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A novel strategy towards the atorvastatin lactone

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ABSTRACT

We describe a novel strategy to the atorvastatin lactone based on a Paal–Knorr synthesis of pyrrole **24** by condensing diketone **23** with primary amine **22**. The latter contains the *syn*-1,3-diol subunit and a benzyl ether function at the other end of the chain. This allowed for manipulations on the pyrrole ring via iodination at C2, metalation with *t*-BuLi and carboxylation. The obtained acid **26** could be converted via amide formation, debenzylation, oxidation and lactonization to atorvastatin lactone **6**. The key building block, 2-((4*R*,6*S*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanamine (**22**) was obtained by two sequential asymmetric transfer hydrogenative carbonyl allylations according to Krische.

1. Introduction

Statins, like compounds **1**–**4** represent a well established class of drugs for reducing plasma cholesterol levels (Fig. 1).[1] They are commonly prescribed to lower the risk of cardiovascular disease. Over the years the broad use of statins revealed a range of additional, mostly positive effects of these compounds.[2] These include increased nitric oxide bioavailability, antioxidant effects, and in particular anti-inflammatory effects.[3] For lovastatin (**1**) and some derivatives thereof it could be shown that they suppress the inflammatory response in an animal model of peritonitis by binding to the β2 integrin leukocyte function antigen-1 (LFA-1).[4] However, it seems that other statins like atorvastatin do not bind to this heterodimeric glycoprotein.[5] In order to detect other cellular targets than 3-hydroxy-3-methylglutaryl coenzyme-A reductase,[6] an atorvastatin affinity probe might be useful.[7,8] Since we wanted to keep the side chain δ-valerolactone part intact, the carboxyl function in the pyrrole part appeared as a promising handle. In this paper we describe the synthesis of atorvastatin carboxylic acid **26** and its conversion to atorvastatin lactone (**6**).

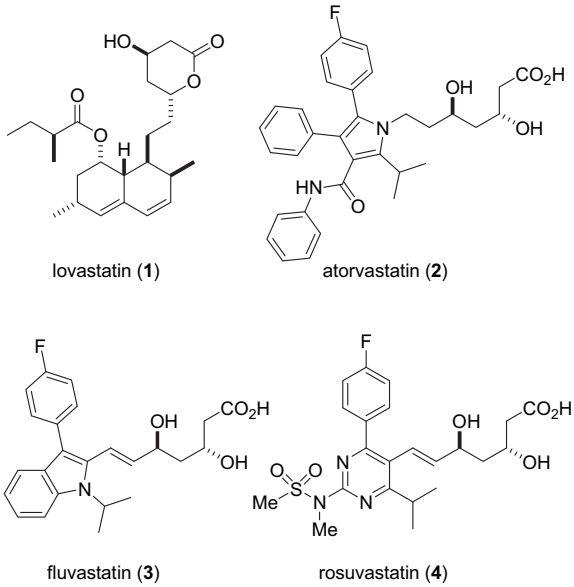

Fig. 1. Structures of some important statins.

2. Results and discussion

In the original synthesis of atorvastatin the fully functionalized pyrrole ring **5** with a 3-oxopropyl substitutent on the nitrogen was obtained via [3+2] cycloaddition of a mesoionic heterocycle with a propynamide.[9] This aldehyde was then extended by a sequence of an acetate aldol reaction, a Claisen condensation to a δ-hydroxy-β-ketoester, and a hydroxyl-directed reduction leading to chiral lactone **6** (Fig. 2).

In a later report atorvastatin (**1**) was prepared by Paal–Knorr condensation of diketoamide **7** with primary amine **8** leading to

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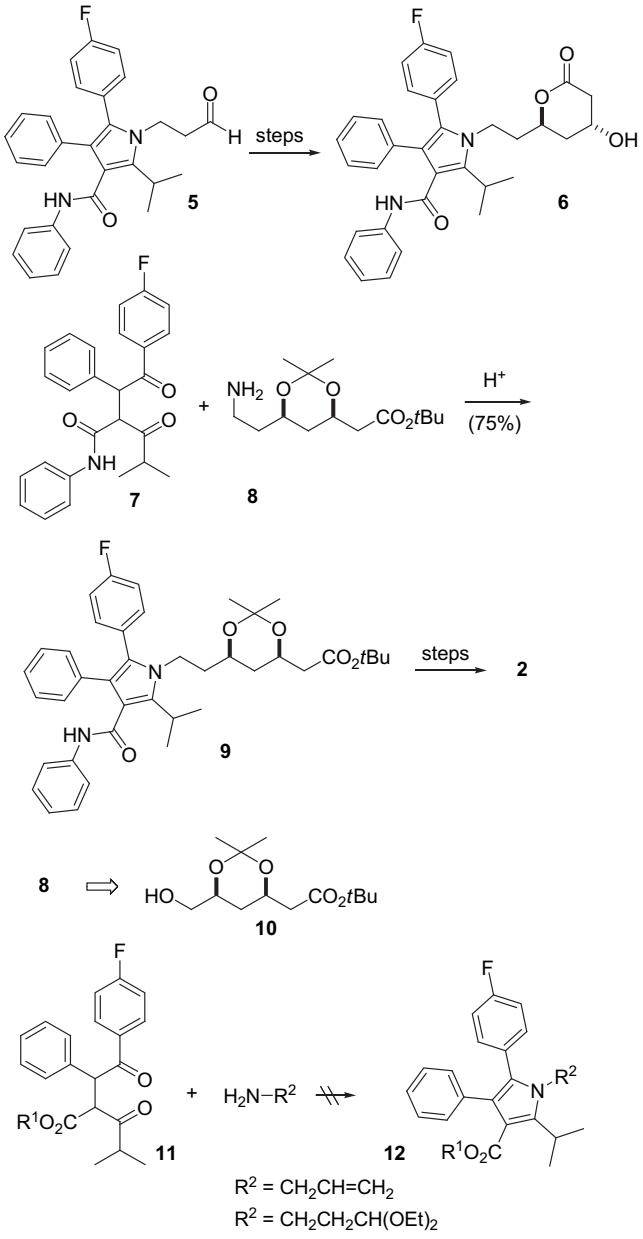


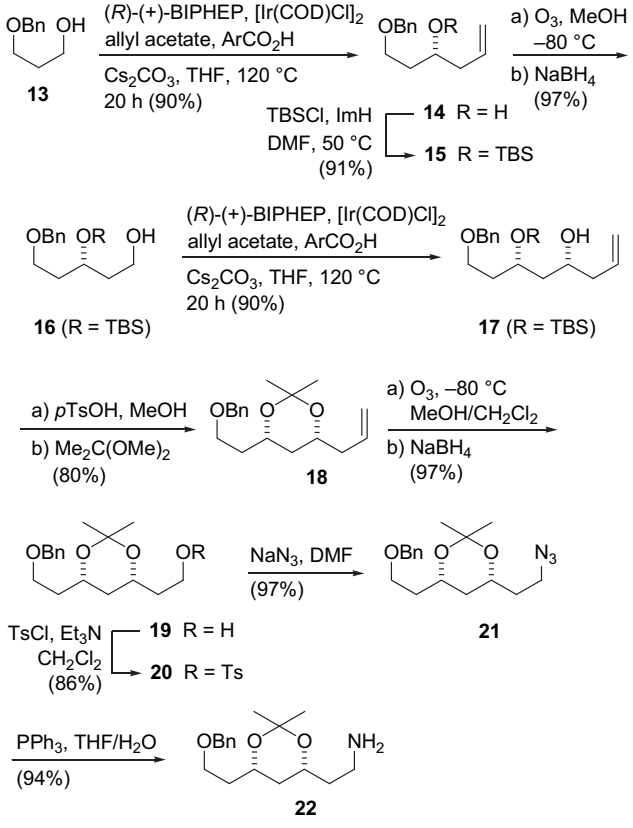
Fig. 2. Approaches to atorvastatin with regard to the side chain.

