Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 8124–8134
Tetrahedron

Development of a practical synthesis of novel, pyrrole-based HMG-CoA reductase inhibitors

Jeffrey A. Pfefferkorn,* Daniel M. Bowles, William Kissel, David C. Boyles, Chulho Choi, Scott D. Larsen, Yuntao Song, Kuai-Lin Sun, Steven R. Miller and Bharat K. Trivedi

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

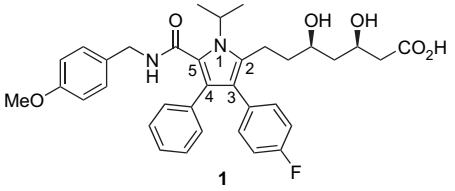
Received 3 April 2007; revised 30 May 2007; accepted 2 June 2007
Available online 9 June 2007

Abstract—This paper describes the development of an efficient and scalable second generation synthesis of novel, pyrrole-based HMG-CoA reductase inhibitors. Compound **1** was identified as part of a discovery program aimed at finding improved treatments for hypercholesterolemia. Herein, we describe an efficient synthesis of its highly functionalized pyrrole core followed by attachment of the 3,5-dihydroxyhexanoic acid side chain via ylide olefination chemistry.

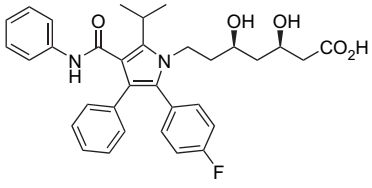
1. Introduction

Coronary heart disease (CHD) is a leading cause of death worldwide.[1] Epidemiological evidence indicates that there is a strong link between hypercholesterolemia and the risk of CHD.[2] As a consequence, significant efforts have been undertaken to lower the cholesterol levels in hypercholesterolemic patients to mitigate this risk factor. Currently, the most successful and widely utilized method for treating hypercholesterolemia is the use of HMG-CoA reductase inhibitors, which block the rate limiting step of cholesterol synthesis.[3] As a class, HMG-CoA reductase inhibitors have proven to be well tolerated and remarkably effective. However, as revisions to National Cholesterol Education Program (NCEP-ATP-III) cholesterol treatment guidelines call for increasingly aggressive low density lipoprotein (LDL) lowering in at-risk patients (for example, LDL <70 mg/dL for highest risk patients)[4] there is continued need for new HMG-CoA reductase inhibitors with improved efficacy relative to those currently available.

As part of a discovery program aimed at identifying novel HMG-CoA reductase inhibitors, we investigated a series of substituted pyrroles represented by inhibitor **1** (Fig. 1).[5] Structurally, compound **1** and related analogs represent a regioisomeric variation of the atorvastatin (Lipitor®, **2**) template, but they offer a distinct pharmacological profile.[5] From a synthetic viewpoint, transposition of the 3,5-dihydroxyheptanoic acid side chain from the 1-position (atorvastatin)[6] to the 2-position (**1**) of the central pyrrole



1



2: atorvastatin

Figure 1. Structure of HMG-CoA reductase inhibitor **1** and atorvastatin (**2**).

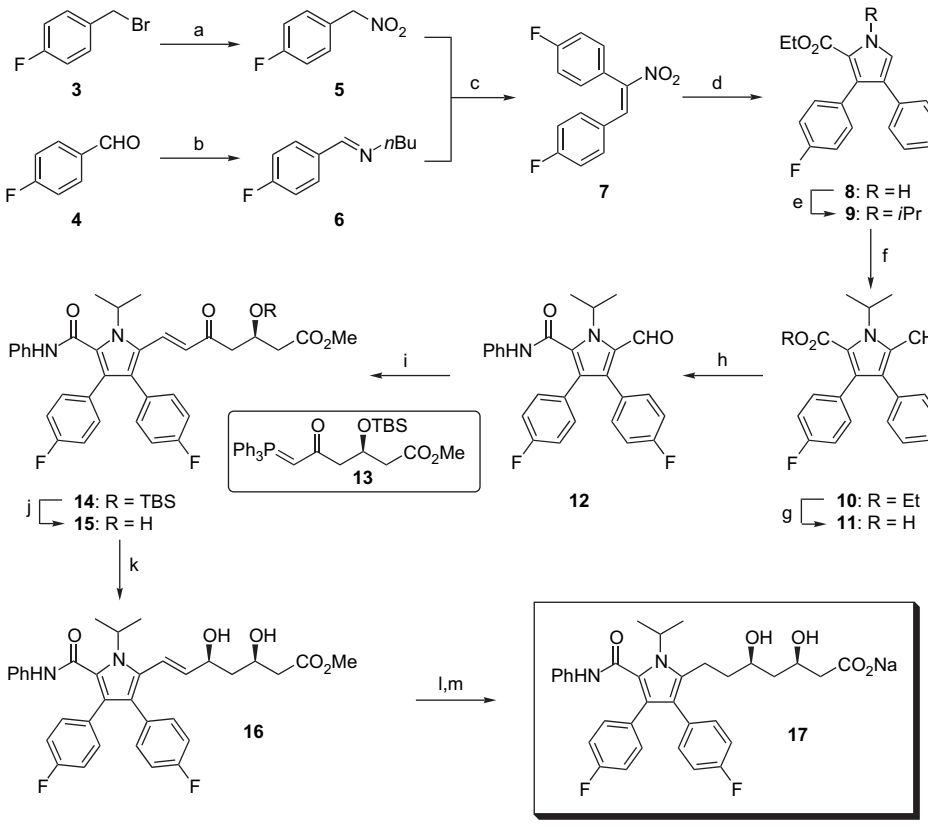
necessitated the development of a new synthetic strategy. An early medicinal chemistry synthesis (Scheme 1) of this template enabled access to key analogs for structure–activity studies; however, the multi-gram preparation of compounds of interest for further pre-clinical evaluation was hampered by the limited scalability of this first generation route. As a consequence, a second generation synthesis of **1** and related analogs was developed and is described herein.

2. First generation synthesis

Scheme 1 highlights the original medicinal chemistry route to compound **17**, a representative analog that was utilized

* Corresponding author. E-mail: jeffrey.a.pfefferkorn@pfizer.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.06.005



Scheme 1. First generation synthetic route illustrated for HMG-CoA reductase inhibitor **17**. Reagents and conditions: (a) $AgNO_2$, Et_2O, 0 °C, 12 h, 36%; (b) nBuNH$_2$, C_6H_6, 80 °C, 2 h, 100%; (c) AcOH, 25 °C, 12 h, 82%; (d) $CNCH_2CO_2Et$, DBU, THF, 25 °C, 12 h, 38%; (e) KOH (powdered), ^{i}PrI, DMSO, 25 °C, 1.5 h, 62%; (f) $POCl_3$, DMF, dichloroethane, 80 °C, 3 h, 45%; (g) NaOH, MeOH, 60 °C, 2 h, 100%; (h) (i) $SOCl_2$, 80 °C; (ii) $PhNH_2$, Et_3N, THF, 25 °C, 12 h, 57%; (i) **13**, toluene, 110 °C, 48 h, 66%; (j) HF (48% in H_2O), MeCN, 0 °C, 2 h, 99%; (k) $Et_2B(OMe)$, $NaBH_4$, AcOH (cat), THF, −78 °C, 2 h, 58%; (l) 10% Pd/C, H_2, EtOH/THF (1:1), 25 °C, 3 h, 100%; (m) NaOH, EtOH, 1 h, 100%.

