SYNTHESIS OF SOME IMPURITIES AND/OR DEGRADATION PRODUCTS OF ATORVASTATIN

Jan STACH[1,*], Jaroslav HAVLÍČEK[2], Lukáš PLAČEK[3] and Stanislav RÁDL[4]

Zentiva, U Kabelovny 130, 102 37 Prague 10, Czech Republic; e-mail: [1] jan.stach@zentiva.cz, [2] jaroslav.havlicek@zentiva.cz, [3] lukas.placek@zentiva.cz, [4] stanislav.radl@zentiva.cz

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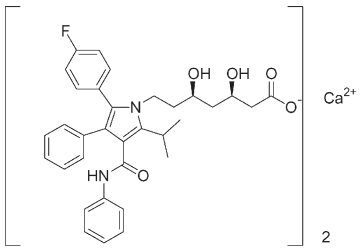
Synthesis of some impurities and/or degradation products of atorvastatin, calcium (3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrol-1-yl]-3,5-dihydroxyheptanoate, is described. These include its desfluoro analog, the corresponding (3*S*,5*S*)- and (3*S*,5*R*)-epimers, atorvastatin lactone, and some other potential impurities. The synthesized compounds as well as the corresponding intermediates were characterized by ^{1}H NMR, ^{13}C NMR and MS.

Keywords: Atorvastatin; Impurities; Degradation products; Lactones; Esters; Lipitor; Pyrroles.

Atorvastatin (**1**; Lipitor®, Sortis®) is a leading HMG-CoA reductase inhibitor on the market[1–3], with the potential becoming one of the most successful generic drugs of this decade. Probably all producers of this drug use compound **2** as the key intermediate.



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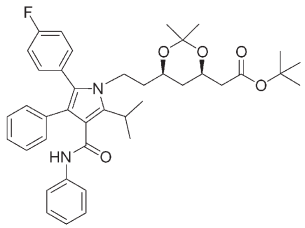

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There are several efficient methods of synthesis of this intermediate, mostly based on the convergent synthesis using *tert*-butyl [(4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**3**). This compound is usually prepared by catalytic reduction of *tert*-butyl [(4*R*,6*R*)-6-(cyano-

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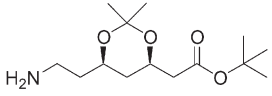
methyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**4**)[3–5]. We have recently published a new method of preparation of **3** from *tert*-butyl [(4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**5**) based on the Henry reaction[6].



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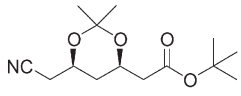

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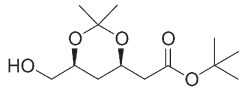

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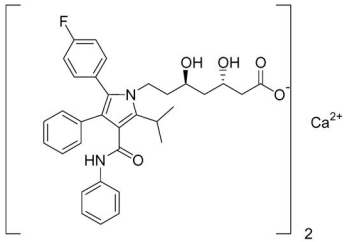
We have also developed our own method of preparation of amorphous atorvastatin[7] and a generic atorvastatin version using this substance has been launched. Beside impurities that cannot be completely eliminated during the substance preparation and purification, degradation products formed at various stages of handling and storing may impose a problem. The specification for a generic drug substance should include a list of impurities, with the specified impurities being either identified or unidentified. The identified impurities should be included in the specification when they are present at a level greater than the identification threshold which is usually 0.10%. Thus, identification and setting specifications for the evaluation of the quality of a drug substance are important aspects of any generic project, which must also include identification and synthesis of all key impurities and degradation products.

As far as we know, no paper on impurities of atorvastatin has been published, and the only published report[8] on degradation products deals with atorvastatin photodegradation products, which are not present in well-handled substance. In this paper, we would like to report the synthesis of some impurities used as HPLC standards for the API evaluation.

Since atorvastatin has two stereogenic carbon atoms, four possible diastereomers are possible. For chiral HPLC analysis, we prepared atorvastatin in the form of its *cis*-racemate via the (*cis*)-*tert*-butyl 6-(cyanomethyl)-2,2-dimethyl-1,3-dioxane-4-acetate[9]. On the other hand, *trans*-atorvastatin, which is a common atorvastatin impurity, is usually determined by HPLC as the sum of both isomers **6** and **7**. We prepared compound **6** as a standard for this determination.

During the development of generic atorvastatin, we identified several impurities formed during the multistep synthesis of this substance. Some of them usually accompany the substance independently of the procedure, others are specific to the procedure used. The most frequently encountered impurity as well as degradation product is atorvastatin lactone (**8**). This

substance is formed both during atorvastatin synthesis and from atorvastatin under acidic conditions. Another commonly present impurity is the desfluoro derivative of atorvastatin **9**.



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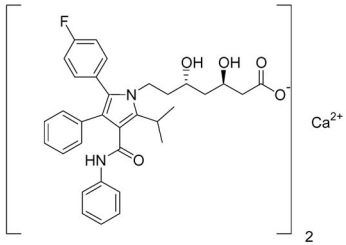

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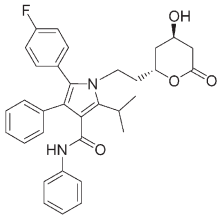

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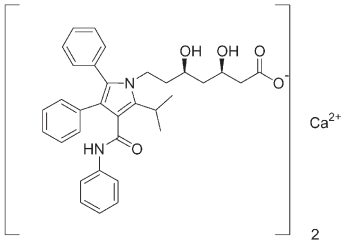

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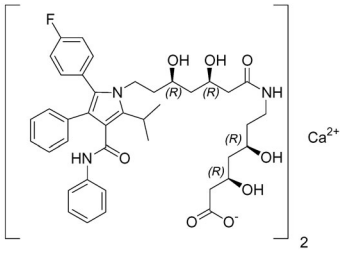
Impure amine **3** probably causes the presence of "diamino atorvastatin" **10** in the atorvastatin API. This impurity could also be formed during the formation of the pyrrole ring. Several atorvastatin esters can be present in the atorvastatin substance, depending on the procedure used. Methyl ester **11a** can be found in the product prepared by the original Parke–Davis procedure[10] since methanol is used as a cosolvent. On the other hand, small amounts of *tert*-butyl ester **11b** are sometimes present due to an incomplete hydrolysis of the *tert*-butyl group of **2**.

Elimination of the 3-hydroxy group of atorvastatin can lead to the corresponding unsaturated atorvastatin derivative, which can be present either as the *E*- or *Z*-form (**12**). Interestingly, only the *trans* isomer **12** was detected in the real samples.

Standard of (*S*,*S*)-atorvastatin (**13**) for chiral HPLC method was also needed.



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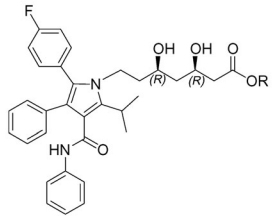
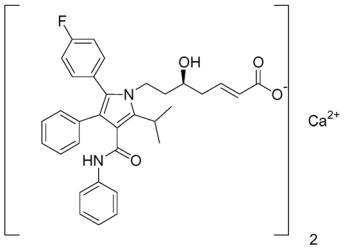


11a R = Me
11b R = *tert*-Bu



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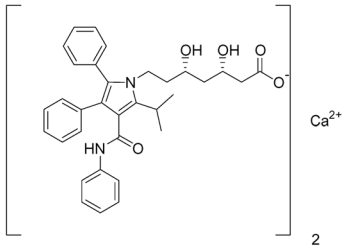

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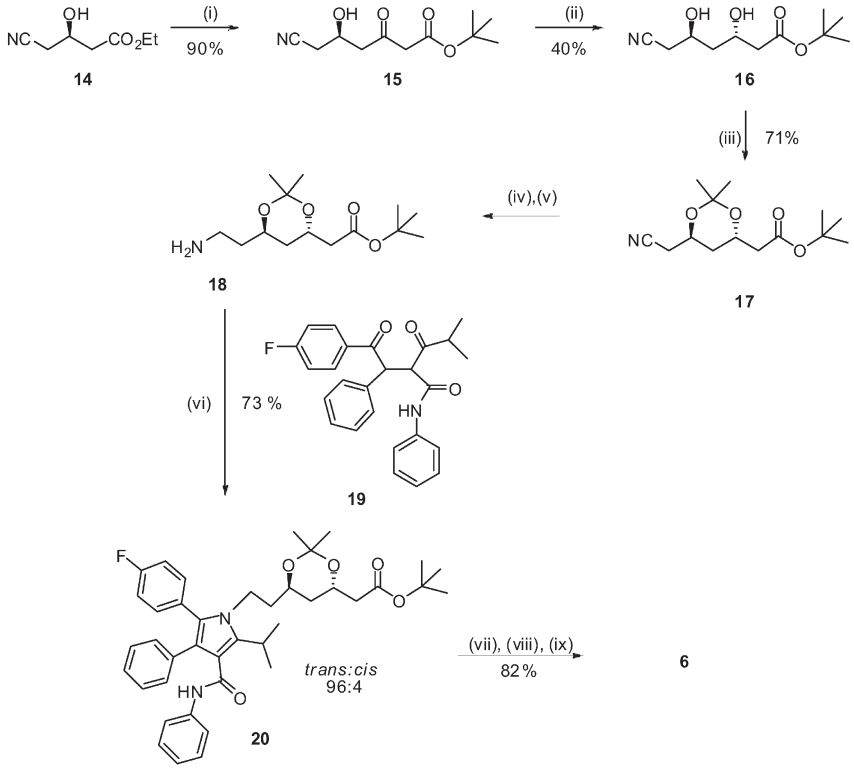
In the subsequent part of the paper, synthesis of the discussed impurities and/or degradation products will be described.