advanced intermediate **9**.[10,11] The key amine **8** is generally prepared from *tert*-butyl-[(4*R*,6*S*)-6-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate (**10**) via chain extension.[12] Several preparations of this or related compounds have been described in the literature.[13] In several cases biocatalytic methods have been used to reduce prochiral precursors like 4-chloro-/4-bromo-3-oxobutyrate or 3,5-dioxo-6-benzyloxy-hexanoate.[14] In addition, enzymatic symmetry breaking of 3-hydroxyglutaronitrile[15] or 3-alkoxyglutaric acid ester[11] have been employed to create building blocks with one stereocenter. Another paper describes the lipase-mediated resolution of 1-chloro-3-arylmethoxy-2-propanols and their conversion into hydroxy ester **10**.[16] Furthermore, organocatalytic aldol reactions to compounds like **10** have been reported.[17] A highly practical route to compound **10** involves the Noyori-type hydrogenation of ethyl 4-benzyloxy acetoacetate followed by Claisen condensation and *syn*-reduction of the hydroxy ketone function.[18] Finally, L-malic acid has served as a precursor to hydroxy ester **10**.[19]

The initial idea was to perform a Paal–Knorr synthesis between diketoester **11** and a primary amine like **8** (Fig. 2) since this would allow for facile manipulations at the carboxylic function of the corresponding pyrrole. We tried this condensation with allylamine, 3,3-diethoxypropan-1-amine and amine **8**. These reactions were carried out in a toluene/heptane/THF (6:10:5) mixture in presence of pivalic acid under reflux and checked by TLC. These conditions[20] led to a series of spots on TLC, however, the desired pyrroles were not formed.

This required a redesign of the synthetic route. The plan called for pyrrole formation without the carboxylic function followed by halogenation, metalation and carboxylation of the pyrrole ring. Accordingly, an ester function at the amine terminus seemed not compatible with these conditions. As an ideal building block we identified amine **22**. While in principle this amine could be prepared from known *tert*-butyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**10**) this was considered lengthy and redox-inefficient.[21]

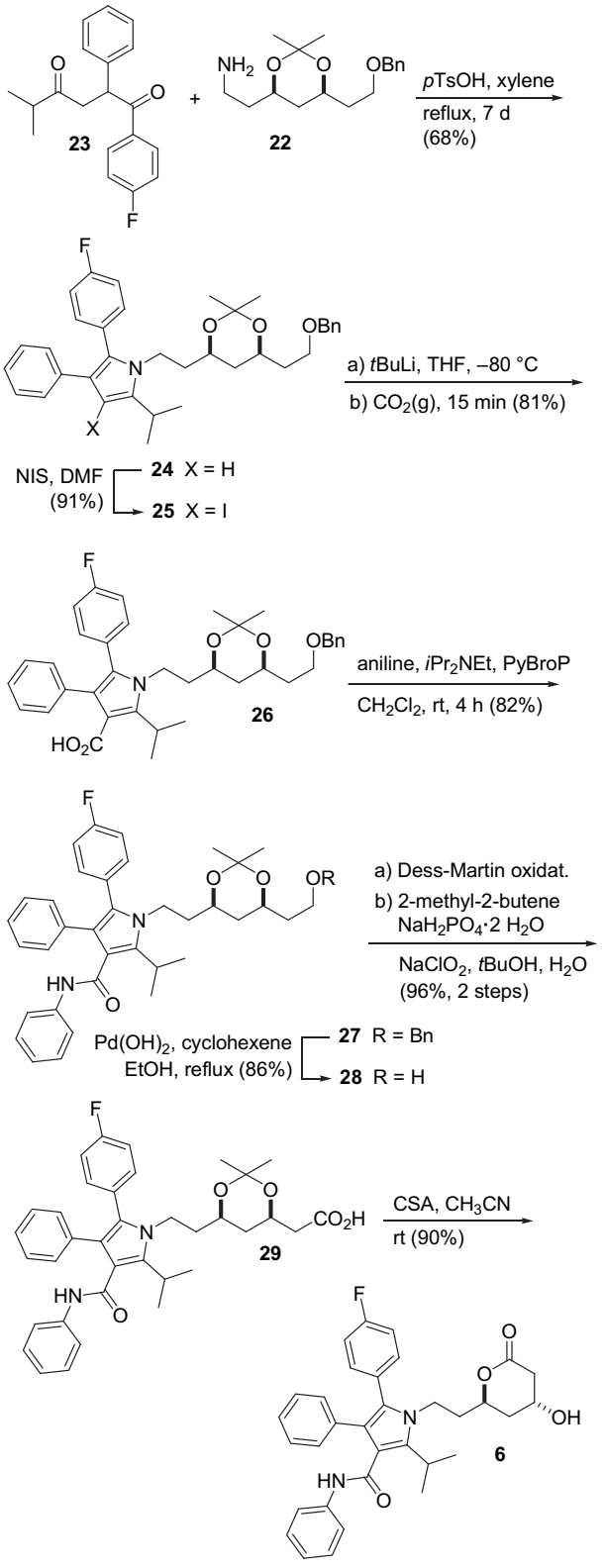
The synthesis of amine **22** is described in Scheme 1. The *syn*-1,3-diol subunit was fashioned from benzyloxy-propanol[22] (**13**) by two iterative asymmetric transfer hydrogenative carbonyl allylations as described by Krische et al.[23] Thus, using a catalyst generated from $[Ir(cod)Cl_2]$, (*R*)-Cl, Meo-BIPHEP and 4-chloro-3-nitro-benzoic acid, alcohol **13** was coupled with allyl acetate (2 equiv) to give homoallylic alcohol **14** in 90% yield (92% ee). Alcohol protection to **15** followed by ozonolysis and in situ reduction furnished alcohol **16**. Applying similar conditions to alcohol **16** *syn*-diol derivative **17** was obtained. Protection of the diol as acetal to building block **18** and oxidative degradation of the double bond led to alcohol **19**. Via the corresponding tosylate **20**, azide **21** was prepared by the reaction of **20** with sodium azide in DMF. Reduction of the azide **21** with triphenylphosphine[24] in a THF/H_2O mixture gave rise to amine **22**.



Scheme 1. Synthesis of primary amine **22**; $ArCO_2H$=4-Cl-3-NO_2-$C_6H_3CO_2H$.

Continuing with the synthesis, diketone[9] **23** was condensed with amine **22** in xylene in presence of *p*TsOH·H_2O (0.2 equiv) (Scheme 2). The reaction was rather slow and required heating for 7 days to give pyrrole **24** in 68% yield. The acetal remained stable under these conditions. Treatment of pyrrole **24** with *N*-

iodosuccinimide (NIS) in DMF delivered iodopyrrole **25** in excellent yield.[25] Due to its somewhat sensitive nature it was subjected without prolonged storage to halogen–metal exchange with *t*-BuLi. Trapping of the lithiated intermediate with gaseous carbon dioxide furnished carboxylic acid **26** in good yield. In order to reach atorvastatin, acid **26** was then condensed with aniline in presence of PyBroP[26,27] to afford amide **27**. Now we could refocus on the aliphatic part and the oxidation of its terminus. Accordingly, the benzyl ether group was cleaved by hydrogenation in the presence of $Pd(OH)_2$ and cyclohexene as hydrogen source[28] to produce alcohol **28**. Oxidation[29] of the alcohol to acid **29** and treatment with acid furnished the known atorvastatin lactone[9] **6**.