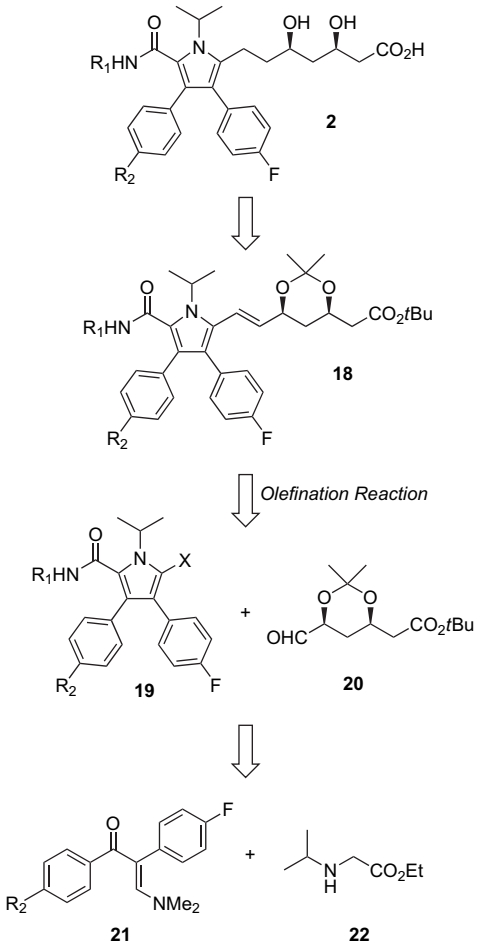
for much of our exploratory synthetic studies.[5] This first generation route relied upon a Barton–Zard synthesis for construction of the central pyrrole heterocycle.[7] Initially, 4-fluorobenzyl bromide (**3**) was treated with silver nitrite[8] to afford 1-fluoro-4-nitromethyl-benzene (**5**). In parallel, benzaldehyde (**4**) was converted to imine **6** by treatment with *n*-butylamine. Subsequent reaction of **5** and **6** in glacial acetic acid provided 1-fluoro-4-(1-nitro-2-phenyl-vinyl)-benzene (**7**). To complete the pyrrole synthesis, intermediate **7** was reacted with ethyl isocyanatoacetate in the presence of DBU to generate pyrrole **8**, regioselectively. *N*-Alkylation of **8** was then accomplished using *iso*-propyl iodide and powdered KOH in DMSO to provide pyrrole **9**, which was subjected to formylation under Vilsmeier–Haack conditions to generate pyrrole carboxaldehyde **10**. The ethyl ester of **10** was saponified with aqueous NaOH, converted to the corresponding acid chloride via treatment with $SOCl_2$, and reacted with aniline to afford anilide **12**. Installation of the 3,5-dihydroxyhexanoic acid side chain commenced with a Wittig olefination reaction between pyrrole carboxaldehyde **12** and stabilized phosphonium ylide **13** (prepared stereoselectively in eight steps from diethyl 3-hydroxyglutarate according to the method of Konoike and Araki[9]) to provide olefin **14** in 66% yield. Any unreacted **12** could be recycled via a tedious chromatography. The TBS-protected side chain hydroxyl of **14** was then liberated by treatment with aqueous HF to provide β-hydroxy ketone **15**, which was subjected to a stereoselective *syn*-reduction with $Et_2B(OMe)$ and $NaBH_4$ to produce *syn*-diol **16**.[10] The synthesis was completed by hydrogenation of the side chain olefin over 10% Pd/C followed by saponification of the terminal ester to provide compound **17** as its sodium salt.

While this original route proved valuable for structure–activity studies, it posed a number of challenges for the multigram scale-up synthesis of selected compounds of interest. These limitations included: (a) a length of 21 steps (including the required preparation of side chain reagent **13**); (b) an overall yield of <1%; (c) the use of potentially hazardous high energy intermediates **5** and **7**; (d) the use of several expensive reagents including silver nitrate and ethyl isocyanoacetate; and (e) the need for at least 10 chromatographic purifications.

3. Second generation synthesis

In light of the limited scalability of the original route, we sought to develop an alternative synthesis as outlined retrosynthetically in Scheme 2. Key elements of this second generation route included: (a) reversing the reacting partners in the Wittig olefination (i.e., intermediate **19** as the ylide) thereby enabling the use of aldehyde **20** (available in one step from commercially available material) as a side chain precursor; (b) utilization of an efficient pyrrole synthesis previously reported by Gupton and co-workers where

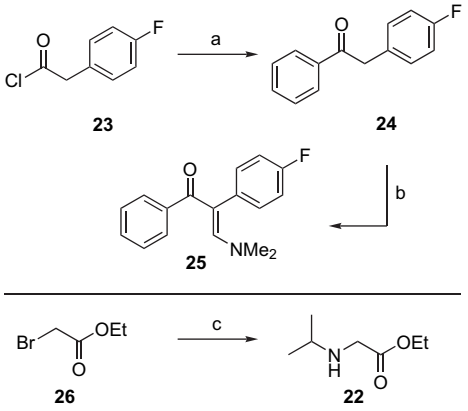
a vinylogous amide (i.e., **21**) or vinylogous iminium salt equivalent is reacted with an α-amino acid ester (i.e., **22**), resulting in regioselective pyrrole formation.[11] Of most importance, this latter approach was anticipated to be both scalable and amenable to the construction of pyrroles (such as **19**), which contain a high degree of non-symmetric substitution (i.e., $R_2 \neq F$).



Scheme 2. Second generation retrosynthetic disconnections.

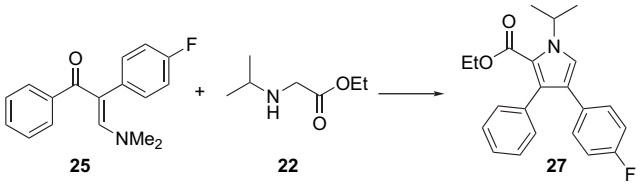
3.1. Pyrrole construction

Preliminary efforts to develop this second generation route focused on constructing the central pyrrole using the method of Gupton and co-workers as described. The requisite reaction components were synthesized as outlined in Scheme 3. Friedel–Crafts arylation between 4-fluoro-phenyl acetyl chloride (**23**) and benzene in the presence of $AlCl_3$ provided 2-(4-fluoro-phenyl)-1-phenylethanone (**24**), which was then treated with *N*,*N*-dimethylformamide dimethyl acetal at elevated temperature to provide vinylogous amide **25**.[11] Separately, α-amino acid ester **22** was prepared by reaction of ethyl bromoacetate (**26**) with *iso*-propyl amine. Next, a variety of conditions were examined for the reaction of **22** and **25** to form pyrrole **27** as outlined in Table 1. According to Gupton report, the anticipated pyrrole synthesis could occur under both base and acid mediated conditions.[11] In our case, representative base mediated conditions (Table 1, entries 1 and 2) afforded low yields and long reaction times. By contrast, acid mediated conditions (Table 1, entries 3 and 4) resulted in good conversion to the desired pyrrole **27** in a regioselective manner. Comparison of entries 3 and 4 revealed that a 2-fold excess of α-amino acid ester **22** (entry 3) afforded slightly improved yields relative to a stoichiometric amount (entry 4).



Scheme 3. Synthesis of pyrrole precursors **25** and **22**. Reagents and conditions: (a) $AlCl_3$, C_6H_6, 50 °C, 8 h, 97%; (b) *N*,*N*-dimethylformamide dimethyl acetal, toluene, 100 °C, 15 h, 100%; (c) $^{i}PrNH_2$, MTBE, 5 °C, 16 h, 95%.

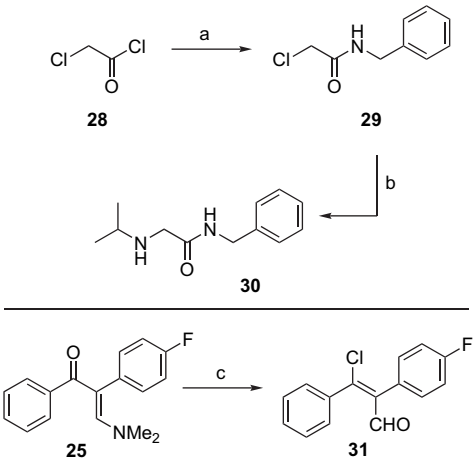
Table 1. Optimization of pyrrole synthesis using amino acid ester **22**



Entry	Ratio of **22**/**25**	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	2:1	Cs_2CO_3	NMP	150	16	33
2	2:1	NaOEt	EtOH	100	12	36
3	2:1	—	AcOH	120	2	85
4	1:1	—	AcOH	120	2	72

Given that our final target, **1**, contained an amide moiety at the site of the current ester in pyrrole **27**, we next sought to investigate whether or not the pyrrole forming reaction shown in Table 1 could tolerate an α-amino amide in place of α-amino acid ester **22**. Such an adaptation would eliminate the need for conversion of the ester to the amide at a later stage in the synthesis. To evaluate this possibility, model α-amino amide **30** was prepared as outlined in Scheme 4 where chloroacetyl chloride (**28**) was reacted with benzyl amine in the presence of triethylamine, and the resulting product **29** was then treated with *iso*-propyl amine to provide α-amino amide **30**. Gupton and co-workers had reported that, in many cases, similar pyrrole forming reactions were more facile if the vinylogous amide component was first converted into a synthetically equivalent (yet more reactive) β-chloroenal. Fearing that the desired transformation would also be somewhat sluggish in our system, vinylogous amide **25** was also converted to β-chloroenal **31** as outlined in Scheme 4.[11] With α-amino amide **30**, vinylogous amide **25**, and β-chloroenal **31** in hand, we investigated whether or not the

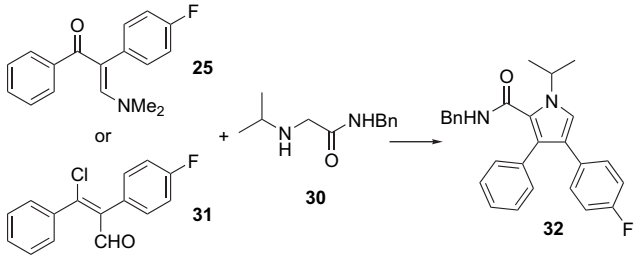
pyrrole formation would work with the amide motif already in place as highlighted in Table 2. Attempted reaction of vinylogous amide **25** with **30** under acidic conditions (Table 2, entry 1) failed to afford any product. Limited formation of the desired product **32** was noted when **30** and the more reactive β-chloroenal **31** were reacted under neutral conditions in either DMF (8% yield, entry 2) or NMP (24% yield, entry 3).