Preparation of "*trans*-atorvastatin" (**6**) started from commercially available ethyl (*R*)-4-cyano-3-hydroxybutanoate (**14**). This compound (Scheme 1) treated with *tert*-butyl lithioacetate in tetrahydrofuran using the methodology described in a U.S. patent[11] provided **15** in good yield. Reduction with sodium borohydride in acetic acid yielded dihydroxy intermediate **16** with moderate diastereoselectivity (82:18); subsequent crystallization from ethyl acetate/hexane gave the product with satisfactory diastereoselectivity (95:5). Reduction with tetramethylammonium triacetoxyborohydride in acetic acid/acetonitrile provided **16** with a slightly better diastereoselectivity (88:12). The protection with acetone and subsequent catalytic hydrogenation afforded unstable crude amine **18**. Reaction with the commercially available diketone **19** provided **20** in good yield. Deprotection and alkaline hydrolysis using the method described in a patent[7] then furnished "*trans*-atorvastatin" (**6**).

Atorvastatin lactone (**8**) is easily formed from the corresponding atorvastatin acid under acidic conditions. Atorvastatin acid can be obtained both from intermediate **2** by the procedure used for the synthesis of atorvastatin and directly from atorvastatin itself.

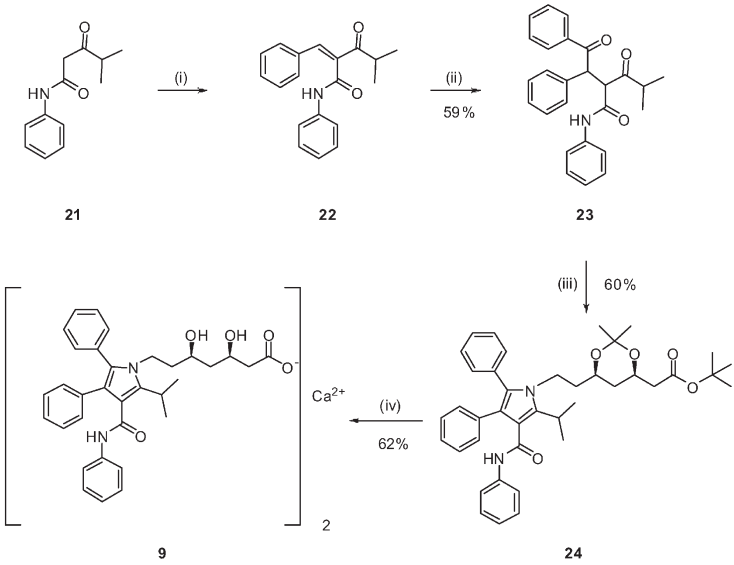


SCHEME 1

Reagents and conditions: (i) LDA, *tert*-butyl acetate, THF, –78 °C; (ii) $NaBH_4$, acetic acid, r.t.; (iii) 2,2-dimethoxypropane, acetone, *para*-TsOH, r.t.; (iv) H_2, Ra–Ni, 40 °C; (v) pivalic acid, heptane; (vi) heptane/toluene 9:1, reflux; (vii) HCl, THF; (viii) NaOH; (ix) calcium acetate

Preparation of desfluoroatorvastatin (**9**) used the procedure starting from anilide **21**, patented for the preparation of atorvastatin itself, in which 4-fluorobenzaldehyde was replaced by benzaldehyde (Scheme 2). The starting compound **21** treated with benzaldehyde in the presence of aminoacetic acid and acetic acid with azeotropic removal of water provided **22** in 59% yield[10b]. Compound **22** treated with benzaldehyde in ethanol under the catalysis with 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide yielded diketone **23** in good yield. This is, in fact, a modification of the Stetter reaction[12]. The next step, i.e. reaction of **23** with amine **3** was catalyzed by pivalic acid and the intermediate **24** was obtained in 60% yield.

Subsequent acid and alkaline treatment of compound **24** provided the corresponding acid, which was transformed into desfluoroatorvastatin **9** by a procedure used in the atorvastatin synthesis.

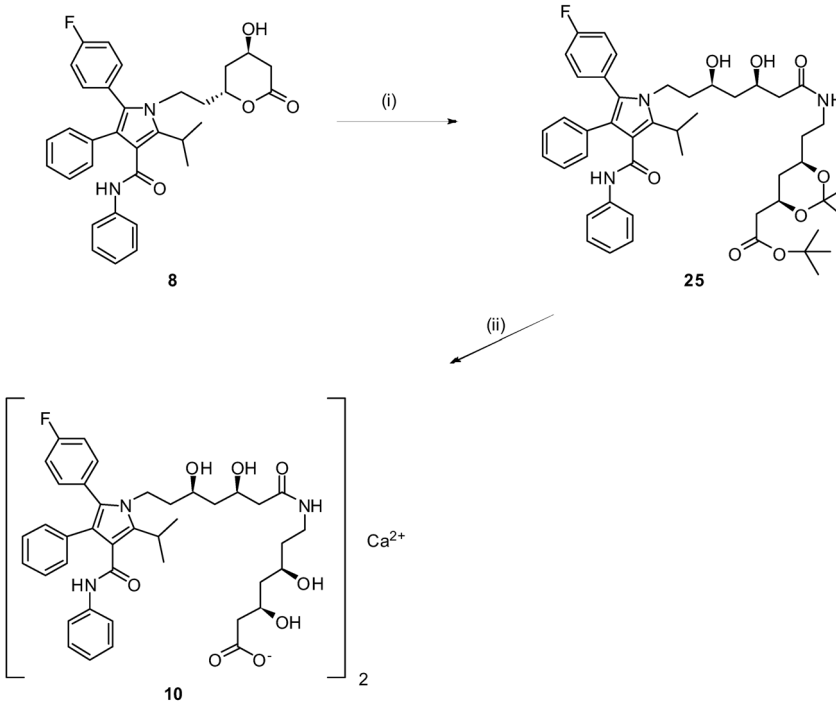


SCHEME 2
Reagents and conditions: (i) toluene, acetic acid, benzaldehyde; (ii) acetic acid, hexane, benzaldehyde; (iii) **3**, pivalic acid, heptane/toluene 9:1, reflux; (iv) HCl, NaOH, calcium acetate

Synthesis of diamino atorvastatin (**10**) (Scheme 3) started from lactone **8** which, when treated with amino derivative **3**, provided the corresponding amide **25**. This compound was deprotected in usual way without isolation and the obtained sodium salt was transformed into the corresponding calcium salt **10**.

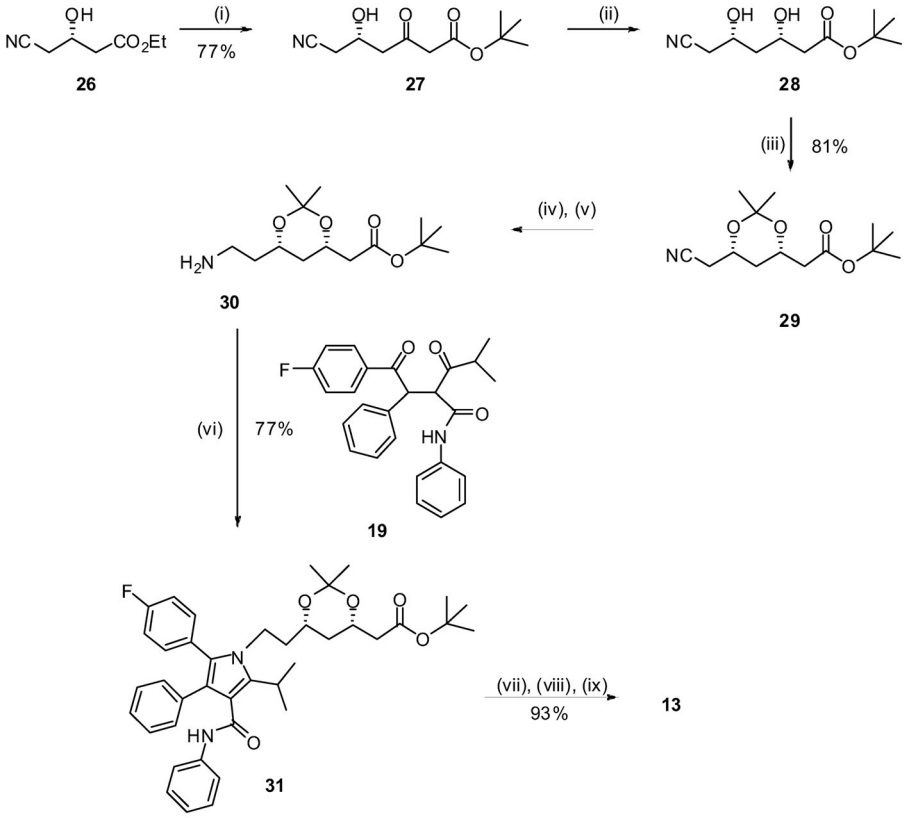
Ester **11a** was easily prepared by esterification of atorvastatin free acid with methanol or by treatment of atorvastatin lactone with methanol. The corresponding *tert*-butyl ester **11b** was obtained by mild acidic hydrolysis of the penultimate atorvastatin intermediate **2**.