Scheme 2. Condensation of amine **22** with diketone **23** to pyrrole **24** and conversion of **24** to atorvastatin lactone **6**.

3. Conclusion

In summary, we could illustrate a new strategy to atorvastatin. One element includes a double Krische allylation to fashion the *syn*-1,3-diol subunit of the aliphatic side chain. While this reaction requires rather drastic conditions (heating to 120 °C) it is practical for simple substrates. Amine **22** derived from building block **19** was subjected to a Paal–Knorr condensation with diketone **23** to give pyrrole **24**. Via iodination and metalation, the carboxylic group could be introduced in the 2-position of the pyrrole. Conversion of the acid **26** to amide **27** and oxidation of the side chain terminus led to atorvastatin lactone **6**. The developed strategy should open the way to new amide derivatives of atorvastatin and should allow for attachment of a linker to the pyrrole carboxylic group.

4. Experimental section

4.1. (3*R*)-1-(Benzyloxy)hex-5-en-3-ol (14)

In a oven dried screw cap glass bottle (250 mL size) a mixture of alcohol **13** (4.0 g, 24.07 mmol), allyl acetate (5.24 mL, 48.13 mmol), $[Ir(cod)Cl]_2$, (404 mg, 2.5 mol%), (*R*)-(+)-Cl, MeO-BIPHEP, (784 mg, 5 mol%), 4-chloro-3-nitro-benzoic acid (485 mg, 2.41 mmol), Cs_2CO_3 (1.57 g, 4.81 mmol) in THF (130 mL) was heated at 120 °C under nitrogen for 20 h. The reaction mixture was adsorbed on silica gel and purified by flash chromatography (ethyl acetate/petroleum ether, 2:8) to furnish alcohol **14** (4.50 g, 90%,) as colourless oil. Enantiomeric ratio as determined by Mosher analysis 96:4. R_f (ethyl acetate/petroleum ether, 2:8) 0.34; $[\alpha]_D^{20}$ +2.7 (*c* 1.0, $CHCl_3$); δH (400 MHz,$CDCl_3$) 1.71–1.81 (m, 2H, $BnOCH_2CH_2$), 2.22–2.26 (m, 2H, $CH_2CH{=}CH_2$), 3.61–3.74 (m, 2H, $BnOCH_2$), 3.84–3.90 (m, 1H, CHOH), 4.52 (s, 2H, $PhCH_2O$), 5.07–5.13 (m, 2H, $CH{=}CH_2$), 5.78–5.88 (m, 1H, $CH{=}CH_2$), 7.26–7.36 (m, 5H, Ar-H); δC (100 MHz, $CDCl_3$) 35.8 (CH_2), 41.9 (CH_2), 68.9 (CH_2), 70.3 (CH), 73.3 (CH_2), 117.5 ($CH{=}CH_2$), 127.6 (CH, phenyl), 127.7 (CH, phenyl), 128.4 (CH, phenyl), 134.8 ($CH{=}CH_2$), 137.9 (C, phenyl).

4.2. ({(1*R*)-1-[2-(Benzyloxy)ethyl]but-3-enyl}oxy)(*tert*-butyl) dimethylsilane (15)

A mixture of alcohol **14** (877 mg, 4.3 mmol), imidazole (723 mg, 10.6 mmol) and TBSCl (1.28 g, 8.5 mmol) in DMF (5 mL) was stirred at 50 °C overnight. Thereafter, water (10 mL) was added and the mixture extracted with diethyl ether (3×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 2:98) to give silyl ether **15** (1.27 g, 91%) as colourless oil. R_f (petroleum ether/diethyl ether, 98:2) 0.34; $[\alpha]_D^{20}$ –17.3 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.30 (s, 3H, $Si(CH_3)_2$), 0.50 (s, 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$), 1.66–1.83 (m, 2H, $BnOCH_2CH_2$), 2.16–2.28 (m, 2H, $CH_2CH{=}CH_2$), 3.52–3.55 (m, 2H, $BnOCH_2$), 3.87–3.92 (m, 1H, CHOH), 4.43 (d, *J*=11.9 Hz, 1H, $PhOCH_2$), 4.49 (d, *J*=11.9 Hz, 1H, $PhOCH_2$), 5.02 (m, 2H, $CH{=}CH_2$), 5.75–6.86 (m, 1H, $CH{=}CH_2$), 7.26–7.36 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) –4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 36.7 (CH_2), 42.3 (CH_2), 67.0 ($BnOCH_2$), 68.9 (CHOH), 72.9 ($PhCH_2$), 116.9 ($CH{=}CH_2$), 127.6 (CH, phenyl), 128.3 (CH, phenyl), 134.9 ($CH{=}CH_2$), 138.5 (C, phenyl); HRMS (ESI) calcd for $C_{19}H_{32}O_2Si$ $[M+Na]^+$ 343.20638, found 343.206354.

4.3. (3*R*)-5-(Benzyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy} pentan-1-ol (16)

To a solution of **15** (5.61 g, 17.5 mmol) in methanol (74 mL, 0.15 M), 2–3 drops of Sudan III (1% in methanol) were added as an indicator resulting in a pink colour solution. The mixture was cooled to −80 °C and ozone gas was bubbled through the solution until it turned pink to colourless (about 50 min). Residual O_3 was removed by passing nitrogen through the reaction (about 5 min). Thereafter, $NaBH_4$ (6.62 g, 175 mmol) was added and the reaction mixture was slowly allowed to reach room temperature, with the flask kept in the cooling bath. Water (30 mL) was added and the mixture was concentrated to ~50 mL on a rotary evaporator before it was extracted with ethyl acetate (3×120 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to provide alcohol **16** (5.52 g, 97%) as colourless oil. R_f (petroleum ether/ethyl acetate, 5:1) 0.24; $[\alpha]_D^{20}$ +3.2 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $C(CH_3)_3$), 1.62–1.69 (m, 1H, $BnOCH_2CH_2$), 1.79–1.90 (m, 3H, $BnOCH_2CH_2$, CH_2CH_2OH), 2.18 (br s, 1H, OH), 3.52 (t, *J*=6.3 Hz, 2H, $BnOCH_2$), 3.67–3.73 (m, 1H, CH_2OH), 3.78–3.84 (m, 1H, CHOH), 4.07–4.13 (m, 1H, CH_2OH), 4.43 (d, *J*=11.9 Hz, 1H, $PhOCH_2$), 4.49 (d, *J*=11.9 Hz, 1H, $PhOCH_2$); 7.26–7.36 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) −4.7 ($2Si(CH_3)_2$), 17.9 (C, silyl), 25.8 ($C(CH_3)_3$), 36.7 (CH_2), 38.3 (CH_2), 60.0 (CH_2OH), 66.8 ($BnOCH_2$), 69.0 (CHOH), 73.0 ($PhCH_2O$), 127.6 (CH, phenyl), 127.7 (CH, phenyl), 128.4 (CH, phenyl), 138.3 (C, phenyl); HRMS (ESI) calcd for $C_{18}H_{32}O_3Si$ $[M+Na]^+$ 347.20129, found 347.201340.