Scheme 4. Synthesis of pyrrole precursors **30** and **31**. Reagents and conditions: (a)$BnNH_2$, Et_3N, CH_2Cl_2, 0 °C, 12 h, 74%; (b) $^iPrNH_2$, THF/Et_2O, 25 °C, 48 h, 32%; (c) (i) $POCl_3$, CH_2Cl_2, 45 °C; (ii) H_2O/THF, 25 °C, 48 h, 99% (two steps).

Attempts to improve the conversion by addition of a base (entry 4) resulted in no product formation. Additional modification (not shown) to improve the conversion of this reaction was also unsuccessful and as such this approach was abandoned in favor of the previous ester strategy illustrated in Table 1.

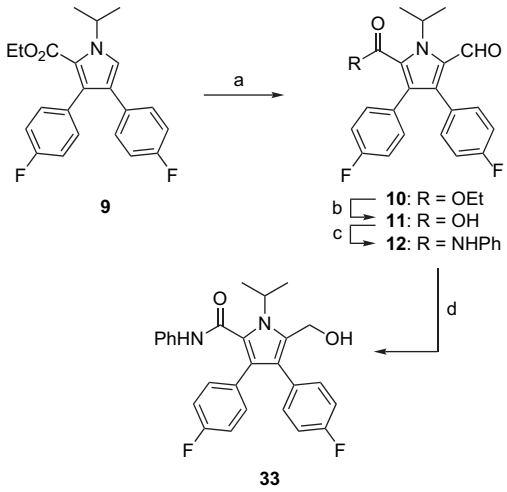
Table 2. Efforts toward synthesis of amide pyrrole **32** using amino amide **30**



Entry	Substrate	Equivalents of **30**	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	**25**	2.0	—	AcOH	125	2	0
2	**31**	1.0	—	DMF	150	12	8
3	**31**	2.0	—	NMP	100	1	24
4	**31**	2.0	Cs_2CO_3	NMP	100	2	0

3.2. Side chain installation

The next stage of the synthesis required functionalization of the pyrrole core in anticipation of installation of the 3,5-dihydroxyhexanoic acid side chain (Scheme 5). Vilsmeier–Haack formylation of **9** provided pyrrole carboxaldehyde **10**, which was saponified with aqueous NaOH to afford carboxylic acid **11**. This intermediate was converted to the corresponding acid chloride and was reacted with aniline to afford anilide **12**. Finally, the carboxaldehyde of **12** was reduced to the corresponding alcohol **33** using $NaBH_4$.

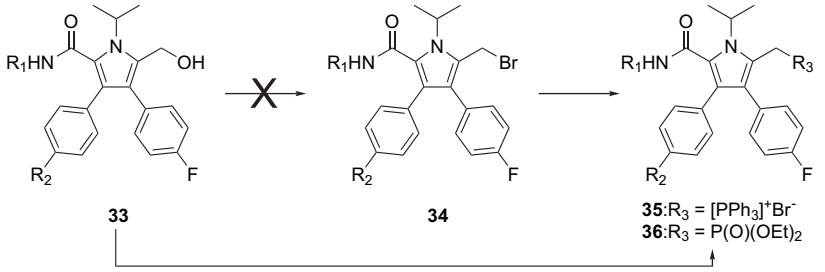


Scheme 5. Synthesis of alcohol **33**. (a) $POCl_3$, DMF, dichloroethane, 80 °C, 3 h, 45%; (b) NaOH, MeOH, 60 °C, 2 h, 100%; (c) (i) $SOCl_2$, 80 °C; (ii) $PhNH_2$, Et_3N, THF, 25 °C, 12 h, 57%; (d) $NaBH_4$, MeOH, 0 °C, 1 h, 47%.

To prepare for installation of the side chain via Wittig olefination, the alcohol of model pyrrole **33** needed to be transformed into an appropriate ylide precursor as outlined in Table 3. Preparation of both a phosphonium salt and a phosphonate ester was investigated. Initially, we sought to convert alcohol **33** into bromide **34** that is to be used as a common precursor for the preparation of both phosphonium salt **35** and phosphonate ester **36**. However, after several attempts (Table 2, entries 1–3) at this transformation failed (presumably due to the high reactivity of bromide **34**), we instead sought direct conversion of alcohol **33** into **35** and **36** as illustrated by entries 4 and 5, respectively. Specifically, alcohol **33** was directly and quantitatively converted to phosphonium bromide **35** via treatment with $Ph_3P{\cdot}HBr$ at 50 °C.[12] Alternatively, alcohol **33** was converted to phosphonate ester **36** by treatment with $P(OEt)_3$, NaBr, and $BF_3{\cdot}OEt_2$ at 25 °C.[13] This latter transformation presumably preceded though a transient alkyl bromide formed by the action of NaBr on **33**.

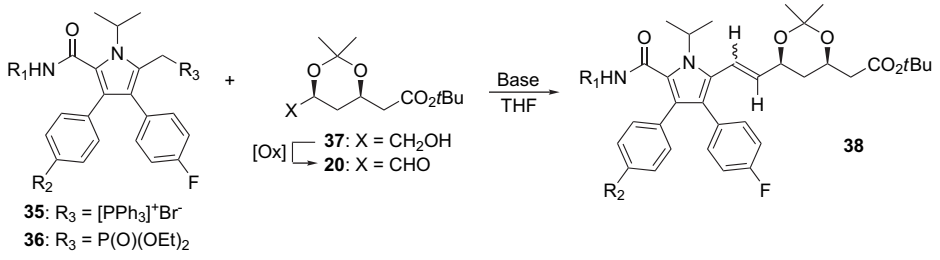
With the ylide precursors **35** and **36** in hand, attention was focused on optimization of the downstream olefination reaction. As shown in Table 4, the requisite aldehyde coupling partner **20** was readily prepared by Swern oxidation of the commercially available alcohol **37**.[14] A variety of conditions were evaluated to prepare olefin **38** starting from either phosphonium salt **35** or phosphonate ester **36**. Initial experimentation with **35** (Table 4, entries 1–3) revealed that use of either *n*BuLi or NaHMDS at low temperature afforded the desired olefin product (1:2 cis/trans mixture) in relatively low yields 31–46%. The use of KO^{t}Bu did not afford the desired product. Closer examination of the reaction products in entries 1 and 2 revealed that in addition to the desired product **38** the other major product from these reaction was a methyl pyrrole of general structure **42** (Scheme 6). This

Table 3. Preparation of phosphonium salt **35** and phosphonate ester **36** as ylide precursors



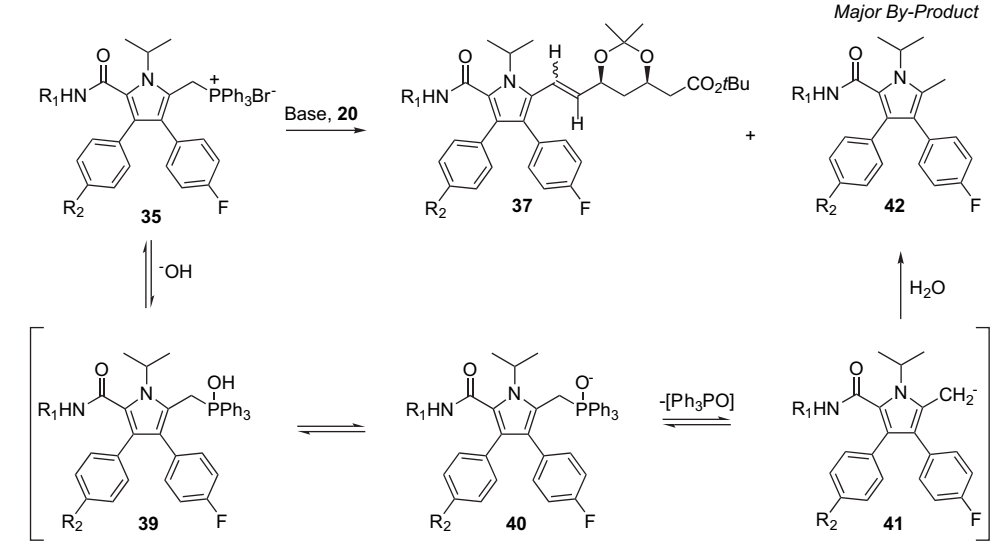
Entry	R_1	R_2	Product	Reagent	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Ph	F	**34**	CBr_4, Ph_3P	CH_2Cl_2	25	12	0
2	Ph	F	**34**	PBr_3, pyridine	CH_2Cl_2	0	12	0
3	Ph	F	**34**	Ph_3PBr_2	MeCN	50	12	0
4	Ph	F	**35**	Ph_3PHBr	CH_2Cl_2	50	2	100
5	Bn	H	**36**	$P(OEt)_3$, NaBr, $BF_3 \cdot OEt_2$	CH_2Cl_2	25	12	99