All attempts to synthesize the *E*-isomer **12** or its free acid **12b** failed, the impurity standard was eventually obtained as the acid from a complex reaction mixture containing 9% of **12b** using flash chromatography. The mixture was obtained by a nonselective dehydration of atorvastatin methyl ester **11a** with acetic anhydride followed by alkaline hydrolysis.



SCHEME 3
Reagents and conditions: (i) **3**, toluene, reflux; (ii) HCl, THF, NaOH, calcium acetate

Synthesis of (*S*,*S*)-atorvastatin (Scheme 4) started with the commercially available ethyl (*S*)-4-cyano-3-hydroxybutanoate (**26**). This compound, treated with *tert*-butyl lithioacetate in tetrahydrofuran using the methodology described in the U.S. patent[11], provided **27** in good yield. Reduction with sodium borohydride in the presence of diethyl(methoxy)borane provided diol **28** which was protected as an acetal to give a highly crystalline ester **29**. Catalytic hydrogenation of ester **29** afforded crude amine **30**, which was subjected to pyrrole cyclization with the commercially available diketone **19** to give the protected compound **31**. Deprotection and alkaline hydrolysis using the method described in the patent for the synthesis of atorvastatin then provided (*S*,*S*)-atorvastatin (**13**).



SCHEME 4

Reagents and conditions: (i) LDA, *tert*-butyl acetate, THF, –78 °C; (ii) Et_2BOMe, $NaBH_4$, THF, –78 °C; (iii) 2,2-dimethoxypropane, acetone, *para*-TsOH, r.t.; (iv) H_2, Ra–Ni, 40 °C; (v) pivalic acid, heptane; (vi) heptane/toluene 9:1, reflux; (vii) HCl, THF; (viii) NaOH; (ix) calcium acetate

In summary, we have prepared several impurities and degradation products of atorvastatin needed for analytical support of our commercially produced atorvastatin.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Perkin Elmer Spectrum BX FT-IR machine in KBr pellets, wavenumbers are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker instruments (250 and 500 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The purity of the sub-

stances prepared was evaluated by TLC on silica gel (FP KG F 254, Merck). Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Mass spectra were measured using a Sciex API 3000 mass spectrometer with positive atmospheric pressure ionization (TurboIonspray) or using LTQ Orbitrap hybrid mass spectrometer with direct injection into APCI (Atmospheric Pressure Chemical Ionisation) source in positive mode.

The following intermediates were prepared according to the literature: 2-isobutyryl-*N*,3-diphenylacrylamide (**22**)[10b]; *tert*-butyl (5*R*)-6-cyano-5-hydroxy-3-oxohexanoate (**15**) and *tert*-butyl (5*S*)-6-cyano-5-hydroxy-3-oxohexanoate (**27**)[12].

(3*S*,5*R*)-*tert*-Butyl 6-Cyano-3,5-dihydroxyhexanoate (**16**)

Sodium borohydride (2.1 g, 55.5 mmol) was added with stirring to cold acetic acid (30 ml) at a rate sufficient to maintain the temperature of the reaction mixture at 20–25 °C. A solution of compound **15** (3.5 g, 15.4 mmol) in acetic acid (5 ml) was added dropwise over 10 min. After stirring at 25 °C for additional 30 min, the mixture was diluted with ethyl acetate (200 ml), the resultant solution was washed with saturated sodium carbonate (3 × 20 ml) and dried with anhydrous magnesium sulfate. The desiccant was filtered off and the filtrate was evaporated to give compound **16** as an oil (3.1 g). The crude product was crystallized from ethyl acetate/hexane to give **16** (1.41 g, 40%), m.p. 58–63 °C. *Cis*:*trans* ratio (5:95) was determined by GC on the corresponding acetonide. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): 4.28 m, 1 H (C**H**OH); 4.28 m, 1 H (C**H**OH); 2.59 dd, 2 H, *J* =5.6, 1.8 (CH_2CN); 2.44 d, 2 H, *J* = 6.4 (CH_2CO); 1.72 m, 2 H [CH(OH)C**H**$_2$CH(OH)]; 1.47 s, 9 H [$C(CH_3)$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 172.1 (CO); 117.7 (CN); 81.7 [**C**(CH_3)]; 65.0 (3-CHOH); 64.6 (5-CHOH); 42.0 (CH_2CO); 41.3 [CH(OH)C**H**$_2$CH(OH)]; 28.0 [C(**C**H_3)]; 26.0 (CH_2CN). IR: 2246 (CN), 1710 (ester C=O). HR-MS: for $C_{11}H_{20}NO_4$ $[M + H]^+$ calculated 230.1387 *m/z*, found 230.1383.

tert-Butyl (4*S*,6*R*)-6-(Cyanomethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**17**)

2,2-Dimethoxypropane (6 ml) and 4-methylbenzene-1-sulfonic acid monohydrate (30 mg) were added to a stirred solution of **16** (1.28 g, 5.58 mmol) in dry acetone (4 ml). After stirring at 25 °C for additional 60 min, triethylamine (0.1 ml) was added and the reaction mixture was evaporated. The residual oil was purified by column chromatography using hexane/acetone (7:3, v/v) to provide **17** (1.07 g, 71%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): 4.28 m, 1 H [(CH(O)]; 4.18 m, 1 H [(CH(O)]; 2.51 dd, 2 H, *J* = 1.6, 5.6 (CH_2CN); 2.47 d, 1 H, *J* = 6.4 (CH_2CO); 1.72 m, 2 H [CH(OH)C**H**$_2$CH(OH)]; 1.47 s, 9 H [$C(CH_3)$]; 1.45 q, 3 H, *J* = 0.6 (CH_3); 1.38 q, 3 H, *J* = 0.6 (CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 169.7 (CO); 117.0 (CN); 101.2 (OCO); 80.8 [**C**$(CH_3)_3$]; 63.5 [CH(O)]; 62.6 [CH(O)]; 41.8 (CH_2CO); 36.7 [CH(O)C**H**$_2$CH(O)]; 28.0 [C(**C**$H_3)_3$]; 24.6 (CH_2CN); 24.3 (CH_3); 24.3 (CH_3). IR: 2246 (CN), 1725 (ester C=O). MS, *m/z* (%): 270 $[M + H]^+$ (10), 231 (25), 214 (30), 156 (100), 149 (50), 138 (45).

tert-Butyl (4*S*,6*R*)-6-(2-Aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**18**)

A solution of compound **17** (2.54 g, 9.4 mmol) in MeOH (50 ml) saturated with ammonia gas was hydrogenated at 40 °C (810 kPa). After 5 h, the mixture was filtered and the filtrate evaporated to give crude amine **18** (2.7 g, 100%) which was used without further purification.

tert-Butyl (4*S*,6*R*)-6-{2-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (**20**)