4.4. (4*R*,6*S*)-8-(Benzyloxy)-6-{[*tert*-butyl(dimethyl)silyl]oxy} oct-1-en-4-ol (17)

An oven dried screw cap bottle (200 mL) was charged under nitrogen with alcohol **16** (5.90 g, 18.2 mmol), $[Ir(cod)Cl]_2$ (305 mg, 0.46 mmol), (*R*)-(+)-Cl, MeO-BIPHEP (592 mg, 0.91 mmol), Cs_2CO_3 (1.18 g, 1.2 mmol) and 4-chloro-3-nitro-benzoic acid (366 mg, 1.82 mmol) in THF (100 mL) to which allyl acetate (3.64 g, 36.4 mmol) was added. The mixture was heated at 100 °C for 40 h. The mixture was cooled and then absorbed on silica gel (about 40 g) loaded on a column and purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to afford homoallyl alcohol **17** (5.26 g, 93%) as colourless oil. R_f (petroleum ether/ethyl acetate, 6:1) 0.38; $[\alpha]_D^{20}$+14.2 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.08 (s, 3H, $SiC(CH_3)_2$), 0.10 (s, 3H, $SiC(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.52–1.59 (m, 1H, CH_2CHOH), 1.63–1.68 (m, 1H, CH_2CHOH), 1.76–1.90 (m, 2H, $BnOCH_2CH_2$), 2.18–2.22 (m, 2H, $CH_2CH{=}CH_2$), 3.51 (t, *J*=6.3 Hz, 2H, $BnOCH_2$), 3.77–3.83 (m, 1H, CHOH), 4.04–4.10 (m, 1H, CHOTBS), 4.44 (d, *J*=11.9 Hz, 1H, $PhCH_2O$), 4.48 (d, *J*=11.9 Hz, 1H, $PhCH_2O$), 5.07–5.11 (m, 2H, $CH{=}CH_2$), 5.75–5.86 (m, 1H, $CH{=}CH_2$), 7.26–7.35 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) −4.6 ($Si(CH_3)_2$), −4.3 ($Si(CH_3)_2$), 17.9 ($C(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 37.7 (CH_2), 42.2 (CH_2), 42.8 (CH_2), 66.6 (CHOH), 69.7 ($BnOCH_2$), 70.2 (CHOTBS), 73.0 ($PhCH_2O$), 117.5 ($CH{=}CH_2$), 127.6 (CH, phenyl), 127.6 (CH, phenyl), 128.4 (CH, phenyl), 134.8 ($CH{=}CH_2$), 138.3 (C, phenyl); HRMS (ESI) calcd for $C_{21}H_{37}O_3Si$ $[M+Na]^+$ 387.23259, found 387.232566.

4.5. (4*R*,6*S*)-4-Allyl-6-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxane (18)

A mixture of *p*-toluenesulphonic acid monohydrate (268 mg, 1.51 mmol) and alcohol **17** (5.49 g, 15.06 mmol) in methanol (150 mL) was stirred at room temperature for 1 h to complete the deprotection (confirmed by TLC). The reaction mixture was concentrated on the rotary evaporator to about 50 mL before it was diluted with 2,2-dimethoxypropane (150 mL, 602 mmol) and stirred for further 30 min at room temperature. The reaction mixture was concentrated in vacuo, the residue diluted with CH_2Cl_2 (500 mL), then washed with saturated $NaHCO_3$ solution (150 mL) and saturated NaCl solution (150 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated on a rotary evaporator. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 19:1) to yield acetal **18** (3.51 g, 80%) as colourless oil. R_f (petrol ether/ethyl acetate, 17:3) 0.48; $[\alpha]_D^{20}$ −9.0 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15 (dd, *J*=11.6, 12.9 Hz, 1H, dioxane CH_2), 1.37 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.50 (dt, *J*=2.5, 12.9 Hz, 1H, dioxane CH_2), 1.70–1.81 (m, 2H, $BnOCH_2CH_2$), 2.10–2.17 (m, 1H, $CH_2CH{=}CH_2$), 2.26–2.33 (m, 1H, $CH_2CH{=}CH_2$), 3.50–3.61 (m, 2H, $BnOCH_2$), 3.83–3.90 (m, 1H, dioxane CH), 3.99–4.05 (m, 1H, dioxane CH), 4.48 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 4.52 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 5.03–5.10 (m, 2H, $CH{=}CH_2$), 5.74–5.84 (m, 1H, $CH{=}CH_2$), 7.27–7.36 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) 19.8 ($C(CH_3)_2$), 30.2 ($C(CH_3)_2$), 36.5 (CH_2), 36.6 (CH_2), 40.8 (CH_2), 66.0 (dioxane CH), 66.2 ($BnOCH_2$), 68.6 (dioxane CH), 73.0 ($PhCH_2O$), 98.5 ($C(CH_3)_2$), 117.2 ($CH{=}CH_2$), 127.5 (CH, phenyl), 127.6 (CH, phenyl), 128.3 (CH, phenyl), 134.2 ($CH{=}CH_2$), 138.5 (C, phenyl); HRMS (ESI) calcd for $C_{18}H_{26}O_3$ $[M+Na]^+$ 313.17742, found 313.177541.

4.6. 2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethanol (19)

A solution of alkene **18** (2.69 g, 9.3 mmol) in methanol/CH_2Cl_2 (7:3, 100 mL), containing 4-5 drops of Sudan III (1% in methanol) was cooled to −80 °C followed by bubbling ozone through the solution for 1 h until it become colourless. Residual O_3 was removed by bubbling nitrogen through the solution. Thereafter, $NaBH_4$ (3.50 g, 92.6 mmol) was added and the reaction mixture allowed to reach room temperature with the flask kept in the cooling bath. Now, H_2O (40 mL) was added and the mixture concentrated to ~50 mL before it was extracted with ethyl acetate (3×60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:5) to furnish primary alcohol **19** (2.60 g, 96%) as colourless oil. R_f (petroleum ether/ethyl acetate, 5:5) 0.2; $[\alpha]_D^{20}$ −10.0 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.28 (dd, *J*=11.6, 12.6 Hz, 1H, dioxane CH_2), 1.36 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 1.45 (dt, *J*=2.5, 12.6 Hz, 1H, dioxane CH_2), 1.64–1.80 (m, 4H, $BnOCH_2CH_2$, CH_2CH_2OH), 2.16 (s, 1H, OH), 3.49–3.67 (m, 2H, CH_2OH), 3.71–3.84 (m, 2H, $BnOCH_2$), 4.02–4.18 (m, 2H, dioxane CH), 4.48 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 4.52 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 7.27–736 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) 19.9 ($C(CH_3)_2$), 30.2 ($C(CH_3)_2$), 36.5 (CH_2), 36.8 (CH_2), 38.0 (dioxane CH_2), 61.1 ($BnOCH_2$), 66.0 (dioxane CH), 66.1 (CH_2OH), 69.6 (dioxane CH), 73.0 ($PhCH_2O$), 98.7 ($C(CH_3)_3$), 127.6 (CH, phenyl), 127.7 (CH, phenyl), 128.4 (CH, phenyl), 138.5 (C, phenyl); HRMS (ESI) calcd for $C_{17}H_{26}O_4$ $[M+Na]^+$ 317.17233, found 317.172357.