Table 4. Summary of Wittig and Horner–Wadsworth–Emmons strategies for side chain installation



Entry	R_1	R_2	R_3	Base	Equivalents of base	Temp (°C)	Time (h)	Yield (%)
1	Ph	F	$[PPh_3]^+Br^-$	*n*BuLi	1.2	−78→25	2	46
2	Ph	F	$[PPh_3]^+Br^-$	NaHMDS	1.2	−78→25	2	31
3	Ph	F	$[PPh_3]^+Br^-$	KO*t*Bu	1.2	0	2	0
4	4-(OMe)Bn	H	$[PPh_3]^+Br^-$	NaHMDS	1.4	−78→25	2	25
5	4-(OMe)Bn[a]	H	$[PPh_3]^+Br^-$	NaHMDS	1.4	−78→25	2	75
6	Bn	H	$P(O)(OEt)_2$	NaHMDS	1.2	0	2	0
7	Bn	H	$P(O)(OEt)_2$	LDA	1.2	0	2	0
8	Bn	H	$P(O)(OEt)_2$	LDA	2.4	0	2	0
9	Bn	H	$P(O)(OEt)_2$	NaH	2.5	25	8	0

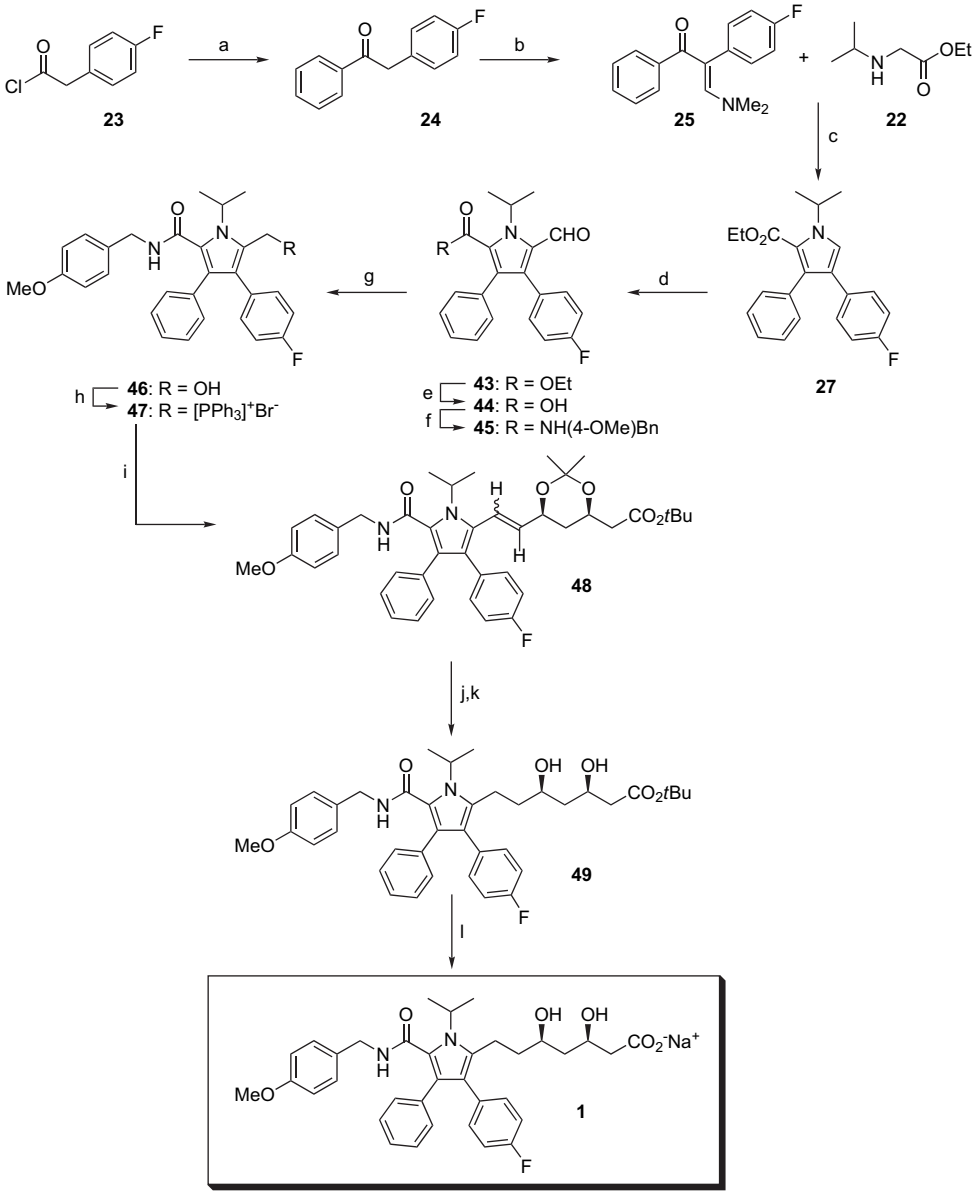
[a] Azeotropic drying of phosphonium salt **35** prior to use in order to reduce residual water content.



Scheme 6. Proposed mechanism for formation of by-product **42**.

type of by-product was observed regardless of the base employed in the olefination reaction. The formation of by-product **42** was presumed to be a result of hydrolytic cleavage of the carbon–phosphorous bond of phosphonium salt **35**. Such a hydrolytic cleavage is precedented as outlined mechanistically in Scheme 6.[15] Hydroxide (generated from residual water and base) undergoes nucleophilic addition to phosphonium salt **35** generating pentavalent phosphorous intermediate **39**, which undergoes deprotonation and loss of Ph_3PO to generate carbon-centered anion **41**, which is protonated to form the observed by-product **42**. The residual water enabling this side reaction was likely to be present in phosphonium salt **35** from the preceding step (i.e., phosphonium salt formation). After some experimentation, it was found that conversion to the desired olefin could be markedly improved by first removing all residual water from phosphonium salt **35** via azeotropic drying with IPA.[16] This improvement is illustrated in Table 4 by comparison of entry 4 (25% yield) versus entry 5 (75% yield). This modification was adopted for all subsequent Wittig olefination reactions.

We also investigated the construction of the requisite olefin linkage via a Horner–Wadsworth–Emmons reaction using phosphonate ester **36** (Table 4). This strategy offers improved atom economy and purification advantages relative to the Wittig approach. Disappointingly, reaction of phosphonate **36** with several bases at various stoichiometries (Table 4, entries 6–9) followed by the addition of aldehyde **20** did not result in the formation of the desired olefination product **38**. In most cases unreacted phosphonate ester **36** was recovered. The relative success of the former Wittig approach and contrasting failure of the Horner–Wadsworth–Emmons



Scheme 7. Complete second generation synthesis of HMG-CoA reductase inhibitor **1**. Reagents and conditions: (a) $AlCl_3$, C_6H_6, 50 °C, 8 h, 97%; (b) *N*,*N*-dimethylformamide dimethyl acetal, toluene, 100 °C, 15 h, 100%; (c) AcOH, 125 °C, 2.5 h, 81%; (d) $POCl_3$, DMF, dichloroethane, 80 °C, 18 h, 98%; (e) NaOH, MeOH, 25 °C, 24 h, 83%; (f) (i) $SOCl_2$, 75 °C, 2 h; (ii) (4-OMe)$BnNH_2$, Et_3N, CH_2Cl_2, 0 °C, 2 h, 55%; (g) $LiAl(O^tBu)_3H$, THF, 0 °C, 0.5 h, 41%; (h) $Ph_3P{\cdot}HBr$, CH_2Cl_2, 50 °C, 100%; (i) NaHMDS, **20** (see Table 4), THF, −78 °C, 75%; (j) 10% Pd/C, H_2, MeOH, 25 °C, 3 h; (k) 1 N HCl, MeOH, 25 °C, 3 h, 77% over two steps; (l) NaOH, MeOH, 25 °C, 48 h, 93%.

strategy were attributed to pK_a differences between the respective ylide precursors **35** and **36**. In the case of phosphonium salt **35**, the methylene protons (adjacent to the phosphorous) are predicted to be more acidic (estimated pK_a=17) than the N–H of the amide (estimated pK_a=19). By contrast, the methylene protons of phosphonate **36** (estimated pK_a=27) are expected to be less acidic than the N–H the amide (pK_a=19) suggesting that, in this case, initial deprotonation occurred at the amide functionality. In an effort to overcome this problem, excess base (Table 4, entries 8 and 9) was employed to attempt a double deprotonation reaction of phosphonate ester **36**; however, despite this modification only recovered starting material was isolated, and as such the synthesis was executed using the previous Wittig olefination strategy.