A mixture of amine **18** (2.3 g, 8.4 mmol), diketone **19** (3 g, 7.2 mmol) and pivalic acid (0.61 g, 6.1 mmol) was refluxed in a mixture of heptane (40 ml) and toluene (5 ml) for 19 h. The mixture was then evaporated and crystallized from propan-2-ol to give **20** (4 g, 73%) as a white solid, m.p. 165–167 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.20 m, 2 H (anilide H-3); 7.19 m, 2 H (Ph H-2); 7.19 m, 1 H (Ph H-4); 7.19 m, 2 H (4-FC_6H_4 H-2); 7.16 m, 2 H (Ph H-3); 7.07 d, 2 H, *J* = 8.8 (anilide H-2); 6.99 m, 2 H (FC_6H_4H-3); 6.99 m, 1 H (anilide H-4); 6.87 s, 1 H (NH); 4.14 m, 1 H (dioxane H-4); 4.06 m, 1 H ($NC\mathbf{H}_2CH_2$); 3.80 m, 1 H ($NC\mathbf{H}_2CH_2$); 3.63 m, 1 H (dioxane H-6); 3.59 sept, 1 H, *J* = 7.1 [C**H**$(CH_3)_2$]; 2.37 dd, 1 H, *J* = 15.4, 6.9 (CH_2COO); 2.29 dd, 1 H, *J* = 15.4, 6.2 (CH_2COO); 1.70 m, 2 H ($NCH_2C\mathbf{H}_2$); 1.54 d, 3 H, *J* = 7.5 [$CH(C\mathbf{H}_3)_2$]; 1.54 d, 3 H, *J* = 7.5 [$CH(C\mathbf{H}_3)_2$]; 1.48 m, 2 H (dioxane H-5); 1.44 s, 9 H [$C(CH_3)_3$]; 1.29 s, 3 H [$C(CH_3)_2$]; 1.24 s, 3 H [$C(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 170.0 (COO); 164.8 (CONH); 162.3, $J_{C,F}$ = 248.5 (4-FC_6H_4 C-4); 141.6 (pyrrole C-5); 138.5 (anilide C-1); 134.7 (C-1 of Ph); 133.2, $J_{C,F}$ = 8.2 (4-FC_6H_4 C-2); 130.5 (2 C-3 Ph); 128.8 (pyrrole C-2); 128.6 (Ph C-2); 128.3 (C-3 of anilide); 128.2, $J_{C,F}$ = 2.8 (4-FC_6H_4 C-1); 126.6 (Ph C-4); 123.5 (anilide C-4); 121.8 (pyrrole C-3); 119.6 (anilide C-2); 115.3 (pyrrole C-4); 115.3, $J_{C,F}$ = 21.4 (4-FC_6H_4 C-3); 100.4 (dioxane C-2); 80.6 [$C(CH_3)_3$]; 64.3 (dioxane C-6); 63.6 (dioxane C-4); 42.1 (CH_2COO); 41.4 (NCH_2); 37.6 (NCH_2CH_2); 37.3 (dioxane C-5); 28.1 [$C(CH_3)_3$]; 26.1 [$CH(CH_3)_2$]; 24.6 [$C(CH_3)_2$]; 24.6 [$C(CH_3)_2$]; 21.7 [$CH(CH_3)_2$]; 21.6 [$CH(CH_3)_2$]. IR: 1660 (C=O), 1718 (ester C=O). HR-MS: for $C_{40}H_{48}FN_2O_5$ $[M + H]^+$ calculated 655.3541 *m/z*, found 655.3543.

Calcium (3*S*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-3,5-dihydroxyheptanoate (**6**)

Dilute hydrochloric acid (10%; 3 ml) was added to a solution of **20** (1 g, 1.5 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at 25 °C for 6 h and then a concentrated solution of sodium hydroxide (40%; 2 ml) was added over 5 min, maintaining the temperature below 35 °C. The resultant heterogeneous mixture was vigorously stirred for 15 h, and then poured into a separating funnel containing water (30 ml) and hexane (10 ml). The organic layer was removed and the aqueous layer was extracted with a mixture of hexane (8 ml) and tetrahydrofuran (2 ml). After complete separation, the aqueous layer was extracted with ethyl acetate (3 × 8 ml) and the combined extracts shaken with a solution of calcium acetate (20%; 3 × 1 ml). The resulting ethyl acetate solution was washed with water (2 × 1 ml) and, after drying with anhydrous calcium sulfate, concentrated in vacuo to 4 ml. After filtration, the clear solution was added dropwise over 5 min to hexane (40 ml) under vigorous stirring, and the mixture was stirred for additional 20 min. The precipitate was filtered off, washed with hexane (20 ml) and dried to give 0.72 g (82%) of **6**, m.p. 160 °C (dec.). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): 7.3–6.9 (NH); 7.29 m, 2 H, *J* = 8.1 (anilide H-2); 7.23 m, 2 H (4-FC_6H_4 H-2); 7.22 m, 2 H (Ph H-2); 7.13 m, 2 H (Ph H-3); 7.09 m, 2 H (anilide H-3); 7.06 m, 2 H (4-FC_6H_4 H-3); 7.04 m, 1 H (Ph H-4); 7.02 m, 1 H (anilide H-4); 4.09 m, 1 H ($C\mathbf{H}_2CH_2CHOH$); 4.09 m, 1 H [$CH(OH)CH_2C\mathbf{H}OH$]; 3.92 m, 1 H ($C\mathbf{H}_2CH_2CHOH$); 3.61 m, 1 H [$C\mathbf{H}(OH)CH_2CHOH$]; 3.37 sept, 1 H, *J* = 7.5 [C**H**$(CH_3)_2$]; 2.25 m, 2 H (CH_2CO); 1.67 m, 2 H ($CH_2C\mathbf{H}_2CHOH$); 1.48 d, 6 H, *J* = 7.5 [$CH(C\mathbf{H}_3)_2$]; 1.37 m, 2 H [$CH(OH)C\mathbf{H}_2CHOH$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 182.2 (COO); 169.5 (CONH); 163.8 $J_{C,F}$ = 247.2 (C-4 of 4-FC_6H_4); 139.8 (anilide C-1); 139.0 (pyrrole C-2); 136.3 (Ph C-1); 134.7, $J_{C,F}$ = 7.8 (2 C-2

4-FC_6H_4); 130.9 (2 C-3 Ph); 130.2, $J_{C,F}$ = 2.9 (4-FC_6H_4 C-1); 129.6 (pyrrole C-5); 129.6 (2 C-2 Ph); 128.9 (2 C-3 of anilide); 126.9 (Ph C-4); 125.2 (anilide C-4); 123.3 (pyrrole C-4); 121.5 (2 C-2 of anilide); 118.1 (pyrrole C-3); 116.3, $J_{C,F}$ = 21.5 (2 C-3 of 4-FC_6H_4); 67.0 (5-CHOH); 66.9 (3-CHOH); 45.5 (CH_2CO); 44.7 [CH(OH)CH_2CHOH]; 42.5 (CH_2CH_2CHOH); 41.0 (CH_2CH_2CHOH); 27.7 [$CH(CH_3)_2$]; 22.8 [$CH(CH_3)_2$]; 22.8 [$CH(CH_3)_2$]. IR: 1559 (C=O), 1700 (acid C=O). HR-MS: for $C_{33}H_{36}FN_2O_5$ $[M + H]^+$ calculated 559.2603 *m/z*, found 559.2608.

(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-3,5-dihydroxyheptano-5-lactone (**8**)

Aqueous hydrochloric acid (10%; 22 ml, 0.06 mol) was slowly added to a solution of **2** (6.5 g, 10 mmol) in tetrahydrofuran (300 ml) and the mixture was stirred at room temperature for 24 h. Powdered sodium hydroxide (5.4 g, 0.135 mol) was added and the mixture was stirred for another 5 h. Water (200 ml) was then added and the mixture was extracted with hexane (150 ml) and diethyl ether (2 × 50 ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (200 ml). The solution was washed with brine (2 × 50 ml) and dried with anhydrous magnesium sulfate; the residue after evaporation was dissolved in toluene (100 ml) and the solution refluxed for 6 h. Toluene was evaporated and the residue (5.4 g) was crystallized from ethyl acetate (charcoal) to give 3.9 g (72%) of white crystals, m.p. 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.18 m, 2 H (anilide H-3); 7.18 m, 2 H (Ph H-2); 7.17 m, 2 H (Ph H-4); 7.17 m, 1 H (4-FC_6H_4 H-2); 7.14 d, 2 H, *J* = 7.6 (Ph H-3); 7.05 d, 2 H, *J* = 8.8 (anilide H-2); 7.02 m, 2 H (4-FC_6H_4 H-3); 6.99 m, 1 H (anilide H-4); 6.87 s, 1 H (NH); 4.52 m, 1 H (lactone H-5); 4.20 m, 1 H (NC**H**$_2$$CH_2$); 4.09 m, 1 H (lactone H-3); 4.02 m, 1 H (NC**H**$_2$$CH_2$); 3.52 sept, 1 H, *J* = 7.2 [C**H**(CH_3)]; 2.65 dd, 1 H, *J* = 15.4, 3.8 (H-2 of lactone); 2.55 dd, 1 H, *J* = 15.5, 8.7 (lactone H-2); 2.25 s, 1 H (OH); 1.85 m, 1 H (NCH_2C**H**$_2$); 1.73 m, 1 H (NCH_2C**H**$_2$); 1.70 m, 1 H (lactone H-4); 1.60 m, 1 H (lactone H-4); 1.54 d, 3 H, *J* = 7.5 [C**H**(CH_3)]; 1.52 d, 3 H, *J* = 7.5 [C**H**(CH_3)]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 169.4 (COO); 164.8 (CONH); 162.3, $J_{C,F}$ = 248.4 (4-FC_6H_4 C-4); 141.3 (pyrrole C-2); 138.2 (anilide C-1); 134.4 (Ph C-1); 133.5, $J_{C,F}$ = 8.4 (2 C-2 of 4-FC_6H_4); 130.4 (2 C-3 Ph); 128.7 (pyrrole C-5); 128.7 (2 C-2 Ph); 128.4 (2 C-3 of anilide); 128.0, $J_{C,F}$ = 3.6 (4-FC_6H_4 C-1); 126.7 (Ph C-4); 123.7 (anilide C-4); 122.1 (pyrrole C-4); 119.7 (2 C-2 of anilide); 115.6, $J_{C,F}$ = 21.2 (2 C-3 of 4-FC_6H_4); 115.6 (pyrrole C-3); 73.0 (lactone C-5); 62.4 (lactone C-3); 40.7 (NCH_2CH_2); 38.4 (lactone C-2); 37.1 (NCH_2CH_2); 35.6 (lactone C-4), 26.1 [$CH(CH_3)$]; 22.0 [$CH(CH_3)$]; 21.7 [$CH(CH_3)$]. IR: 1700 (lactone C=O), 1660 (C=O). HR-MS: for $C_{33}H_{34}FN_2O_4$ $[M + H]^+$ calculated 541.2497 *m/z*, found 541.2489.