4.7. 2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethyl 4-methylbenzenesulfonate (20)

To a mixture of alcohol **19** (2.60 g, 8.83 mmol), Et_3N (3.69 mL, 26.5 mmol), DMAP (323 mg, 2.65 mmol) in CH_2Cl_2 (50 mL), *p*-toluene sulphonyl chloride (3.37 g, 17.66 mmol) was added in one portion at 0 °C. The reaction mixture was allowed to stir at room temperature overnight before it was diluted with CH_2Cl_2 (70 mL), washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to afford tosylate **20** (3.42 g, 86%) as colourless oil. R_f (petroleum ether/ethyl acetate, 8:2) 0.28; $[\alpha]_D^{20}$ −2.6 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.09 (dd, *J*=11.6, 12.6 Hz, 1H, dioxane CH_2), 1.27 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.39 (dt,

J=2.5, 12.6 Hz, 1H, dioxane CH_2), 1.63–1.81 (m, 4H, $BnOCH_2CH_2$, CH_2CH_2OTs), 2.43 (s, 3H, CH_3, tosyl), 3.47–3.58 (m, 2H, $BnOCH_2$), 3.87–4.01(m, 2H, CH_2OTs), 4.05–4.10 (m, 1H, dioxane CH), 4.12–4.19 (m, 1H, dioxane CH), 4.44 (d, J=12.1 Hz, 1H, $PhCH_2O$), 4.47 (d, J=12.1 Hz, 1H, $PhCH_2O$), 7.26–7.36 (m, 5H, phenyl), 7.33 (d, J=8.3 Hz, 2H, tosyl), 7.78 (d, J=8.3 Hz, 2H, tosyl); δ_C (100 MHz, $CDCl_3$) 19.7 ($C(CH_3)_2$), 21.6 (CH_3, tosyl), 30.0 ($C(CH_3)_2$), 35.5 (CH_2), 36.5 (CH_2), 36.8 (CH_2), 64.9 (dioxane CH), 65.9 (dioxane CH), 66.1 ($BnOCH_2$), 66.8 (CH_2OTs), 73.0 (CH_2, benzyl), 98.6 ($C(CH_3)_2$), 127.6 (CH, benzyl), 127.6 (CH, benzyl), 127.9 (CH, tosyl), 128.4 (CH, benzyl), 129.8 (CH, tosyl), 133.1 (C, tosyl), 138.5 (C, benzyl), 144.7 (C, tosyl); HRMS (ESI) calcd for $C_{24}H_{32}O_6S$ $[M+Na]^+$ 471.18118, found 471.181152.

4.8. (4*R*,6*S*)-4-(2-Azidoethyl)-6-[2-(benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxane (21)

A mixture of tosylate **20** (3.41 g, 7.60 mmol) and sodium azide (1.05 g, 15.20 mmol) in DMF (40 mL) was stirred for 12 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude azide was purified by a simple filtration column (flash silica gel, petroleum ether/ethyl acetate, 8:2) yielding pure azide **21** (2.35 g, 97%) as colourless oil. R_f (petroleum ether/ethyl acetate, 8:2) 0.53; $[\alpha]_D^{20}$ −3.0 (c 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.17 (dd, J=11.6, 12.6 Hz, 1H, dioxane CH_2), 1.36 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.46 (dt, J=2.5, 12.9 Hz, 1H, dioxane CH_2), 1.65–1.81 (m, 4H, $BnOCH_2CH_2$, $CH_2CH_2N_3$), 3.31–3.44 (m, 2H, CH_2N_3), 3.49–3.61 (m, 2H, $BnOCH_2$), 3.92–3.99 (m, 1H, dioxane CH), 4.01–4.08 (m, 1H, dioxane CH), 4.46 (d, J=12.1 Hz, 1H, $PhCH_2O$), 4.49 (d, J=12.1 Hz, 1H, $PhCH_2O$), 7.26–7.36 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) 17.8 ($C(CH_3)_2$), 28.1 ($C(CH_3)_2$), 33.6 (CH_2), 34.5 (CH_2), 35.0 (CH_2), 45.5 (CH_2N_3), 63.9 (dioxane CH), 64.0 (dioxane CH), 64.1 ($BnOCH_2$), 73.0 ($PhCH_2O$), 98.7 ($C(CH_3)_2$), 127.6 (CH, phenyl), 127.6 (CH, phenyl), 128.3 (CH, phenyl), 138.5 (C, phenyl); HRMS(ESI) calcd for $C_{17}H_{25}N_3O_3$ $[M+Na]^+$ 342.17881, found 342.178839.

4.9. 2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethylamine (22)

To a solution of azide **21** (2.55 g, 7.98 mmol) in a mixture (10:1) of THF (50 mL) and H_2O (5 mL), triphenylphosphine (4.19 g, 15.97 mmol) was added and the mixture was stirred at room temperature for 10–12 h. The reaction mixture was concentrated to remove most of the THF. Benzene (100 mL) was added and the reaction mixture was concentrated to remove water as azeotrope. This manipulation was repeated once. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N, 9.5:0.4:0.1) to furnish amine **22** (2.2 g, 94%) as colourless oil. R_f (CH_2Cl_2/MeOH/Et_3N, 9.5:0.4:0.1) 0.29; $[\alpha]_D^{20}$ −10.0 (c 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 (dd, J=11.6, 12.6 Hz, 1H, dioxane CH_2), 1.35 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 1.44 (dt, J=2.3, 12.6 Hz, 1H, dioxane CH_2), 1.53–1.80 (m, 4H, $CH_2CH_2NH_2$, $BnOCH_2CH_2$), 1.97 (s, 2H, NH_2), 2.79–2.82 (m, 2H, CH_2NH_2), 3.49–3.60 (m, 2H, $BnOCH_2$), 3.91–3.97 (m, 1H, dioxane CH), 3.99–4.06 (m, 1H, dioxane CH), 4.45 (d, J=11.9 Hz, 1H, benzyl CH_2), 4.49 (d, J=11.9 Hz, 1H, benzyl CH_2), 7.26–7.35 (m, 5H, phenyl); δ_C (100 MHz, $CDCl_3$) 19.9 ($C(CH_3)_2$), 30.2 ($C(CH_3)_2$), 36.5 (CH_2), 37.1 (CH_2), 38.4 (CH_2), 38.5 (CH_2), 39.4 (CH_2), 66.0 (dioxane CH), 66.1 (OCH_2), 67.7 (dioxane CH), 73.0 (CH_2, benzyl), 127.5 (CH, phenyl), 127.6 (CH, phenyl), 128.34 (CH, phenyl), 138.49 (C, phenyl); HRMS (ESI) calcd for $C_{17}H_{27}NO_3$ $[M+Na]^+$ 294.20637, found 294.206401.