3.3. Complete second generation synthesis

With reliable methods for construction of the pyrrole core and attachment of the 3,5-dihydroxyhexanoic acid side chain in place, the second generation synthesis of this new class of HMG-CoA reductase inhibitors could be completed. Scheme 7 illustrates the optimized route in a cohesive sequence for the synthesis of inhibitor **1**. Pyrrole **27** was constructed from vinylogous amide **25** and amino acid ester **22** as previously described. Elaboration of **27** via Vilsmeier–Haack reaction followed by saponification and amidation provided amide **45** in good yield. Subsequent reduction of **45** to the corresponding alcohol **46** and treatment with $Ph_3P\cdot HBr$ afforded phosphonium salt **47**. Azeotropic drying of **47** followed by Wittig olefination provided compound **48** as an inconsequential mixture of cis/trans isomers. Finally, hydrogenation of the olefin over Pd/C, cleavage of the acetonide protecting group (HCl/MeOH), and saponification afforded the final product **1** as its sodium salt.

4. Conclusion

In conclusion, the second generation route offered several advantages over the original synthesis (Scheme 1) including reducing the overall synthetic length from 21 to 13 steps and increasing the overall yield from <1 to 8%. The number of chromatographic separations was also reduced significantly improving material throughput. Additionally, the second generation route eliminated the use of two potentially hazardous high energy intermediates and a variety of expensive reagents. Overall, this new route enabled the preparation of multi-gram quantities of **1** to support pre-clinical evaluation of this novel HMG-CoA reductase inhibitor.

5. Experimental

5.1. General procedures

All reagents and solvents were used as received from commercial sources unless otherwise noted. Specifically, alcohol **37** was purchased from Kanaka Corporation and converted to aldehyde **20** as previously described.[13] Raw material 2-(4-fluoro-phenyl)-1-phenyl-ethanone (**24**) was initially prepared as described below and subsequently purchased in multi-kilogram quantities from Precursor Chemicals, Inc. All experiments were conducted under an inert nitrogen atmosphere unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz Nuclear Magnetic Resonance Spectrometer. NMR spectra were recorded in $CDCl_3$, CD_3OD, or DMSO-d_6 and chemical shifts are reported relative to the residual solvent peak. The following abbreviations were used to assign spectra: s=singlet, d=doublet, t=triplet, q=quartet, s=septet, m=multiplet, br s=broad singlet. Mass spectral analysis was conducted on a Waters Micromass ZQ instrument. Melting points were determined on an Electrothermal Melting Point Apparatus and are uncorrected.

Complete experimental procedures and spectral data for the original synthesis of this template (Scheme 1, **5**–**17**) will be published separately along with structure–activity studies and complete biological data.

5.2. 2-(4-Fluoro-phenyl)-1-phenyl-ethanone (24)

To a solution of benzene (182 mL) at 0 °C was added $AlCl_3$ (46.4 g, 348 mmol). A portion of 4-fluoro-phenyl acetyl chloride (50.0 g, 290 mmol) was then added drop-wise over 0.5 h maintaining the reaction temperature below 5 °C. Once the addition was complete, the reaction was allowed to warm to 25 °C and then heated to 50 °C for 8 h. Subsequently, the reaction mixture was cooled to 25 °C and poured onto ice (400 g). To the resulting suspension was added 10% HCl (50 mL) with stirring. The organic layer was separated and washed with 10% HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was then dried (Na_2SO_4) and concentrated to afford a solid that was triturated twice with hexane (200 mL) and then dried at 35 °C under vacuum to afford **24** (59.90 g, 97%): ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J=6.0 Hz, 2H), 7.53 (t, J=7.6 Hz, 1H), 7.43 (t, J=6.0 Hz, 2H), 7.22–7.17 (m, 2H), 7.00–6.97 (t, J=8.8 Hz, 2H), 4.23 (s, 2H); MS (APCI$^+$): m/z 215.0 (M+H). Characterization data were consistent with previous literature reports of **24**.[17] Additional quantities of **24** were subsequently purchased from Precursor Chemicals, Inc.

5.3. 3-Dimethylamino-1-(4-fluoro-phenyl)-2-phenyl-propenone (25)

To a solution of **24** (56.90 g, 266 mmol) in toluene (400 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (141 mL, 1.06 mol) and the reaction was heated to reflux for 16 h. After cooling to 25 °C, the solvent was removed under reduced pressure to afford an orange solid that was recrystallized from toluene (175 mL). The solid was isolated by filtration and washed with hexane (60 mL) to afford **25** (57.1 g, 80%) as a brown solid: ^{1}H NMR (DMSO-d_6) δ 7.33–7.28 (m, 5H), 7.15 (s, 1H), 7.14–7.01 (m, 4H), 3.31 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 195.1, 154.3, 141.8, 133.7, 133.6, 129.5, 128.8, 127.9, 114.9, 114.7, 111.1, 52.3, 42.7; MS (APCI$^+$): m/z 270.1 (M+H). Mp 110–111 °C.

5.4. Isopropylamino-acetic acid ethyl ester (22)

A 5-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, temperature probe, addition funnel, and nitrogen bubbler was charged with *iso*-propyl amine (2.22 kg, 37.2 mol) and methyl *tert*-butyl ether (2.5 L). The resulting solution was cooled to 5 °C and treated with

ethyl bromoacetate (2.70 kg, 16.2 mol) by addition funnel at a sufficient rate to maintain the pot temperature less than 30 °C (~1 h). The reaction mixture was stirred at 22 °C for 16 h, and *iso*-propyl amine hydrobromide was removed by filtration though Celite. The filtrates were then concentrated under reduced pressure to produce **22** (2.27 kg, 95%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.14 (q, J=7.2 Hz, 2H), 3.56 (s, 2H), 2.74 (sept, J=6.0 Hz, 1H), 1.59 (s, 1H), 1.23 (t, J=7.2 Hz, 3H), 1.01 (d, J=6.4 Hz, 6H). Characterization data were consistent with previous literature reports of **22**.[18]

5.5. 4-(4-Fluoro-phenyl)-1-isopropyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (27)

To a 5-L round-bottomed flask equipped with mechanical stirring were charged **25** (868.5 g, 3.23 mol) and glacial acetic acid (1.3 L). The resulting solution was treated with **22** (953.3 g, 6.57 mol, 2.04 equiv) and the mixture was heated to 120 °C for 6 h, until full consumption of **25** was confirmed by HPLC analysis. The reaction mixture was cooled to 85 °C and was diluted with water (325 mL) in one portion. The mixture was allowed to cool to 20 °C with stirring, and was held at this temperature for 5 h. The resulting solid was collected by filtration, washed with water (3×1 L), and dried at 60 °C under vacuum for 60 h to afford **27** (868.8 g, 77%) as a pale tan solid: ^{1}H NMR ($CDCl_3$) δ 7.24–7.10 (m, 6H), 7.01–6.97 (m, 2H), 6.86 (t, J=8.7 Hz, 2H), 5.45 (sept, J=6.6 Hz, 1H), 4.02 (q, J=7.0 Hz, 2H), 1.50 (d, J=6.6 Hz, 6H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.7, 162.1, 136.3, 131.1, 130.8, 129.8, 129.7, 127.6, 126.6, 123.7, 120.8, 120.4, 115.2, 59.9, 49.0, 24.1, 13.7; MS(APCI$^+$): m/z 352.3 (M+H). Anal. Calcd for $C_{22}H_{22}F_1N_1O_2$: C, 75.19; H, 6.31; N, 3.99. Found: C, 75.17; H, 6.40; N, 3.89. Mp 104–105 °C.