4-Methyl-3-oxo-2-(2-oxo-1,2-diphenylethyl)-*N*-phenylpentanamide (**23**)

Solvent (8 ml) was distilled off from a solution of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.6 g, 2.4 mmol) in dry ethanol (10 ml). Then 2-isobutyryl-*N*,3-diphenylacrylamide (**22**; 3.3 g, 11 mmol), triethylamine (1.2 g, 12 mmol) and benzaldehyde (1.4 g, 13 mmol) were added and the mixture was stirred at 80 °C under argon for 24 h. Crystallization from propan-2-ol provided 2.6 g (59%) of white crystals as a mixture of isomers, m.p. 193–198 °C. IR: 1670 (C=O), 1718 (C=O), 1650 (C=O amide). HR-MS: for $C_{26}H_{26}NO_3$ $[M + H]^+$ calculated 400.1907 *m/z*, found 400.1906.

tert-Butyl (4*R*,6*R*)-6-{2-[2-Isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-pyrrol-1-yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (**24**)

A mixture of diketone **23** (2.33 g, 5.83 mmol), amine **3** (1.9 g, 7.1 mmol) and pivalic acid (0.72 g, 7.1 mmol) was refluxed in a mixture of heptane (40 ml) and toluene (5 ml) for 30 h. The mixture was then evaporated and the residue crystallized from propan-2-ol to give **23** (2.23 g, 60%) as a white solid, m.p. 127–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.28 m, 2 H (4-Ph H-2); 7.26 m, 1 H (4-Ph H-4); 7.20 m, 2 H (5-Ph H-2); 7.19 m, 2 H (4-Ph H-3); 7.17 m, 2 H (anilide H-3); 7.16 m, 2 H (5-Ph H-3); 7.14 m, 1 H (5-Ph H-4); 7.07 d, 2 H, *J* = 8.8 (anilide H-2); 6.97 m, 1 H (anilide H-4); 4.13 m, 1 H (dioxane H-4); 4.07 m, 1 H (NCH_2CH_2); 3.87 m, 1 H (NCH_2CH_2); 3.65 m, 1 H (dioxane H-6); 3.62 sept, 1 H, *J* = 7.4 [$CH(CH_3)_2$]; 2.37 dd, 1 H, *J* = 15.2, 6.9 (CH_2COO); 2.21 dd, 1 H, *J* = 15.2, 6.2 (CH_2COO); 1.67 m, 2 H (NCH_2CH_2); 1.54 d, 3 H, *J* = 7.5 [$CH(CH_3)_2$]; 1.53 d, 3 H, *J* = 7.5 [$CH(CH_3)_2$]; 1.48 m, 2 H (dioxane H-5); 1.44 s, 9 H [$C(CH_3)_3$]; 1.34 s, 3 H [$C(CH_3)_2$]; 1.28 s, 3 H [$C(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 170.2 (COO); 164.9 (CONH); 141.5 (pyrrole C-2); 138.5 (anilide C-1); 134.9 (4-Ph C-1); 132.3 (5-Ph C-1); 131.5 (2 C-2 of 5-Ph); 130.6 (2 C-3 of 4-Ph); 130.0 (pyrrole C-5); 128.6 (2 C-2 of 4-Ph); 128.6 (2 C-3 of anilide); 128.2 (2 C-3 of 5-Ph); 126.7 (4-Ph C-4); 126.4 (5-Ph C-4); 123.4 (anilide C-4); 121.5 (pyrrole C-4); 119.6 (2 C-2 of anilide); 115.3 (pyrrole C-3); 98.6 (dioxane C-2); 80.6 [$C(CH_3)_3$]; 66.5 (dioxane C-6); 65.9 (dioxane C-4); 40.9 (NCH_2); 42.5 (CH_2COO); 38.0 (NCH_2CH_2); 35.9 (dioxane C-5); 28.1 [$C(CH_3)_3$]; 26.1[$CH(CH_3)_2$]; 21.7 [$CH(CH_3)_2$]; 21.6 [$CH(CH_3)_2$]; 19.7 [2 $C(CH_3)_2$]. IR: 1635 (C=O), 1710 (ester C=O). HR-MS: for $C_{40}H_{49}N_2O_5$ $[M + H]^+$ calculated 637.3636 *m/z*, found 637.3641.

Calcium (3*R*,5*R*)-3,5-Dihydroxy-7-[2-isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-pyrrol-1-yl]heptanoate (**9**)

A solution of hydrochloric acid (10%; 3 ml) was added to a solution of compound **24** (1 g, 1.57 mmol) in tetrahydrofuran (15 ml), and the mixture was stirred at 25 °C for 6 h. A solution of concentrated sodium hydroxide (40%; 2 ml) was then added over 5 min, maintaining the temperature below 35 °C. The heterogeneous mixture formed was vigorously stirred for 15 h, and then poured into a separatory funnel containing water (30 ml) and hexane (10 ml). The organic layer was removed, and the aqueous layer extracted with a mixture of hexane (8 ml) and tetrahydrofuran (2 ml). After complete separation, the aqueous layer was extracted with ethyl acetate (3 × 8 ml), and the combined ethyl acetate extracts were shaken with a solution of calcium acetate (20%; 3 × 1 ml). The resulting ethyl acetate solution was washed with water (2 × 1 ml), dried with anhydrous calcium sulfate and concentrated in vacuo to 4 ml. After filtration, the clear solution was added dropwise during 5 min to hexane (40 ml) under vigorous stirring, and the mixture was stirred for additional 20 min. The precipitate was filtered off, washed with hexane (20 ml) and dried to give 0.54 g (62%) of **9** as a white solid, m.p. 150 °C (dec.). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): 7.33 m, 2 H (5-Ph H-3); 7.3–6.9, 1 H (NH); 7.30 m, 1 H (anilide H-4); 7.29 d, 2 H, *J* = 8.1 (anilide H-2); 7.29 m, 1 H (5-Ph H-4); 7.21 m, 2 H (4-Ph H-2); 7.21 m, 2 H (5-Ph H-2); 7.13 m, 2 H (4-Ph H-3); 7.06 m, 2 H (anilide H-3); 7.02 m, 1 H (4-Ph H-4); 4.05 m, 1 H (CH_2CH_2CHOH); 3.95 m, 1 H [$CH(OH)CH_2CHOH$]; 3.93 m, 1 H (CH_2CH_2CHOH); 3.63 m, 1 H [$CH(OH)CH_2CHOH$]; 3.37 sept, 1 H, *J* = 7.1 [$CH(CH_3)_2$]; 2.29 dd, 1 H, *J* = 15.4, 3.8 (CH_2CO); 2.19 dd, 1 H, *J* = 15.5, 8.7 (CH_2CO); 1.67 m, 2 H (CH_2CH_2CHOH); 1.49 d, 3 H, *J* = 6.9 [$CH(CH_3)_2$]; 1.48 d, 3 H, *J* = 6.9 [$CH(CH_3)_2$]; 1.48 m, 1 H [$CH(OH)CH_2CHOH$]; 1.33 m, 1 H [$CH(OH)CH_2CHOH$].

^{13}C NMR (125 MHz, CD_3OD, 25 °C): 181.9 (CO); 169.6 (CONH); 139.9 (anilide C-1); 138.9 (pyrrole C-2); 136.5 (4-Ph C-1); 134.1 (5-Ph C-1); 132.8 (2 C-2 of 5-Ph); 130.9 (2 C-3 of 4-Ph); 130.8 (pyrrole C-5); 129.6 (2 C-2 of 4-Ph); 129.5 (2 C-3 of 5-Ph); 128.9 (5-Ph C-4); 128.8 (2 C-3 of anilide); 126.8 (4-Ph C-4); 125.1 (anilide C-4); 123.0 (pyrrole C-4); 121.5 (2 C-2 of anilide); 118.1 (pyrrole C-2); 69.1 (CHOH); 69.1 (CHOH); 44.9 (CH_2CO); 43.8 [CH(OH)CH_2CHOH]; 42.1(CH_2CH_2CHOH); 40.5 (CH_2CH_2CHOH); 27.6 [$CH(CH_3)_2$]; 22.9 [$CH(CH_3)_2$]; 22.9 [$CH(CH_3)_2$]. IR: 1657 (acid C=O), 1591 (C=O). HR-MS: for $C_{33}H_{37}N_2O_5$ $[M + H]^+$ calculated 541.2697 *m/z*, found 541.2696.