4.10. 1-(2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethyl)-2-(4-fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrole (24)

A mixture of 1,4-diketone **23** (500 mg, 1.68 mmol), amine **22** (516 mg, 1.76 mmol) and *p*-toluenesulphonic acid monohydrate (64 mg, 0.335 mmol, 0.2 equiv) in xylene (20 mL) was refluxed for 7 days using a Dean–Stark trap to remove water as azeotrope. The completion of the reaction was checked by TLC. The reaction mixture was diluted with diethyl ether (30 mL), washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl solution (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/diethyl ether, 9:1) to afford pyrrole **24** (520 mg, 68%) as colourless sticky solid. R_f (petroleum ether/diethyl ether, 9:1) 0.25; $[\alpha]_D^{20}$ +4.0 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (dd, J=11.6, 12.6 Hz, 1H, dioxane CH_2), 1.15 (dt, J=2.3, 12.6 Hz, 1H, dioxane CH_2), 1.31–1.35 (m, 12H, $C(CH_3)_2$, $CH(CH_3)_2$), 1.44–1.75 (m, 4H, NCH_2CH_2, CH_2CH_2OBn), 2.96–3.06 (septet, J=6.8 Hz, 1H, $CH(CH_3)_2$), 3.44–3.59 (m, 3H, dioxane CH, CH_2OBn), 3.76–3.84 (m, 1H, NCH_2), 3.88–3.99 (m, 2H, dioxane CH, NCH_2), 4.44 (d, J=12.1 Hz, 1H, $PhCH_2O$), 4.47 (d, J=12.1 Hz, 1H, $PhCH_2O$), 6.18 (s, 1H, pyrrole CH), 7.02–7.07 (m, 3H, aryl), 7.10–7.16 (m, 4H, aryl), 7.26–7.35 (m, 7H, aryl); δ_C (100 MHz, $CDCl_3$) 19.8 ($C(CH_3)_2$), 23.3 ($CH(CH_3)_2$), 23.7 ($CH(CH_3)_2$), 25.5 ($CH(CH_3)_2$), 30.1 ($C(CH_3)_2$), 36.4 (CH_2), 36.5 (CH_2), 37.9 (dioxane CH_2,), 39.8 (NCH_2), 65.7 (dioxane CH), 66.0 (OCH_2Ph), 66.3 (dioxane CH), 72.9 (OCH_2Ph), 98.4 ($C(CH_3)_2$), 103.4 (pyrrole C-3), 115.6 (C-3, $J_{C,F}$=21.2 Hz, 4-F–C_6H_4), 122.0 (C, aryl), 124.8 (CH, aryl), 127.5 (CH, aryl), 127.5 (CH, aryl), 127.6 (CH, aryl), 127.8 (C, aryl), 128.0 (CH, aryl), 128.3 (CH, aryl), 129.8 (C-2, $J_{C,F}$=3.7 Hz, 4-F–C_6H_4), 132.9 (C-1, $J_{C,F}$=8.1 Hz, 4-F–C_6H_4), 136.5 (C, aryl), 138.5 (C, aryl), 140.4 (C, aryl), 162.2 (C-4, $J_{C,F}$=246.6 Hz, 4-F–C_6H_4); HRMS (ESI) calcd for $C_{36}H_{42}FNO_3$ $[M+Na]^+$ 578.30409, found 578.304437.

4.11. 1-(2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethyl)-2-(4-fluorophenyl)-4-iodo-5-isopropyl-3-phenyl-1*H*-pyrrole (25)

To a solution of pyrrole **24** (206 mg, 0.37 mmol) in DMF (5 mL) *N*-iodosuccinimide (100 mg, 0.45 mmol) was added in one portion and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with diethyl ether (15 mL), washed with 10% $Na_2S_2O_3$ solution (5 mL), saturated $NaHCO_3$ solution (10 mL) and saturated NaCl solution (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1) to give iodopyrrole **25** (230 mg, 91%) as colourless oil. R_f (petroleum ether/ethyl acetate, 9:1) 0.3; $[\alpha]_D^{20}$ −2.0 (c 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (dd, J=11.6, 12.9 Hz, 1H, dioxane CH_2), 1.20 (dt, J=2.3, 12.9 Hz, 1H, dioxane CH_2), 1.29 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$), 1.49 (d, J=7.1 Hz, 3H, $CH(CH_3)_2$), 1.51 (d, J=7.1 Hz, 3H, $CH(CH_3)_2$), 1.56–1.75 (m, 4H, NCH_2CH_2, CH_2CH_2OBn), 3.26–3.37 (septet, J=7.1 Hz, 1H, $CH(CH_3)_2$), 3.45–3.65 (m, 3H, dioxane CH, CH_2OBn), 3.76–3.84 (m, 1H, NCH_2), 3.89–3.96 (m, 1H, dioxane CH), 4.00–4.07 (m, 1H, NCH_2), 4.44 (d, J=12.1 Hz, 1H, $PhCH_2O$), 4.48 (d, J=12.1 Hz, 1H, $PhCH_2O$), 6.92–6.97 (m, 2H, aryl), 7.09–7.22 (m, 7H, aryl), 7.26–7.35 (m, 5H, aryl); δ_C (100 MHz, $CDCl_3$) 19.8 ($C(CH_3)_2$), 21.4 ($CH(CH_3)_2$), 21.5 ($CH(CH_3)_2$), 27.2 ($CH(CH_3)_2$), 30.0 ($C(CH_3)_2$), 36.4 (CH_2), 36.5 (CH_2), 38.3 (dioxane CH_2), 41.2 (NCH_2), 65.7 (dioxane CH), 66.0 (CH_2OBn), 66.5 (dioxane CH), 72.9 (OCH_2Ph), 98.5 ($C(CH_3)_2$), 117.2 (C-3, $J_{C,F}$=21.2 Hz, 4-F–C_6H_4,), 126.0 (CH, aryl), 126.5 (C, aryl), 127.4 (CH, aryl), 127.5 (CH, aryl), 127.6 (CH, aryl), 128.3 (CH, aryl), 129.8 (C-2, $J_{C,F}$=3.7 Hz, 4-F–C_6H_4), 128.7 (C, aryl), 129.7 (C, aryl), 130.9 (2 CH, aryl), 132.9 (C-1, $J_{C,F}$=8.1 Hz, 4-F–C_6H_4), 135.9 (C, aryl), 137.1 (C, aryl), 138.5 (C, aryl), 162.1 (C-4,

$J_{C,F}$=247.4 Hz, 4-F–C_6H_4); HRMS (ESI) calcd for $C_{36}H_{41}FINO_3$ $[M+Na]^+$ 704.20074, found 704.200369.

4.12. 1-(2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid (26)