5.6. *N*-Benzyl-2-(isopropylamino)acetamide (30)

To a solution of chloroacetyl chloride (2.84 g, 25.1 mmol) in CH_2Cl_2 at 0 °C was added benzyl amine (2.69 g, 25.1 mmol) followed by triethylamine (7.62 g, 75.3 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to 25 °C for 12 h. Subsequently, a saturated solution of $NaHCO_3$ was added to the reaction mixture and the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to afford **29** (3.42 g, 18.6 mmol), which was taken up in THF/Et_2O (1:2, 100 mL). To this solution at 25 °C was added *iso*-propyl amine (2.20 g, 37.2 mmol) and the resulting reaction mixture was stirred at 25 °C for 48 h. The precipitate that developed was removed by filtration and the filtrate concentrated to an oil that was purified by silica gel chromatography (5–10% MeOH/CH_2Cl_2) to afford **30** (1.21 g, 32%): ^{1}H NMR (DMSO-d_6) δ 8.22 (br s, 1H), 7.27–7.17 (m, 5H), 4.24 (d, J=6.0 Hz, 2H), 3.07 (s, 2H), 2.61 (sept, J=6.4 Hz, 1H), 2.21 (br s, 1H), 0.90 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.2, 138.6, 128.8, 127.8, 127.5, 50.3, 49.9, 43.1, 23.0; MS (APCI$^+$): m/z 207.2 (M+H).

5.7. (*E*)-3-Chloro-2-(4-fluoro-phenyl)-3-phenylacrylaldehyde (31)

To a solution of **25** (57.1 g, 212 mmol) in CH_2Cl_2 (250 mL) at 25 °C was added $POCl_3$ (65.1 g, 424 mmol). The reaction mixture was heated to 45 °C for 5 h. After cooling, the solvent was removed under reduced pressure and THF/water (1:1, 100 mL) was added in one portion and the resulting reaction mixture was stirred at 25 °C for 48 h. Subsequently, THF was removed under reduced pressure and CH_2Cl_2 (500 mL) was added. The organic layer was separated, dried (Na_2SO_4), and concentrated to afford **31** (54.5 g, 99%) as a light yellow solid that was a ca. 2:1 mixture of *E*/*Z* isomers. This mixture could be utilized without additional purification; however, an analytical sample of the *E*-isomer (identified by comparison to Ref. 11b) was isolated by silica gel chromatography (10–20% EtOAc/hexane) and characterized: ^{1}H NMR ($CDCl_3$) δ 9.62 (s), 7.55–7.50 (m, 5H), 7.24–7.17 (m, 2H), 6.93–6.85 (m, 2H); MS (APCI$^+$): m/z 261.0 (M+H).

5.8. Diethyl-(5-(benzylcarbamoyl)-3-(4-fluoro-phenyl)-1-isopropyl-4-phenyl-1*H*-pyrrol-2-yl)methylphosphonate (36, R_1=Bn, R_2=F, R_3=P(O)(OEt)$_2$)

To a solution of **33** (1.14 g, 2.56 mmol) in CH_2Cl_2 (100 mL) at 25 °C were added triethyl phosphate (0.43 g, 2.56 mmol), NaBr (0.26 g, 2.56 mmol), and $BF_3\cdot OEt_2$ (0.36 g, 2.56 mmol), and the reaction mixture was stirred at 25 °C for 16 h. Subsequently, a saturated $NaHCO_3$ solution (20 mL) was added and the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to afford **36** (1.43 g, 99%), which was used without additional purification: ^{1}H NMR ($CDCl_3$) δ 7.14–7.10 (m, 8H), 7.00–6.95 (m, 2H), 6.87–6.79 (m, 4H), 5.50 (br s, 1H), 4.84 (sept, J=7.2 Hz, 1H), 4.25 (d, J=5.6 Hz, 2H), 4.09–3.94 (m, 4H), 3.14 (d, J=20.8 Hz, 2H), 1.64 (d, J=7.2 Hz, 6H), 1.33–1.20 (m, 6H); MS (APCI$^+$): m/z 563.1 (M+H).

5.9. 3,4-Bis(4-fluoro-phenyl)-5-formyl-1-isopropyl-*N*-phenyl-1*H*-pyrrole-2-carboxamide (12)

Neat **9** (3.00 g, 8.12 mmol) was treated with thionyl chloride (30 mL) and the resulting mixture was heated to 70 °C for 1 h and then cooled to 25 °C. The excess thionyl chloride was removed under reduced pressure and CH_2Cl_2 (50 mL) was added. The reaction mixture was cooled to 0 °C and was subsequently treated with aniline (0.91 g, 9.75 mmol) and triethylamine (1.23 g, 12.2 mmol). The reaction mixture was stirred for 12 h at 25 °C after which time a saturated $NaHCO_3$ solution was added. The organic layer was separated, dried (Na_2SO_4), and concentrated to afford a crude oil that was purified by silica gel chromatography (10% EtOAc/hexanes) to provide **12** (3.61 g, 34%). ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 1H), 9.36 (s, 1H), 7.43–7.41 (m, 2H), 7.35–7.11 (m, 6H), 7.07–6.96 (m, 5H), 5.20 (sept, J=6.2 Hz, 1H), 1.51 (d, J=6.2 Hz, 6H); MS (APCI$^+$): m/z 445.1 (M+H).

5.10. 3,4-Bis(4-fluoro-phenyl)-5-(hydroxymethyl)-1-isopropyl-*N*-phenyl-1*H*-pyrrole-2-carboxamide (33)

To a solution of **12** (1.23 g, 2.77 mmol) in MeOH (40 mL) at 0 °C was added $NaBH_4$ (0.16 g, 4.15 mmol) in one portion and the reaction mixture was stirred at 0 °C for 0.5 h and then at 25 °C for an additional 0.5 h. Subsequently, the reaction solvent was removed under reduced pressure and then CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ (50 mL) were added. The organic layer was separated, dried (Na_2SO_4), and concentrated to afford a crude oil that was purified by

silica gel chromatography (20% EtOAc/hexanes) to provide **33** (0.58 g, 47%): ^{1}H NMR (DMSO-d_6) δ 10.0 (s, 1H), 7.41–7.39 (m, 2H), 7.22–7.18 (m, 2H), 7.12–6.91 (m, 9H), 5.12 (t, J=4.4 Hz, 1H), 4.75 (sept, J=7.2 Hz, 1H), 4.33 (d, J=4.4 Hz, 1H), 1.55 (d, J=7.2 Hz, 6H); MS (APCI$^+$): m/z 447.1 (M+H).

5.11. [3-(4-Fluoro-phenyl)-1-isopropyl-5-(phenylcarbamoyl)-4-(4-fluoro-phenyl)-1*H*-pyrrol-2-ylmethyl]-triphenyl-phosphonium bromide (35)

To a solution of **33** (0.21 g, 0.47 mmol) in CH_2Cl_2 (20 mL) was added triphenylphosphine hydrobromide (0.16 g, 0.47 mmol). The reaction mixture was heated to 50 °C for 2.5 h after which time all starting material was consumed as determined by TLC. The reaction solvent was removed under reduced pressure and the resulting yellow foam was dried under high vacuum for 12 h to provide **35** (0.36 g, 100%) in sufficient purity for use in the next step. ^{1}H NMR (DMSO-d_6) δ 9.98 (s, 1H), 7.83–7.81 (m, 2H), 7.65–7.47 (m, 6H), 7.35–7.33 (m, 4H), 7.26–7.16 (m, 8H), 7.05–6.92 (m, 4H), 6.82–6.77 (m, 2H), 6.52–6.49 (t, J=6.0 Hz, 2H), 5.13 (d, J=12.4 Hz, 2H), 4.31 (sept, J=6.0 Hz, 1H), 1.01 (d, J=6.0 Hz, 6H); MS (APCI$^+$): m/z 691.2 (M+H).

5.12. 4-(4-Fluoro-phenyl)-5-formyl-1-isopropyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (43)

A 5-L, four-necked, round-bottomed flask with mechanical stirrer and reflux condenser was charged with phosphorus oxychloride (306 g, 1.99 mol). The reactor was cooled between −35 and −40 °C, and a solution of *N*,*N*-dimethylformamide (154 mL, 1.99 mol) in 475 mL of 1,2-dichloroethane was slowly added via addition funnel maintaining the temperature of solution between −35 and −40 °C. The reaction mixture was then allowed to slowly warm to 10 °C and stirred for 1 h. A solution of **27** (350 g, 1.0 mol) in 1,2-dichloroethane (1.8 L) was then added via addition funnel maintaining a reaction temperature of 10 °C. The reaction mixture was then heated to 80 °C for 18 h. The reaction mixture was then cooled to 25 °C, diluted with heptane/ethyl acetate (1:1, 3.5 L), and poured over ice (3.5 L). The layers were separated, the aqueous layer (8.8 L) was extracted with two portions of 1:1 ethyl acetate/heptane (4 L). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated under vacuum to give **43** (371 g, 98%) as a light brown solid that was utilized without additional purification: ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 7.21–7.17 (m, 3H), 7.12–6.93 (m, 6H), 5.54 (sept, J=6.9 Hz, 1H), 4.13 (q, J=7.0 Hz, 2H), 1.69 (d, J=6.9 Hz, 6H), 0.79 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 181.7, 163.2, 161.2, 133.2, 132.9, 132.8, 130.2, 129.6, 129.2, 128.2, 128.0, 127.1, 115.3, 115.1, 61.8, 51.3, 21.7, 13.6; MS (APCI$^+$): m/z 380.1 (M+H). Anal. Calcd for $C_{23}H_{12}F_1N_1O_3$: C, 72.81; H, 5.84; N, 3.69. Found: C, 72.80; H, 5.76; N, 3.65. Mp 88–90 °C.

