 MHz): 0.96–1.06 (*m*, 2 H); 1.105 (*s*, *t*BuOMe); 1.15–1.26 (*m*, 3 H); 1.32 (*d*, J = 7, 3 H); 1.42–1.49 (*m*, 1 H); 2.17 (*dd*, *J* = 14.2, 5, 1 H); 2.22 (*dd*, *J* = 14.2, 7.5, 1 H); 2.49–2.56 (*m*, 1 H); 3.32 (*s*, *t*BuOMe); 3.77–3.85 (*m*, 1 H); 4.10–4.17 (*m*, 1 H); 4.69 (*d*, *J* = 4.7, 1 H); 4.83 (*d*, *J* = 4.4, 1 H); 4.90–4.98 (*m*, 1 H); 5.62 (*dd*, *J* = 16.2, 6, 1 H); 6.47 (*dd*, *J* = 16.2, 1.1, 1 H); 7.15–7.20 (*m*, 1 H); 7.23–7.35 (*m*, 9 H); 7.38 (*ddd*, *J* = 8.2, 6.9, 1.2, 1 H); 7.63 (*ddd*, *J* = 8.2, 6.9, 1.3, 1 H); 7.86 (*d*, *J* = 8.4, 1 H); 8.23 (*d*, *J* = 8.1, 1 H). $^{13}$C-NMR ((D$_6$)DMSO, 125 MHz): 11.13; 11.28; 15.86; 23.0; 27.26 (*t*BuOMe); 43.93; 44.95; 48.05; 49.16 (*t*BuOMe); 65.75; 69.22; 72.50 (*t*BuOMe); 115.71 (*d*, *J*(C,F) = 21, 2 C); 123.90; 126.00; 126.05; 126.11; 126.36 (2 C); 126.95; 128.60 (2 C); 128.81; 129.26; 129.89; 132.26 (*d*, *J*(C,F) = 7.7); 132.52 (*d*, *J*(C,F) = 7.9); 133.40 (*d*, *J*(C,F) = 2.8); 142.37; 144.08; 145.18; 146.36; 160.94; 162.04 (*d*, *J*(C,F) = 244); 170.26. Anal. calc. for $C_{38}H_{45}FN_2O_4$: C 74.48, H 7.40, N 4.57, F 3.10; found: C 74.47, H 7.30, N 4.64, F 3.13.

*(3*R,*5*S,*6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-hept-6-enoic Acid Calcium Salt 1:2)* (= *Pitavastatin*). To a soln. of **11** (4.0 g, 6.53 mmol) in EtOH (40 ml), $H_2O$ (40 ml) and NaOH powder (2.64 g, 66 mmol) were added, and the mixture was heated at 50–55° for 26 h, until an in-process control (HPLC) indicated complete hydrolysis. Then, 1M HCl (59 ml, 59 mmol) was added within 15 min. The solvent was distilled under reduced pressure, and the residue was dissolved in $H_2O$ (80 ml). The $H_2O$ soln. was extracted with *t*BuOMe (3 × 80 ml), and the org. phase was removed. The aq. phase was evaporated and the residue redissolved in $H_2O$ (176 ml). Then, 1M HCl (6.53 ml, 6.53 mmol) was added to precipitate the acid, followed by the addition of AcOEt (176 ml). The mixture was stirred for 15 min to obtain 2 clear phases. The org. phase was washed with $H_2O$ (90 ml). Charcoal (0.5 g) was added to the org. phase, and the mixture was stirred at 30–35° for 2 h. Filter-aid (*Cellflock*; 1.0 g) was added, and stirring was continued for additional 30 min. Filtration and evaporation of the solvent at 30–35° gave the crude *(3*R,*5*S,*6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxyhept-6-enoic acid* as a white solid.

The crude acid (2.55 g, 6.05 mmol) was suspended in $H_2O$ (40.5 ml), and NaOH (0.260 g, 6.5 mmol) was added to obtain a clear soln. of the corresponding sodium salt. A $CaCl_2$ soln. (0.399 g, 3.49 mmol) in $H_2O$ (2 ml) was added to the sodium salt soln. The immediately formed suspension was stirred for 4 h at 20–25° and for 2 h at 15–17°. The product was isolated by filtration and the filter cake washed with cold $H_2O$ and dried *in vacuo* at 20–25°: 2.95 g of pitavastatin comprising 10.6% (*w*/*w*) $H_2O$ as a white, crystalline powder, corresponding to 2.637 g (92%) of pure, anh. pitavastatin. $[\alpha]_D^{20} = +22.9$ ($c = 1$, MeCN/$H_2O$ 1:1) ([17]: $[\alpha]_D^{20} = +23.1$ ($c = 1$, MeCN/$H_2O$ 1:1)). Column electrophoresis: absence of the (3*S*,5*R*)-enantiomer (detection limit 0.05%). HPLC, MS, NMR, and IR: identical to an authentic sample of pitavastatin, the drug substance of *Levalo*®. Anal. calc. for $C_{50}H_{46}CaF_2N_2O_8$: Ca 4.55%; found: Ca 4.51% for anh. pitavastatin.