A solution of iodopyrrole **25** (201 mg, 0.29 mmol) in THF (10 mL) was cooled to −80 °C, then *t*-BuLi (0.387 mL, 0.62 mmol, 2.5 M in hexane) was added dropwise. After 10 min, excess of CO_2 was bubbled through the reaction mixture with stirring for 15 min. Thereafter, the mixture was allowed to reach room temperature within 1 h. The progress of the reaction was checked by TLC. The reaction mixture was treated with saturated NH_4Cl solution and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to furnish acid **26** (144 mg, 81%) as white solid, mp 73–78 °C. R_f (petroleum ether/ethyl acetate, 7:3) 0.3; $[\alpha]_D^{20}$ −1.7 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (dd, *J*=11.6, 13.1 Hz, 1H, dioxane CH_2), 1.19 (dt, *J*=2.5, 13.1 Hz, 1H, dioxane CH_2), 1.28 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.45 (d, *J*=7.1 Hz, 3H, $CH(CH_3)_2$), 1.46 (d, *J*=7.1 Hz, 3H, $CH(CH_3)_2$), 1.55–1.74 (m, 4H, NCH_2CH_2, CH_2CH_2OBn), 3.44–3.65 (m, 4H, dioxane CH, CH_2OBn, $CH(CH_3)_2$), 3.74–3.81(m, 1H, NCH_2), 3.89–3.95 (m, 1H, dioxane CH), 4.00–4.07 (m, 1H, NCH_2), 4.43 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 4.47 (d, *J*=12.1 Hz, 1H, $PhCH_2O$), 6.91–6.95 (m, 2H, aryl), 7.03–7.14 (m, 7H, aryl), 7.27–7.35 (m, 5H, aryl); δ_C (100 MHz, $CDCl_3$) 19.8 ($C(CH_3)_2$), 20.8 ($CH(CH_3)_2$), 20.8 ($CH(CH_3)_2$), 26.0 ($CH(CH_3)_2$), 30.0 ($C(CH_3)_2$), 36.4 (CH_2), 36.4 (CH_2), 37.9 (dioxane CH_2), 41.1 (NCH_2CH_2), 65.7 (dioxane CH), 66.0 (CH_2OBn), 66.5 (dioxane CH), 72.9 ($PhCH_2O$), 98.5 ($C(CH_3)_2$), 109.4 (C, aryl), 115.2 (C-3, $J_{C,F}$=21.2 Hz, 4-F–C_6H_4,), 125.8 (CH, aryl), 127.2 (CH, aryl), 127.6 (CH, aryl), 127.6 (CH, aryl), 128.1 (C-2, $J_{C,F}$=2.9 Hz, 4-F–C_6H_4), 128.3 (CH, aryl), 130.0 (C, aryl), 130.5 (2 CH, aryl), 133.2 (C-1, $J_{C,F}$=8.1 Hz, 4-F–C_6H_4), 135.4 (C, aryl), 138.4 (C, aryl), 144.9 (C, aryl), 162.2 (C-4, $J_{C,F}$=248.1 Hz, 4-F–C_6H_4), 170.7 (C, aryl), 177.3 (COOH); HRMS (ESI) calcd for $C_{37}H_{42}FNO_5$ $[M+Na]^+$ 622.29392, found 622.293491.

4.13. 1-(2-{(4*R*,6*S*)-6-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (27)

To a solution of acid **26** (73 mg, 0.12 mmol) and aniline (13 μL, 0.15 mmol) in CH_2Cl_2 (5 mL), *N*-ethyldiisopropyl amine (63 μL, 0.36 mmol) was added and the reaction mixture was cooled to 0 °C. PyBrOP (85 mg, 0.18 mmol) was then added and the mixture allowed to stir at room temperature for 4 h. Completion of the reaction was checked by TLC. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3×5 mL) and saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2) to afford amide **27** (65 mg, 82%) as white solid, mp 75–82 °C. R_f (petroleum ether/ethyl acetate, 8:2) 0.29; $[\alpha]_D^{20}$ −1.5 (*c* 1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (dd, *J*=11.6, 12.4 Hz, 1H, dioxane CH_2), 1.14–1.18 (m, 1H, dioxane CH_2), 1.23 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.46 (d, *J*=7.1 Hz, 6H, $CH(CH_3)_2$), 1.53–1.69 (m, 4H, NCH_2CH_2, $BnOCH_2CH_2$), 3.38–3.60 (m, 4H, NCH_2, CH_2OBn, $CH(CH_3)_2$), 3.70–3.78 (m, 1H, NCH_2), 3.85–3.91 (m, 1H, dioxane CH), 3.95–4.03 (m, 1H, dioxane CH), 4.37 (d, *J*=12.4 Hz, 1H, $PhCH_2O$), 4.41 (d, *J*=12.4 Hz, 1H, $PhCH_2O$), 6.78 (s, 1H, NH), 6.89–6.93 (m, 3H, aryl), 6.98–7.00 (m, 2H, aryl), 7.08–7.13 (m, 9H, aryl), 7.20–7.28 (m, 5H, aryl); δ_C (100 MHz, $CDCl_3$) 19.8 ($C(CH_3)_2$), 21.5 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 30.0 ($C(CH_3)_2$), 36.4 (CH_2), 36.4 (CH_2), 38.1 (dioxane CH_2), 40.9 (NCH_2), 65.7 (dioxane CH), 66.0 (CH_2OBn), 66.5 (dioxane CH), 72.9 ($PhCH_2O$), 98.5 ($C(CH_3)_2$), 115.24, 115.3 (4-F–C_6H_4, C-3, $J_{C,F}$=21.2 Hz), 119.5 (CH, aryl), 121.7 (C, aryl), 123.5 (CH, aryl), 126.5 (CH, aryl), 127.6 (CH, aryl), 127.6 (CH, aryl), 128.2 (C, aryl), 128.3 (CH, aryl), 128.6 (CH, aryl), 128.7 (C, aryl), 130.5 (CH, aryl), 133.2 (C-2, $J_{C,F}$=8.1 Hz, 4-F–C_6H_4,), 134.6 (C, aryl), 138.4 (C-1, $J_{C,F}$=7.3 Hz, 4-F–C_6H_4,), 141.5 (C, aryl), 149.9 (C, aryl), 141.5 (C, aryl), 162.2 (C-4, $J_{C,F}$=248.1 Hz, 4-F–C_6H_4), 164.8 (CONH); HRMS (ESI) calcd for $C_{43}H_{47}FO_4$ $[M+Na]^+$ 697.34121, found 697.341636.

4.14. 5-(4-Fluorophenyl)-1-{2-[(4*R*,6*S*)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (28)

A solution of benzyl ether **27** (20 mg, 0.03 mmol) containing 20% $Pd(OH)_2$ (5 mg, 25% by weight of substrate), cyclohexene (1 mL) and ethanol (2 mL) were stirred for 4 h at 80 °C. After cooling, the catalyst was filtered off, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) to afford alcohol **28** (15 mg, 86%) as white solid, mp 75–85 °C. R_f (petroleum ether/ethyl acetate, 6:4) 0.11; $[\alpha]_D^{20}$ −6.0 (*c* 1, in $CHCl_3$); δ_H (400 MHz, CD_3OD) 0.95 (dd, *J*=11.4, 12.6 Hz, 1H, dioxane CH_2), 1.26–1.30 (m, 4H, dioxane CH_2, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.46 (d, *J*=7.1 Hz, 3H, $CH(CH_3)_2$), 1.47 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.52–1.65 (m, 4H, NCH_2CH_2, CH_2CH_2OH), 3.34–3.39 (m, 1H, $CH(CH_3)_2$), 3.53–3.62 (m, 2H, CH_2OH), 3.68–3.78 (m, 1H, dioxane CH), 3.84–3.99 (m, 2H, NCH_2, dioxane CH), 4.03–4.12 (m, 1H, NCH_2), 7.00–7.33 (m, 14H, aryl); δ_C (100 MHz, CD_3OD) 20.1 ($C(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 27.6 ($CH(CH_3)_2$), 30.4 ($C(CH_3)_2$), 37.7 (dioxane CH_2), 39.4 (CH_2), 40.1 (CH_2), 41.4 (NCH_2), 59.0 (CH_2OH), 67.3 (dioxane CH), 67.8 (dioxane CH), 99.8 ($C(CH_3)_2$), 116.2 (C-3, *J*=22.0 Hz, 4-F–C_6H_4), 118.1 (C, aryl), 121.5 (CH, aryl), 123.3 (C, aryl), 125.1 (CH, aryl), 126.80, 126.9, 128.8, 128.9 (CH, aryl), 129.4, 129.6 (2 CH, aryl), 130.2 (C-1, *J*=3.7 Hz, 4-F–C_6H_4), 130.9 (CH, aryl), 132.8 (CH, aryl), 134.8 (C-2, *J*=8.1 Hz, 4-F–C_6H_4), 136.3 (C, aryl), 138.9 (C, aryl), 139.0 (C, aryl), 139.8 (C, aryl), 163.8 (C-4, *J*=246.6 Hz, 4-F–C_6H_4), 169.5 (CONH); HRMS (ESI) calcd for $C_{36}H_{41}FN_2O_4$ $[M+Na]^+$ 607.29426, found 607.294097.