5.13. 4-(4-Fluoro-phenyl)-5-formyl-1-isopropyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (44)

To a solution of **43** (650 g, 1.71 mol) in THF (1.7 L) was slowly added 6 M aqueous sodium hydroxide (1.13 L, 6.8 mol) followed by MeOH (3.8 L). The solution was stirred at room temperature for 24 h after which time the reaction mixture was concentrated to dryness under reduced pressure. The residual solid was dissolved in water (11 L). The aqueous layer was then extracted with two portions of MTBE. The combined organic layers were extracted with 0.5 M aqueous potassium hydroxide. The three aqueous layers were combined, washed with MTBE, acidified to pH 1 with 6 M aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic layers were then washed with 6 L of brine, dried (Na_2SO_4), and concentrated under vacuum to provide **44** (498 g, 83%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) 9.37 (s, 1H), 7.21–7.16 (m, 5H), 7.13–6.99 (m, 4H), 5.37 (sept, J=7.2 Hz, 1H), 1.54 (d, J=7.2 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 181.1, 164.8, 163.9, 160.7, 137.3, 133.7, 131.6, 130.5, 128.9, 128.8, 128.5, 127.5, 126.2, 115.7, 51.3, 21.9; MS (APCI$^+$): m/z 351.9 (M+H). Anal. Calcd for $C_{21}H_{18}F_1N_1O_3$ C, 71.78; H, 5.16; N, 3.99. Found: C, 71.16; H, 5.03; N, 3.95. Mp 219–220 °C.

5.14. 4-(4-Fluoro-phenyl)-5-formyl-1-isopropyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid 4-methoxybenzylamide (45)

Thionyl chloride (100 mL) was added in one portion to **44** (15.0 g, 42.7 mmol), and the reaction mixture was heated to 75 °C for 2 h after which time it was cooled to 25 °C and excess thionyl chloride was removed under reduced pressure. Dichloromethane (250 mL) was added to the crude acid chloride and the solution was cooled to 0 °C, and then 4-methoxybenzyl amine (6.44 g, 47.0 mmol) and triethylamine (8.93 mL, 64.0 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for an additional 2 h. Saturated $NaHCO_3$ solution was added and organic layer was separated, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (10–20% EtOAc/hexane) to afford **45** (11.14 g, 55%): ^{1}H NMR ($CDCl_3$) δ 9.44 (s, 1H), 7.17–7.14 (m, 3H), 7.05–7.00 (m, 2H), 6.98 (d, J=7.6 Hz, 2H), 6.91 (t, J=8.8 Hz, 2H), 6.71 (d, J=8.8 Hz, 2H), 6.65 (d, J=8.8 Hz, 2H), 5.57 (t, J=4.8 Hz, 1H), 5.43 (sept, J=7.2 Hz, 1H), 4.23 (d, J=5.6 Hz, 2H), 3.72 (s, 3H), 1.61 (d, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 181.3, 162.6, 159.2, 132.9, 132.8, 130.1, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 127.3, 124.8, 115.4, 114.2, 76.9, 55.4, 51.5, 43.9, 21.7; MS (APCI$^+$): m/z 471.3 (M+H). Mp 169–170 °C.

5.15. 4-(4-Fluoro-phenyl)-5-hydroxymethyl-1-isopropyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid 4-methoxybenzylamide (46)

To a solution of **45** (11.1 g, 23.7 mmol) in THF (250 mL) at 0 °C was added 1.0 M lithium tri-*tert*-butoxyaluminohydride (28.4 mL, 28.4 mmol). The reaction mixture was stirred for 30 min at 0 °C after which time TLC analysis indicated the reaction was complete. The solvent was removed under reduced pressure, and the residue was charged with ethyl acetate (500 mL) and saturated $NaHCO_3$ solution (150 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. The resulting oil was purified by silica gel chromatography (35% EtOAc/hexane) to afford **46** (4.64 g, 41%): ^{1}H NMR ($CDCl_3$) δ 7.14–7.10 (m, 3H), 7.00–6.96 (m, 4H), 6.85 (t, J=8.8 Hz, 2H), 6.72 (d, J=8.8 Hz, 2H), 6.65 (d, J=8.8 Hz, 2H), 5.45 (t, J=5.2 Hz,

1H), 4.97 (sept, J=7.2 Hz, 1H), 4.57 (d, J=4.8 Hz, 2H), 4.18 (d, J=5.2 Hz, 2H), 3.72 (s, 3H), 1.66 (d, J=7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.7, 159.0, 134.4, 132.1, 130.7, 129.5, 129.2, 128.5, 128.4, 126.7, 125.9, 124.9, 124.0, 115.0, 114.0, 76.9, 62.3, 55.4, 20.0, 43.8, 22.8; MS (APCI$^+$): m/z 473.2 (M+H). Mp 191–192 °C.

5.16. [3-(4-Fluoro-phenyl)-1-isopropyl-5-(4-methoxy-benzylcarbamoyl)-4-phenyl-1*H*-pyrrol-2-ylmethyl]-triphenyl-phosphonium bromide (47)

To a solution of **46** (4.64 g, 9.82 mmol) in CH_2Cl_2 (100 mL) was added triphenylphosphine hydrobromide (3.37 g, 9.82 mmol) in one portion. The reaction mixture was heated to 50 °C for 2.5 h after which time all starting material was determined to be consumed by TLC. The reaction solvent was removed under reduced pressure and the resulting yellow solid was then taken up in *iso*-propanol (150 mL) in a flask equipped with a reflux head. Dry *iso*-propanol was back-filled as necessary to maintain a consistent reaction volume for 5 h. The resulting slurry was cooled to 25 °C and the excess solvent was removed under reduced pressure to afford **47** (7.82 g, 100%): ^{1}H NMR ($CDCl_3$) 7.70 (t, J=6.6 Hz, 3H), 7.61–7.48 (m, 8H), 7.45–7.42 (m, 2H), 7.24–7.19 (m, 5H), 7.11–7.03 (m, 3H), 6.86 (dd, J=8.0, 1.2 Hz, 5H), 6.70–6.67 (m, 3H), 6.61 (d, J=6.4 Hz, 2H), 6.29 (br s, 1H), 5.92 (br s, 1H), 4.84 (br s, 1H), 4.15 (d, J=4.0 Hz, 2H), 3.70 (s, 3H), 1.21 (br s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.4, 163.0, 160.5, 159.0, 135.3, 134.5, 134.2, 133.3, 132.0, 130.5, 130.1, 129.7, 129.3, 129.0, 128.4, 126.8, 126.6, 125.3, 125.2, 119.0, 118.9, 118.1, 117.3, 115.7, 115.0, 114.0, 55.4, 51.6, 43.9, 22.8, 22.4; MS (APCI$^+$): m/z 717.3 (M$^+$).