Calcium (3*R*,5*R*)-7-{(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrol-1-yl]-3,5-dihydroxyheptanamido}-3,5-dihydroxyheptanoate (**10**)

A mixture of lactone **8** (0.25 g, 0.46 mmol) and amine **3** (0.18 g, 0.48 mmol) was refluxed in toluene in the presence of triethylamine (0.2 ml) for 2 h. The reaction mixture was evaporated, dissolved in tetrahydrofuran (4 ml) and a solution of hydrochloric acid (10%; 1 ml) was added. After stirring at 25 °C for 6 h, a solution of concentrated sodium hydroxide (40%; 0.5 ml) was added over 5 min, maintaining the temperature below 35 °C. The mixture was vigorously stirred for 15 h, and then poured into a separatory funnel containing water (5 ml) and hexane (5 ml). The organic layer was removed and the aqueous layer extracted with a mixture of hexane (8 ml) and tetrahydrofuran (2 ml). After complete separation, the aqueous layer was extracted with ethyl acetate (3 × 5 ml) and the combined ethyl acetate extracts were shaken with a solution of calcium acetate (5%; 3 × 1 ml). The resulting ethyl acetate solution was washed with water (2 × 1 ml) and, after drying with anhydrous calcium sulfate, evaporated in vacuo to give 0.16 g (69%) of **10** as a white solid. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): 7.3–6.9, 1 H (NHCO); 7.29 d, 2 H, J = 8.1 (anilide H-2); 7.24 m, 2 H (4-FC_6H_4 H-2); 7.22 m, 2 H (Ph H-2); 7.13 m, 2 H (Ph H-3); 7.10 m, 2 H (anilide H-3); 7.06 m, 2 H (4-FC_6H_4 H-3); 7.05 m, 1 H (Ph H-4); 7.03 m, 2 H (anilide H-4); 4.14 m, 1 H [C**H**(OH)CH_2COO]; 4.07 m, 1 H (NCH_2); 3.95 m, 1 H (NCH_2); 3.95 m, 1 H [C**H**(OH)CH_2CO]; 3.82 m, 1 H [$NHCH_2CH_2$C**H**(OH)]; 3.65 m, 1 H [NCH_2CH_2C**H**(OH)]; 3.37 sept, 1 H, J = 7.3 [C**H**$(CH_3)_2$]; 3.27 m, 2 H (NHC**H**$_2$); 2.38 m, 2 H (CH_2COO); 2.30 m, 2 H (CH_2CO); 1.73 m, 2 H (NCH_2C**H**$_2$); 1.70 m, 1 H (NCH_2C**H**$_2$); 1.65 m, 2 H [C**H**$_2$CH(OH)CH_2COO]; 1.60 m, 1 H ($NHCH_2$C**H**$_2$); 1.55 m, 1 H (C**H**$_2$CH(OH)CH_2CO]; 1.48 d, 6 H, J = 7.0 [CH(C**H**$_3$)$_2$]; 1.45 m, 1 H [C**H**$_2$CH(OH)CH_2CO]. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): 180.5 (COO); 174.0 (CO); 169.6 (CONH); 163.8, $J_{C,F}$ = 246.8 (4-FC_6H_4 C-4); 139.8 (anilide C-1); 139.0 (pyrrole C-2); 134.7 (Ph C-1); 134.7, $J_{C,F}$ = 8.1 (2 C-2 of 4-FC_6H_4); 130.9 (2 C-3 of Ph); 130.2, $J_{C,F}$ = 3.8 (4-FC_6H_4 C-1); 129.6 (2 C-2 of Ph); 128.7 (2 C-3 of anilide); 127.3 (pyrrole C-5); 126.7 (Ph C-4); 125.1 (anilide C-4); 123.3 (pyrrole C-4); 121.5 (2 C-2 of anilide); 118.1 (pyrrole C-3); 116.3, $J_{C,F}$ = 21.9 (2 C-3 of 4-C_6H_4); 69.1 [CH(OH)CH_2COO]; 68.8 [$NHCH_2CH_2$CH(OH)]; 68.5 [NCH_2CH_2CH(OH)]; 68.2 [CH(OH)CH_2CO]; 45.0 [CH(OH)CH_2COO]; 44.5 [CH(OH)CH_2CO]; 44.4 (NCH_2CH_2); 44.4 [CH_2CH(OH)CH_2CO]; 42.2 (NCH_2CH_2); 40.2 [CH_2CH(OH)CH_2COO]; 37.9 ($NHCH_2CH_2$); 37.1 ($NHCH_2CH_2$); 27.6 [$CH(CH_3)_2$]; 22.8 [$CH(CH_3)_2$]. IR: 1645 (acid C=O), 1600 (C=O). MS, *m/z* (%): 718 $[M + H]^+$ (10), 607 (100), 558 (55), 477 (30).

Methyl (3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-3,5-dihydroxyheptanoate (**11a**)

Atorvastatin (2 g, 1.73 mmol) was dissolved in tetrahydrofuran (10 ml) and concentrated hydrochloric acid (0.5 ml) was added. The resulting solution was diluted with ethyl acetate

(40 ml), the solution was washed with brine (2 × 5 ml) and dried with anhydrous magnesium sulfate. After evaporation, the residue was redissolved in a mixture of methanol (20 ml) and concentrated hydrochloric acid (0.2 ml), and the mixture was refluxed for 5 h. The solution was evaporated and the residue was crystallized from hexane/ethyl acetate to give white crystals of **11a** (1.2 g, 61%), m.p. 110–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.18 m, 2 H (anilide H-3); 7.18 m, 2 H (Ph H-2); 7.18 m, 2 H (4-FC_6H_4 H-2); 7.16 m, 1 H (Ph H-4); 7.16 m, 2 H, *J* = 7.4 (Ph H-3); 7.05 d, 2 H, *J* = 8.7 (anilide H-2); 6.99 m, 2 H (4-FC_6H_4 H-3); 6.96 m, 1 H (anilide H-4); 6.85 s, 1 H (NH); 4.15 m, 1 H [CH(OH)CH_2C**H**OH]; 4.10 m, 1 H (C**H**$_2$$CH_2$CHOH); 3.94 m, 1 H (C**H**$_2$$CH_2$CHOH); 3.73 m, 1 H [C**H**(OH)CH_2CHOH]; 3.71 s, 3 H; 3.58 sept, 1 H, *J* = 7.1 [C**H**$(CH_3)_2$]; 2.41 m, 1 H (CH_2CO); 1.64 m, 2 H (CH_2C**H**$_2$CHOH); 1.54 d, 3 H, *J* = 7.1 [CH(C**H**$_3)_2$]; 1.54 d, 3 H, *J* = 7.1 [CH(C**H**$_3)_2$]; 1.36 m, 2 H [(C**H**$_2$CH(OH)]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 172.9 (CO); 164.8 (CONH); 162.2, $J_{C,F}$ = 247.6 (4-FC_6H_4 C-4); 141.3 (pyrrole C-2); 137.4 (anilide C-1); 134.4 (Ph C-1); 133.1, $J_{C,F}$ = 8.2 (2 C-2 of 4-FC_6H_4); 130.4 (2 C-3 of Ph); 128.7 (pyrrole C-5); 128.7 (2 C-2 of Ph); 128.4, $J_{C,F}$ =3.6 (4-FC_6H_4 C-1); 128.2 (2 C-3 of anilide); 126.4 (Ph C-4); 123.2 (anilide C-4); 121.8 (pyrrole C-4); 119.5 (2 C-2 of anilide); 115.3, $J_{C,F}$ = 21.6 (2 C-3 of 4-FC_6H_4); 115.3 (pyrrole C-3); 69.7 [**C**H(OH)CH_2CHOH]; 68.8 [CH(OH)CH_2**C**HOH]; 51.8 (OCH_3); 41.7 [CH(OH)**C**H_2CHOH]; 42.1 (CH_2CO); 41.2 (NCH_2); 38.0 (NCH_2**C**H_2); 26.0 [**C**$H(CH_3)_2$]; 21.8 [CH(**C**$H_3)_2$]; 21.7 [CH(**C**$H_3)_2$]. IR: 1690 (C=O), 17159 (ester C=O). HR-MS: for $C_{34}H_{38}N_2O_5F$ $[M + H]^+$ calculated 573.2759 *m/z*, found 573.2759.

tert-Butyl (3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-3,5-dihydroxyheptanoate (**11b**)