4.15. (6-{2-[2-(4-Fluoro-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl pyrrol-1-yl]-ethyl}-2,2-dimethyl-[1,3] dioxan-4-yl)-acetic acid (29)

To a cooled solution alcohol **28** (147 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at 0 °C, Dess–Martin reagent (145 mg, 0.50 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h before it was quenched with a mixture of saturated $NaHCO_3$ solution and 0.1 M $Na_2S_2O_3$ (4 mL, 1:1). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was dissolved in *tert*-butanol (10 mL) and 2-methyl-2-butene (1.2 mL) was added. The mixture was cooled to 0 °C, then a solution of $NaH_2PO_4 \cdot 2H_2O$ (224 mg, 1.44 mmol) and $NaClO_2$ (43 mg, 0.480 mmol) in H_2O (10 mL) was added dropwise and the mixture allowed to stir at room temperature for 6 h. The mixture was diluted with saturated NaCl solution and extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude acid was purified by flash chromatography (CH_2Cl_2/methanol/acetic acid, 25:1:0.1) to furnish acid **29** as white solid (144 mg, 96%). R_f (CH_2Cl_2/methanol/acetic acid, 25:1:0.1) 0.33; $[\alpha]_D^{20}$ +5.0 (*c* 1, in $CHCl_3$); δ_H (400 MHz, CD_3OD) 0.93–1.02 (m, 1H, dioxane CH_2), 1.25 (s, 3H, $C(CH_3)_2$), 1.29–1.34 (m, 1H, dioxane CH_2), 1.34 (s, 3H, $C(CH_3)_2$), 1.46 (d, *J*=7.1 Hz, 3H, $CH(CH_3)_2$), 1.47 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.60–1.65 (m, 2H, NCH_2CH_2), 2.25–2.38 (m, 2H, CH_2CO_2H), 3.32–3.41 (m, 1H, $CH(CH_3)_2$),

3.70–3.82 (m, 1H, dioxane CH), 3.85–3.94 (m, 1H, NCH_2), 4.03–4.12 (m, 1H, NCH_2), 4.16–4.26 (m, 1H, dioxane CH), 7.00–7.36 (m, 14H, aryl); δ_C (100 MHz, CD_3OD) 20.0 ($C(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2$), 27.6 ($CH(CH_3)_2$), 30.3 ($C(CH_3)_2$), 37.1 (CH_2), 39.4 (dioxane CH_2), 41.4 (CH_2CO_2H), 42.2 (NCH_2), 67.2 (dioxane CH), 67.7 (dioxane CH), 100.0 ($C(CH_3)_2$), 116.3 (C-3, $J_{C,F}$=22.0 Hz, 4-F–C_6H_4), 118.1 (C, aryl), 121.5 (CH, aryl), 123.3 (C, aryl), 125.1 (CH, aryl), 126.9, 128.8, 128.9 (CH, aryl), 129.0, 129.5, 129.6 (CH, aryl), 129.6 (C, aryl), 130.2 (C-1, $J_{C,F}$=3.7 Hz, 4-F–C_6H_4), 130.9 (2 CH, aryl), 131.8, 132.8 (CH, aryl), 134.8 (2 C-2, $J_{C,F}$=8.05 Hz, 4-F–C_6H_4), 136.3 (C, aryl), 139.0 (C, aryl), 139.8 (C, aryl), 163.8 (C-4, $J_{C,F}$=246.6 Hz, 4-F–C_6H_4), 169.5 (CONH), 174.6 (COO); HRMS (ESI) calcd for $C_{36}H_{39}FN_2O_5$ $[M+Na]^+$ 621.27352, found 621.27359.

4.16. 5-(4-Fluoro-phenyl)-1-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (6)

A solution of acid **29** (52 mg, 0.08 mmol) and a catalytic amount of camphor sulphonic acid in THF (2 mL) was stirred at room temperature for 3 h. The mixture was concentrated and the residue purified by flash chromatography (diethyl ether/methanol, 50:1) to afford atorvastatin lactone **6** (38 mg, 90%) as white solid. It was recrystallized from petroleum ether/ethyl acetate to give an amorphous white solid, mp 150–155 °C {Ref. 30: 160–162 °C}. R_f (diethyl ether/methanol, 50:1) 0.25; $[\alpha]_D^{20}$ +25.5 (*c* 0.2, $CHCl_3$) {Ref. 9: $[\alpha]_D^{23}$ +24.53 (0.53% in $CHCl_3$), Ref. 10: $[\alpha]_D$ +26.05 (*c* 1, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.50–1.53 (m, 6H, $CH(CH_3)_2$), 1.55–1.60 (m, 1H, lactone H-4), 1.65–1.77 (m, 2H, lactone H-4, NCH_2CH_2), 1.82–1.91 (m, 1H, NCH_2CH_2), 2.37 (s, 1H, OH), 2.49–2.66 (m, 2H, lactone H-2), 3.48–3.58 (m, 1H, $CH(CH_3)_2$), 3.98–4.10 (m, 1H, NCH_2), 4.16–4.29 (m, 2H, NCH_2, lactone H-3), 4.44–4.54 (m, 1H, lactone H-5), 6.87 (s, 1H, NH), 6.96–7.20 (m, 13H, aryl), 7.27–7.33 (m, 1H, aryl); δ_C (100 MHz, CD_3OD) 21.7 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 35.6 (C-4, lactone), 37.0, 37.1 (NCH_2CH_2), 38.5 (C-2, lactone), 40.7 (NCH_2), 62.4 (C-3, lactone), 73.0 (C-5, lactone), 73.1, 115.6 (C-3, $J_{C,F}$=22.0 Hz, 4-F–C_6H_4), 115.6 (C-3, pyrrole), 119.7 (C-2, anilide), 122.1 (C-4, pyrrole), 123.6, 123.7 (C-4, anilide), 126.5, 126.6 (C-4, phenyl), 128.0 (C-1, $J_{C,F}$=2.9 Hz, 4-F–C_6H_4), 128.3, 128.4 (C-3, anilide), 128.4, 128.7 (C-2, anilide), 128.7 (C-5, pyrrole), 130.4 (C-3, phenyl), 131.3, 134.0, 133.1 (C-2, $J_{C,F}$=8.1 Hz, 4-F–C_6H_4), 134.4 (C-1, phenyl), 134.5, 138.2, 138.2 (C-1, anilide), 141.3 (C-2, pyrrole), 162.3 (C-4, $J_{C,F}$=248.8 Hz, 4-F–C_6H_4), 164.9 (CONH), 169.4 (COO); HRMS (ESI) calcd for $C_{33}H_{33}FN_2O_4$ $[M+Na]^+$ 563.23166, found 563.23154.

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Supplementary data

Supplementary data associated with this article (procedure for alcohol **13**, copies of NMR spectra) can be found in the online version, at doi:10.1016/j.tet.2010.10.028. These data include MOL files and InChIKeys of the most important compounds described in this article.

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