5.17. (3*R*,5*R*)-7-[3-(4-Fluoro-phenyl)-1-isopropyl-5-(4-methoxy-benzylcarbamoyl)-4-phenyl-1*H*-pyrrol-2-yl]-3,5-dihydroxy-heptanoic acid *tert*-butyl ester (49)

To a solution of **47** (7.82 g, 9.80 mmol) in THF (200 mL) at −78 °C was added 1.0 M NaHMDS in THF (13.7 mL, 13.7 mmol). An orange color was noted as the base was added. The reaction mixture was stirred below −70 °C for 5 min after which time a solution of **20**[14] (2.79 g, 10.8 mmol) in THF (10 mL) was slowly added. After the addition, the reaction mixture was stirred below −70 °C for 30 min and then allowed to warm to 25 °C over 1.5 h. The reaction was quenched by drop-wise addition of saturated NH_4Cl. Ethyl acetate (250 mL) was added and organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated. The crude product was filtered through a pad of silica gel (15–20% EtOAc/hexane) to remove Ph_3PO and provide **48** (5.11 g, 7.33 mmol) as an inseparable mixture of cis/trans olefin isomers, which was taken up in MeOH (200 mL). To this solution was added 10% Pd/C (500 mg). The reaction vessel was then evacuated and filled with hydrogen gas (50 psi) for 3 h. The reaction mixture was purged with nitrogen and then filtered through a pad of Celite. The filtrates were charged with 1 N HCl (10 mL) and the mixture was stirred for 3 h at 25 °C. Subsequently, the organic solvents were removed under reduced pressure and then ethyl acetate (200 mL) and saturated $NaHCO_3$ (100 mL) were added. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel chromatography (30–70% EtOAc/hexane) to provide **49** (3.74 g, 77%): ^{1}H NMR ($CDCl_3$) δ 7.10–7.08 (m, 3H), 6.98–6.91 (m, 4H), 6.83 (t, J=8.8 Hz, 2H), 6.72 (d, J=8.8 Hz, 2H), 6.64 (d, J=8.8 Hz, 2H), 5.41 (t, J=5.2 Hz, 1H), 4.78 (sept, J=7.2 Hz, 1H), 4.17 (d, J=5.6 Hz, 2H), 4.11–4.05 (m, 1H), 3.72 (s, 3H), 2.81–2.75 (m, 1H), 2.70–2.59 (m, 1H), 2.28–2.27 (m, 2H), 1.63 (d, J=7.2 Hz, 6H), 1.61–1.21 (m, 4H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.3, 163.8, 160.3, 159.0, 135.0, 133.3, 132.2, 131.8, 130.4, 129.7, 129.2, 128.3, 126.5, 123.9, 120.8, 115.1, 114.9, 114.0, 81.3, 71.5, 69.4, 55.4, 49.2, 43.8, 42.5, 41.8, 38.3, 28.3, 22.8, 21.3; MS (APCI$^+$): m/z 659.1 (M+H). Anal. Calcd for $C_{39}H_{47}F_1N_2O_6$: C, 71.10; H, 7.19; N, 4.25. Found: C, 71.03; H, 7.29; N, 4.07. Mp 141–142 °C.

5.18. (3*R*,5*R*)-7-[3-(4-Fluoro-phenyl)-1-isopropyl-5-(4-methoxy-benzylcarbamoyl)-4-phenyl-1*H*-pyrrol-2-yl]-3,5-dihydroxy-heptanoic acid sodium salt (1)

To a solution of **49** (3.39 g, 5.15 mmol) in MeOH (100 mL) was added 1.03 N NaOH (5.11 mL, 5.25 mmol) and the reaction mixture was stirred at 25 °C for 48 h after which time the reaction solvent was removed under reduced pressure. The resulting solid was then azeotroped with toluene (3×100 mL) and triturated with diethyl ether to provide a light yellow solid that was dried under vacuum at 60 °C to afford **1** (2.99 g, 93%): ^{1}H NMR (DMSO-d_6) δ 8.27 (t, J=6.0 Hz, 1H), 7.40 (s, 1H), 7.06–6.89 (m, 9H), 6.81 (d, J=8.4 Hz, 2H), 6.65 (d, J=8.8 Hz, 2H), 4.74 (s, 1H), 4.47 (sept, J=7.2 Hz, 1H), 4.06 (d, J=5.6 Hz, 2H), 3.69–3.65 (m, 1H), 3.64 (s, 3H), 3.55–3.52 (m, 1H), 2.65–2.59 (m, 1H), 2.45–2.42 (m, 1H), 1.95 (dd, J=15.2, 3.6 Hz, 1H), 1.74 (dd, J=15.2, 8.4 Hz, 1H), 1.54–1.17 (m, 4H), 1.43 (d, J=7.2 Hz, 6H). ^{13}C NMR (DMSO-d_6) δ 176.6, 164.9, 159.9, 158.6, 135.4, 132.8, 132.6, 132.5, 131.3, 130.1, 129.2, 128.3, 125.8, 122.9, 119.2, 115.5, 115.3, 114.0, 68.8, 67.4, 55.7, 44.7, 44.5, 44.3, 42.8, 37.6, 23.1, 21.7; MS (APCI$^+$): m/z 603.6 (M+H). Anal. Calcd for $C_{35}H_{38}F_1N_2O_6Na_1\cdot 0.5H_2O$: C, 66.34; H, 6.20; N, 4.42. Found: C, 66.22; H, 6.23; N, 4.20. Mp 210–211 °C.

References and notes

1. Grundy, S. M. *J. Intern. Med.* **1997**, *241*, 295–306.
2. (a) Knopp, R. H. *N. Engl. J. Med.* **1999**, *341*, 498–511; (b) Castelli, W. P. *Am. J. Med.* **1984**, *76*, 4–12.
3. For reviews, see: (a) McKenney, J. M. *Clin. Cardiol.* **2003**, *26 (Suppl. III)*, 32–38; (b) Speidal, K. M.; Hilleman, D. E. *Expert Opin. Pharmacother.* **2006**, *7*, 1291–1304.
4. (a) Grundy, S. M.; Cleeman, J. I.; Merz, N. B.; Brewer, B.; Clark, L. T.; Hunninghake, D. B.; Pasternak, R. C.; Smith, S. C.; Stone, N. J. *Circulation* **2004**, *110*, 227–239; For additional discussion, see: (b) O'Keefe, J. H.; Cordain, L.; Harris, W. H.; Moe, R. M.; Vogel, R. *J. Am. Coll. Cardiol.* **2004**, *43*, 2142–2146.
5. For an account of the structure–activity studies and in vivo pharmacology of this series of HMG-CoA reductase inhibitors, see: Pfefferkorn, J. A.; Song, Y.; Sun, K.-L.; Miller, S. R.; Trivedi, B. K.; Choi, C.; Sorenson, R. J.; Bratton, L. D.; Unangst, P. C.; Larsen, S. D.; Poel, T.-J.; Cheng, X.-M.; Lee, C.; Erasga, N.; Auerbach, B.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G.; Robertson, A.; Olsen, K.; Mertz, T.; Sekerke, C.; Pavlovsky, A.; Harris, M. S.;

Bainbridge, G.; Caspers, N.; Chen, H.; Eberstadt, M. *Bioorg. Med. Chem. Lett.*, in press. doi:10.1016/j.bmcl.2007.05.097
6. For a review on atorvastatin synthesis, see: Li, J.-J.; Johnson, D. S.; Sliskovic, D. R.; Roth, B. D. *Contemporary Drug Synthesis*; John Wiley and Sons: New York, NY, 2004; pp 113–124.
7. Barr, L.; Easton, C. J.; Lee, K.; Lincoln, S. F. *Org. Biomol. Chem.* **2005**, *3*, 2990–2993.
8. Barton, D. H. R.; Zard, S. C. *J. Chem. Soc., Chem. Commun.* **1985**, 1098–1100.
9. Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849–7854.
10. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
11. (a) Gupton, J.; Krumpe, K.; Burnham, B.; Dwornik, K.; Petrich, S.; Du, K.; Bruce, M.; Vu, P.; Vargas, M.; Keertikar, K.; Hosein, K.; Jones, C.; Sikorski, J. *Tetrahedron* **1998**, *54*, 5075–5088; (b) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Webb, T. M.; Shuford, J. S.; Sikorski, J. A. *Tetrahedron* **1999**, *55*, 14515–14522; (c) Gupton, J. T.; Petrich, S. A.; Smith, L. L.; Bruce, M. A.; Vu, P.; Du, K. X.; Dueno, E.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1996**, *52*, 6879–6892; (d) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Vu, P.; Sikorski, J. A.; Dahl, M. L.; Jones, C. R. *J. Org. Chem.* **1992**, *57*, 5480–5483; (e) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Sikorski, J. A.; Riesinger, S. A. *J. Org. Chem.* **1990**, *55*, 4735–4740.
12. Hamanaka, N.; Kosuge, S.; Iguchi, S. *Synlett* **1990**, 139–140.
13. (a) Burkhouse, D.; Zimmer, H. *Synthesis* **1984**, 330–332; (b) Natchev, I. *Synthesis* **1987**, 1079–1084.
14. Radl, S. *Synth. Commun.* **2003**, *33*, 2275–2283.
15. Zanger, M.; VanderWerf, C. A.; McEwen, W. *J. Am. Chem. Soc.* **1959**, *81*, 3806–3807.
16. Karl Fisher water analysis of various phosphonium salts synthesized according to the method described in Table 3 indicated that, as expected, they contained up to 1 equiv of water; however, azeotropic drying with IPA reduced the water content to $<0.5\%$. Attempts to remove this residual water using simply high vacuum and elevated temperature were not effective.
17. Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322–2330.
18. Cavill, J. L.; Elliott, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, C. O. *Tetrahedron* **2006**, *62*, 410–421.