A solution of hydrochloric acid (10%; 15 ml) was slowly added to a solution of compound **2** (4 g, 6.1 mmol) in tetrahydrofuran (60 ml) and the mixture was stirred at ambient temperature for 6 h. A solution of sodium hydroxide (5.4 g, 0.135 mol) in water (100 ml) was then added and the mixture was extracted with heptane (80 ml). The organic layer was washed with water (10 ml) and dried with anhydrous magnesium sulfate. The extract was filtered and evaporated to give **11b** as a white solid (2.7 g, 64%), m.p. 155 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.18 m, 2 H (anilide H-3); 7.18 m, 2 H (Ph H-2); 7.18 m, 2 H (4-FC_6H_4 H-2); 7.17 m, 1 H (Ph H-4); 7.16 m, 2 H, *J* = 7.6 (Ph H-3); 7.07 d, 2 H, *J* = 8.8 (anilide H-2); 6.99 m, 2 H (4-FC_6H_4 H-3); 6.98 m, 1 H (anilide H-4); 6.87 s, 1 H (NH); 4.13 m, 1 H [CH(OH)CH_2C**H**OH]; 4.13 m, 1 H (C**H**$_2$$CH_2$CHOH); 3.95 m, 1 H (C**H**$_2$$CH_2$CHOH); 3.74 m, 1 H [C**H**(OH)CH_2CHOH]; 3.57 sept, 1 H, *J* = 7.4 [C**H**$(CH_3)_2$]; 2.65 m, 1 H (CH_2CO); 1.70 m, 1 H (CH_2C**H**$_2$CHOH); 1.65 m, 1 H (CH_2C**H**$_2$CHOH); 1.54 d, 3 H, *J* = 7.5 [CH(C**H**$_3)_2$]; 1.54 d, 3 H, *J* = 7.5 [CH(C**H**$_3)_2$]; 1.45 m, 1 H (CH_2C**H**$_2$CHOH); 1.43 s, 9 H [C$(CH_3)_3$]; 1.25 m, 1 H (CH_2C**H**$_2$CHOH). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 172.2 (CO); 164.8 (CONH); 162.2, $J_{C,F}$ = 247.6 (4-FC_6H_4 C-4); 141.6 (pyrrole C-2); 138.4 (anilide C-1); 134.6 (Ph C-1); 133.2, $J_{C,F}$ = 8.2 (2 C-2 of 4-FC_6H_4); 130.5 (2 C-3 of Ph); 128.7 (pyrrole C-5); 128.7 (2 C-2 of Ph); 128.4, $J_{C,F}$ = 3.6 (4-FC_6H_4 C-1); 128.3 (2 C-3 of anilide); 126.5 (Ph C-4); 123.5 (anilide C-4); 121.8 (pyrrole C-4); 119.5 (2 C-2 of anilide); 115.3, $J_{C,F}$ = 21.6 (2 C-3 of 4-FC_6H_4); 115.3 (pyrrole C-3); 81.9 [**C**$(CH_3)_3$]; 69.7 [**C**H(OH)CH_2CHOH]; 69.2 [CH(OH)CH_2**C**HOH]; 41.7 [CH(OH)**C**H_2CHOH]; 42.1 (**C**H_2CO); 41.3 (NCH_2); 38.0 (NCH_2**C**H_2); 28.1 [C(**C**$H_3)_3$]; 26.1 [**C**$H(CH_3)_2$]; 21.8 [CH(**C**$H_3)_2$]; 21.7 [CH(**C**$H_3)_2$]. IR: 1698 (C=O), 1725 (C=O ester). HR-MS: for $C_{37}H_{44}N_2O_5F$ $[M + H]^+$ calculated 615.3229 *m/z*, found 615.3223.

(2*E*,5*S*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-5-hydroxyhept-2-enoic Acid (**12b**)

Acetic anhydride (1.5 g, 14.7 mmol) was slowly added to a solution of ester **11a** (10 g, 17.5 mmol), triethylamine (5.2 g, 51.5 mmol) and 4-(dimethylamino)pyridine (0.1 g) in toluene (100 ml) and the mixture was stirred at 60 °C for 2 h. The reaction mixture was then concentrated, tetrahydrofuran (50 ml) and a solution of sodium hydroxide (0.54 g, 13.5 mol) in water (10 ml) were added, and the mixture was stirred at ambient temperature for 16 h. Heptane (50 ml) was then added, the organic layer was removed and the aqueous layer was acidified and extracted with ethyl acetate (100 ml). The organic extract was evaporated to give a foam containing 30% of atorvastatin, 9% of "*E* alkene" **12** and 30% of the corresponding "*Z* alkene" (HPLC). The residue was purified by column chromatography using toluene/propan-2-ol/acetic acid (70:25:5, v/v) to afford compound **12b** (0.45 g, 5%) as a white solid, m.p. 125–130 °C. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): 8.54 s, 1 H (NH); 7.29 d, 2 H, J = 8.1 (anilide H-2); 7.23 d, 2 H (4-FC_6H_4 H-2); 7.22 m, 2 H (Ph H-2); 7.13 m, 2 H (Ph H-3); 7.09 m, 2 H (anilide H-3); 7.06 m, 2 H (4-FC_6H_4 H-3); 7.04 m, 1 H (Ph H-4); 7.02 m, 1 H (anilide H-4); 6.55 ddd, 1 H, J = 15.2, 7.3 (C**H**CHCO); 5.81 d, 1 H, J = 15.5 (CHC**H**CO); 4.05 m, 1 H (C**H**$_2$CH$_2$CHOH); 3.85 m, 1 H (C**H**$_2$CH$_2$CHOH); 3.47 q, 1 H, J = 7.0 (C**H**OH); 3.35 sept, 1 H, J = 6.9 [C**H**(CH$_3$)$_2$]; 2.16 m, 2 H [CH(OH)C**H**$_2$]; 1.64 m, 2 H (C**H**$_2$CH$_2$CHOH); 1.48 d, 3 H, J = 7.0 [CH(C**H**$_3$)$_2$]; 1.47 d, 3 H, J = 7.0 [CH(C**H**$_3$)$_2$]. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): 175.9 (COOH); 169.6 (CONH); 163.8, $J_{C,F}$ = 246.4 (4-FC_6H_4 C-4); 140.2 (**C**HCHCO); 139.8 (anilide C-1); 138.9 (pyrrole C-5); 136.4 (Ph C-1); 134.7, $J_{C,F}$ = 8.1 (2 C-2 of 4-FC_6H_4); 131.2 (CH**C**HCO); 130.9 (2 C-3 of Ph); 130.2, $J_{C,F}$ = 3.2 (4-FC_6H_4 C-1); 129.6 (2 C-2 of Ph); 128.9 (pyrrole C-2); 128.8 (anilide 2 C-3); 126.8 (Ph C-4); 125.1 (anilide C-4); 123.3 (pyrrole C-3); 121.5 (anilide 2 C-2); 118.0 (pyrrole C-4); 116.3, $J_{C,F}$ = 22.0 (2 C-3 of 4-FC_6H_4); 69.5 (CHOH); 42.4 (**C**H$_2$CH$_2$CHOH); 41.1 [CH(OH)**C**H$_2$]; 39.8 (CH$_2$**C**H$_2$CHOH); 27.6 [**C**H(CH$_3$)$_2$]; 22.8 [CH(**C**H$_3$)$_2$]; 22.8 [CH(**C**H$_3$)$_2$]. IR: 1566 (C=O), 1668 (acid C=O). HR-MS: for $C_{33}H_{34}FN_2O_4$ $[M + H]^+$ calculated 541.2497 *m/z*, found 541.2496.

tert-Butyl (3*S*,5*S*)-6-Cyano-3,5-dihydroxyhexanoate (**28**)

(5*S*)-*tert*-Butyl 6-cyano-5-hydroxy-3-oxohexanoate (**27**; 2.22 g, 9.8 mmol) was dissolved in a mixture of tetrahydrofuran (20 ml) and methanol (3 ml), the solution was cooled to –78 °C and a 1 M solution of diethyl(methoxy)borane in THF (9.7 ml, 9.7 mmol) was added. Sodium borohydride (0.33 g, 8.7 mmol) was subsequently added in two portions, and the mixture was maintained at –78 °C for 4 h. The reaction was quenched by the addition of acetic acid (10 ml) and water (10 ml), and the resultant mixture was extracted with ethyl acetate (40 ml). The organic layer was washed with water (10 ml), dried with anhydrous magnesium sulfate and evaporated to provide the crude product which was used for the following step without further purification.

tert-Butyl (4*S*,6*S*)-6-(Cyanomethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**29**)

Crude *tert*-butyl (3*S*,5*S*)-6-cyano-3,5-dihydroxyhexanoate (**28**; 2.2 g, 9.6 mmol) was dissolved in a mixture of acetone (5 ml) and 2,2-dimethoxypropane (10 ml). 4-Methylbenzene-1-sulfonic acid was added (200 mg), and the solution was stirred for another 5 h. The reaction was quenched by the addition of triethylamine (0.2 ml), the resultant mixture was evaporated and subjected to column chromatography using hexane/acetone (7:3, v/v) to

provide compound **29** as an oil. Crystallization from hexanes gave **29** as a white solid (2.1 g, 81%), m.p. 65–67 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): 4.28 dddd, 1 H, *J* = 2.5, 4.5, 7.6, 8.2 [(CH(O)]; 4.14 ddt, 1 H, *J* = 1.6, 7.6 [(CH(O)]; 2.51 dd, 2 H, *J* = 1.6, 7.6 (CH_2CN); 2.47 dd, 1 H, *J* = 8.2, 14.2 (CH_2CO); 1.72 m, 2 H [CH(OH)C**H**$_2$CH(OH)]; 1.46 s, 9 H [$C(CH_3)$]; 1.45 q, 1 H, *J* = 0.6 (CH_3); 1.38 q, 3 H, *J* = 0.6 (CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 172.9 (CO); 117.5 (CN); 104.4 (OCO); 80.3 [**C**$(CH_3)_3$]; 68.1 [CH(O)]; 66.7 [CH(O)]; 41.3 (**C**H_2CO); 41.0 [CH(O)**C**H_2CH(O)]; 27.7 [C(**C**$H_3)_3$]; 24.9 (**C**H_2CN); 20.0 (CH_3). IR: 225 (CN), 1724 (C=O ester). HR-MS: for $C_{14}H_{24}NO_4$ $[M + H]^+$ calculated 270.1700 *m/z*, found 270.1701.