*(4*R*,6*S*)-6-{(1*E*)-2-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]ethenyl}tetrahydro-4-hydroxy-2*H*-pyran-2-one* (NK-104). As described for pitavastatin, 1.16 g of **11** were converted to (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-hept-6-enoic acid. The crude free acid was suspended in toluene (25 ml), and the suspension was heated to reflux for 1 h in a $H_2O$ separator. The solvent was evaporated and the crude product purified by FC (silica gel, $^t$BuOMe); 568 mg (74%) of pure NK-104. White solid. The product was crystallized from $^t$BuOMe/hexane. M.p. 137–139°. $[\alpha]_D^{20} = +9.8$ ($c = 1$, $CHCl_3$) ([14]: m.p. 136–139°; $[\alpha]_D^{20} = +9.0$ ($c = 1.0$, $CHCl_3$); [16]: m.p. 138–139°; $[\alpha]_D^{20} = +8.84$ ($c = 0.92$, $CHCl_3$)). IR and NMR: in accord with NK-104. HR-MS: 404.16561 ($[M+H]^+$; calc. 404.16565). Anal. calc. for $C_{25}H_{22}FNO_3$: C 74.43, H 5.50, N 3.47, F 4.71; found: C 74.20, H 5.57, N 3.29, F 4.63.

## REFERENCES


[1] C. E. Nakamura, R. H. Abeles, *Biochemistry* **1985**, *24*, 1364; Y. Jahng, *Drug Future* **1995**, *20*, 387.

[2] A. Endo, M. Kuroda, Y. Tsujita, *J. Antibiot.* **1976**, *29*, 1346; A. Endo, M. Kuroda, K. Tanzawa, *FEBS Lett.* **1976**, *72*, 323; A. Endo, Y. Tsujita, M. Kuroda, K. Tanzawa, *Eur. J. Biochem.* **1977**, *77*, 31; A. Endo, *J. Med. Chem.* **1985**, *28*, 401.

[3] A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp, R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.

[4] A. W. Alberts, J. Chen, G. Kuron, V. Hunt, J. Huff, G. Hoffman, J. Rothrock, M. Lopez, H. Joshua, E. Harris, A. Patchett, R. Monaghan, S. Currie, E. Stapley, G. Albers-Schonberg, O. Hensens, J. Hirschfield, K. Hoogstein, J. Liesch, J. Springer, *J. Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

[5] A. Endo, *J. Antibiot*. **1979**, *32*, 852; A. Endo, *J. Antibiot*. **1980**, *33*, 334.

[6] M. Mueller, *Angew. Chem., Int. Ed.* **2005**, *44*, 362; R. Ozegowski, A. Kunath, H. Schick, *Liebigs Ann. Chem*. **1993**, 805.

[7] C. H. Heathcock, C. R. Hadley, T. Rosen, P. D. Theisen, S. J. Hecker, *J. Med. Chem.* **1987**, *30*, 1858; S. J. Hecker, C. H. Heathcock, *J. Am. Chem. Soc.* **1986**, *108*, 4586; T. Rosen, C. H. Heathcock, *J. Am. Chem. Soc.* **1985**, *107*, 3731.

[8] P. D. Theisen, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 2374.

[9] D. S. Karanewsky, M. F. Malley, J. Z. Gougoutas, *J. Org. Chem*. **1991**, *56*, 3744; Y. Kawakami, J. Hiratake, Y. Yamamoto, J. Oda, *J. Chem Soc., Chem. Commun*. **1984**, 779.

[10] P. M. Wovkulich, P. C. Tang, N. K. Chadha, A. D. Batcho, J. C. Barrish, M. R. Uskokovich, *J. Am. Chem. Soc.* **1989**, *111*, 2596; S. J. Danishefsky, B. Simoneau, *J. Am. Chem. Soc.* **1989**, *111*, 2599.

[11] D. V. Patel, R. J. Schmid, E. M. Gordon, *J. Org. Chem*. **1992**, *57*, 7143.

[12] H. Shin, B. S. Choi, K. K. Lee, H. Choi, J. H. Chang, K. W. Lee, *Synthesis* **2004**, *16*, 2629.

[13] P. V. Ramachandran, K. J. Padiya, V. Rauniyar, M. V. R. Reddy, H. C. Brown, *J. Fluorine Chem*. **2004**, *125*, 615.

[14] H. Iwasaki, M. Suzuki, H. Yanagawa, Y. Fujikawa, M. Kitahara, Abstract Paper, '111$^{th}$ Annual Congress of Pharm. Soc. Japan, April, Tokyo', 1991, 29V, 3-042; Abstract Paper, 'XIth International Symposium on Drugs Affecting Lipid Metabolism, Florence', May, 1992.

[15] T. Minami, T. Hiyama, *Tetrahedron Lett*. **1992**, *33*, 7525; G. B. Reddy, T. Minami, T. Hanamoto, T. Hiyama, *J. Org. Chem*. **1991**, *56*, 5752.

[16] S. Takano, T. Kamikubo, T. Sugihara, M. Suzuki, K. Ogasawara, *Tetrahedron: Asymmetry* **1993**, *4*, 201.
[17] M. Suzuki, Y. Yanagawa, H. Iwasaki, H. Kanda, K. Yanagihara, H. Matsumoto, Y. Ohara, Y. Yazaki, R. Sakoda, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2977.
[18] N. Miyachi, Y. Yanagawa, H. Iwasaki, Y. Ohara, T. Hiyama, *Tetrahedron Lett*. **1993**, *34*, 8267.
[19] K. Prasad, K.-M. Chen, O. Repic, G. E. Hardtmann, *Tetrahedron: Asymmetry* **1990**, *1*, 307; K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, *Tetrahedron Lett.* **1987**, *28*, 155.

*Received January 26, 2007*