tert-Butyl (4*S*,6*S*)-6-(2-Aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**30**)

A solution of compound **29** (2 g, 7.4 mmol) in MeOH (50 ml) saturated with ammonia gas was hydrogenated at 40 °C (810 kPa). After 5 h, the catalyst was filtered off and the filtrate evaporated to give crude amine **30** (2.2 g), which was used in the next step without further purification.

tert-Butyl (4*S*,6*S*)-6-{2-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (**31**)

A mixture of amine **30** (2.2 g, 6 mmol), diketone **19** (2 g, 4.8 mmol) and pivalic acid (0.60 g, 6 mmol) was refluxed in a mixture of heptane (40 ml) and toluene (5 ml) for 19 h. The mixture was then evaporated and the residue was crystallized from propan-2-ol to give **31** (4.05 g, 77%) as a white solid, m.p. 175–177 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 7.18 m, 2 H (anilide H-2); 7.18 m, 2 H (Ph H-2); 7.17 m, 1 H (Ph H-4); 7.17 m, 2 H (4-FC_6H_4 H-2); 7.16 m, 2 H (Ph H-3); 7.07 d, 2 H, *J* = 8.8 (anilide H-3); 6.99 m, 2 H (4-FC_6H_4 H-3); 6.99 m, 1 H (anilide H-4); 6.87 s, 1 H (NH); 4.15 m, 1 H (dioxane H-4); 4.10 m, 1 H (NC**H**$_2$CH$_2$); 3.83 m, 1 H (NC**H**$_2$CH$_2$); 3.67 m, 1 H (dioxane H-6); 3.58 sept, 1 H, *J* = 7.4 [C**H**$(CH_3)_2$]; 2.39 dd, 1 H, *J* = 15.4, 6.9 (CH_2COO); 2.24 dd, 1 H, *J* = 15.4, 6.2 (CH_2COO); 1.67 m, 2 H (NCH$_2$C**H**$_2$); 1.54 d, 3 H, *J* = 7.5 [CH(C**H**$_3)_2$]; 1.54 d, 3 H, *J* = 7.5 [CH(C**H**$_3)_2$]; 1.43 s, 9 H [$C(CH_3)_3$]; 1.36 s, 3 H [$C(CH_3)_2$]; 1.35 m, 1 H (dioxane H-5); 1.30 s, 3 H [$C(CH_3)_2$]; 1.05 m, 1 H (dioxane H-5). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): 170.1 (COO); 164.8 (CONH); 163.2, $J_{C,F}$ = 248.5 (4-FC_6H_4 C-4); 141.5 (pyrrole C-5); 138.4 (anilide C-1); 134.6 (Ph C-1); 133.1, $J_{C,F}$ = 8.2 (4-FC_6H_4 C-2); 130.5 (2 C-3 of Ph); 128.7 (pyrrole C-2); 128.6 (Ph C-2); 128.3 (anilide C-3); 128.2, $J_{C,F}$ = 2.8 (4-FC_6H_4 C-1); 126.5 (Ph C-4); 123.5 (anilide C-4); 122.7 (pyrrole C-3); 119.5 (anilide C-2); 115.3 (pyrrole C-4); 115.3, $J_{C,F}$ = 21.4 (4-FC_6H_4 C-3); 98.6 (dioxane C-2); 80.7 [**C**$(CH_3)_3$]; 66.4 (dioxane C-6); 65.1 (dioxane C-4); 42.4 (NCH_2); 40.8 (**C**H_2COO); 38.0 (NCH_2**C**H_2); 35.9 (dioxane C-5); 29.9 [C(**C**$H_3)_2$]; 28.1 [C(**C**$H_3)_3$]; 26.1 [**C**$(CH_3)_2$]; 21.7 [CH(**C**$H_3)_2$]; 21.5 [CH(**C**$H_3)_2$]; 19.6 [C(**C**$H_3)_2$]. IR: 1615 (C=O), 1715 (ester C=O). HR-MS: for $C_{40}H_{48}FN_2O_5$ $[M + H]^+$ calculated 655.3542 *m/z*, found 655.3543.

Calcium (3*S*,5*S*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-pyrrol-1-yl]-3,5-dihydroxyheptanoate (**13**)

Dilute hydrochloric acid (10%; 3 ml) was added to a solution of **31** (1 g, 1.5 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at 25 °C for 6 h, and then a concentrated solution of sodium hydroxide (40%; 2 ml) was added over 5 min while maintaining the temperature below 35 °C. The formed heterogeneous mixture was vigorously stirred for 15 h,

and then poured into a separatory funnel containing water (30 ml) and hexane (10 ml). The organic layer was removed and the aqueous layer was extracted with a mixture of hexane (8 ml) and tetrahydrofuran (2 ml). After separation, the aqueous layer was extracted with ethyl acetate (3 × 8 ml), and the combined extracts were shaken with a solution of calcium acetate (20%; 3 × 1 ml). The resulting ethyl acetate solution was washed with water (2 × 1 ml), dried with anhydrous calcium sulfate and concentrated in vacuo to 4 ml. After filtration, the clear solution was added dropwise over 5 min to hexane (40 ml) under vigorous stirring, and the mixture was stirred for another 20 min. The precipitate was filtered off, washed with hexane (20 ml) and dried to give 0.82 g (93%) of **13**, m.p. 170 °C (dec.). Chiral purity (HPLC) > 99.5% ee. ^{1}H NMR (500 MHz, CD_3OD, 25 °C): 7.3–6.9, 1 H (NH); 7.28 m, 2 H, J = 8.1 (anilide H-2); 7.22 m, 2 H (4-FC_6H_4 H-2); 7.20 m, 2 H (Ph H-2); 7.13 m, 2 H (Ph H-3); 7.08 m, 2 H (anilide H-3); 7.04 m, 2 H (4-FC_6H_4 H-3); 7.03 m, 1 H (Ph H-4); 7.02 m, 1 H (anilide H-4); 4.05 m, 1 H (C**H**$_2$$CH_2$CHOH); 4.01 m, 1 H [CH(OH)CH_2C**H**OH]; 3.91 m, 1 H (C**H**$_2$$CH_2$CHOH); 3.66 m, 1 H [C**H**(OH)CH_2CHOH]; 3.36 sept, 1 H, J = 7.1 [C**H**$(CH_3)_2$]; 2.33 dd, 1 H, J = 15.4, 3.5 (CH_2CO); 2.22 dd, 1 H, J = 15.6, 8.7 (CH_2CO); 1.68 m, 2 H (CH_2C**H**$_2$CHOH); 1.53 m, 1 H [CH(OH)C**H**$_2$CHOH]; 1.49 d, 3 H, J = 7.2 [CH(C**H**$_3$)$_2$]; 1.48 d, 3 H, J = 7.2 [CH(C**H**$_3$)$_2$]; 1.36 m, 1 H [CH(OH)C**H**$_2$CHOH]. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): 182.0 (COO); 169.3 (CONH); 163.8, $J_{C,F}$ = 247.2 (4-FC_6H_4 C-4); 139.8 (anilide C-1); 139.2 (pyrrole C-2); 136.3 (Ph C-1); 134.7, $J_{C,F}$ = 7.8 (2 C-2 of 4-FC_6H_4); 131.0 (2 C-3 of Ph); 130.2, $J_{C,F}$ = 2.9 (4-FC_6H_4 C-1); 129.6 (pyrrole C-5); 129.6 (2 C-2 of Ph); 128.9 (2 C-3 of anilide); 126.9 (Ph C-4); 125.1 (anilide C-4); 123.3 (pyrrole C-4); 121.5 (2 C-2 of anilide); 118.1 (C-3 of pyrrole); 116.3, $J_{C,F}$ = 21.5 (2 C-3 of 4-FC_6H_4); 67.0 (5-CHOH); 66.9 (3-CHOH); 45.3 (CH_2CO); 44.5 [CH(OH)CH_2CHOH]; 42.4 (CH_2CH_2CHOH); 41.0 (CH_2CH_2CHOH); 27.6 [CH$(CH_3)_2$]; 22.8 [CH(CH_3)$_2$]; 22.8 [CH(CH_3)$_2$]. IR: 1569 (C=O), 1710 (C=O acid). HR-MS: for $C_{33}H_{36}FN_2O_5$ $[M + H]^+$ calculated 559.2603 m/z, found 559.2608.

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