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An Asymmetric Synthesis of Rosuvastatin Calcium

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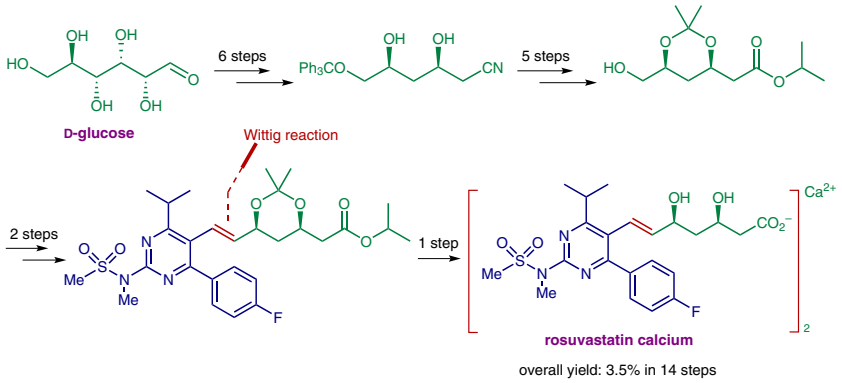

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Abstract A novel asymmetric synthesis of a (3*R*,5*S*)-dihydroxyhexanoic ester is described. The ester, which serves as the precursor for generating the side chain of rosuvastatin, is synthesized from D-glucose and subsequently coupled, under Wittig olefination conditions, with a phosphonium ylide derived from an appropriately substituted pyrimidine moiety. The coupling results in the formation of a precursor containing all the structural features of rosuvastatin. This precursor is converted into rosuvastatin calcium following a well-established procedure.

Key words total synthesis, rosuvastatin calcium, Wittig olefination, lactone reduction, diastereoselective reduction, sugar chemistry, D-glucose

Rosuvastatin[1] belongs to a class of drugs called HMG-CoA reductase inhibitors. These inhibitors are widely known as statins and have been found to be effective in combating hypercholesterolemia (elevated cholesterol levels). Rosuvastatin is the most recent entrant into this class (Figure 1). It is widely prescribed for the treatment of hypercholesterolemia.

Rosuvastatin, like all the other drugs in this class, has a heptanoic acid side chain possessing two chiral centers at positions C-3 and C-5 on its backbone. Each center bears a hydroxy group and the absolute configurations of the groups are *R* and *S*, respectively. However, the structural similarity of rosuvastatin with other statins ends here. The structural feature that distinguishes it from the others in the group is the presence of a substituted pyrimidine ring attached to the aliphatic side chain through a carbon–carbon double bond having *E* stereochemistry. The remaining three available positions on the pyrimidine are substituted

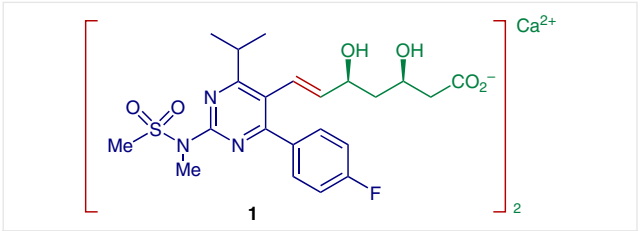
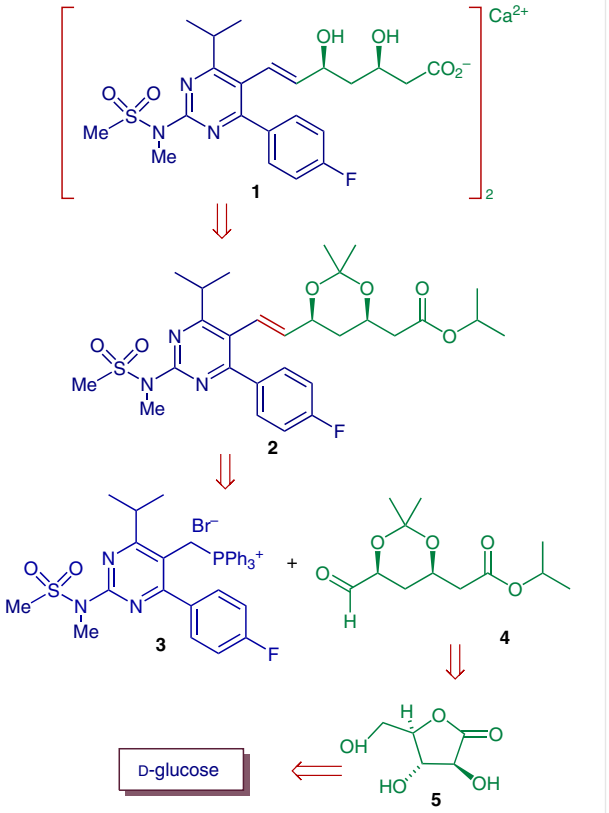


Figure 1 Structure of rosuvastatin calcium

with a 4-fluorophenyl ring, a methane sulfonamide group and an isopropyl group.

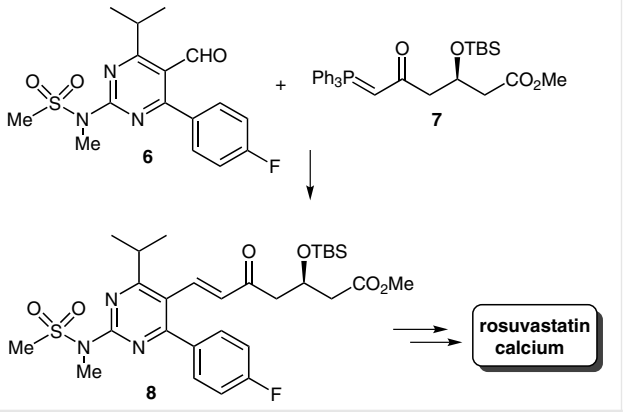
The retrosynthetic analysis of rosuvastatin calcium (**1**)[1] is illustrated in Scheme 1. The ester **2** serves as the key intermediate from which rosuvastatin calcium is synthesized. Disconnecting the ester **2** at the double bond provides two obvious fragments, a pyrimidine moiety and a hexanoic ester moiety. The phosphonium salt **3**, based on the substituted pyrimidine fragment, can be coupled with the aldehyde **4** under Wittig olefination conditions to provide the desired ester **2**. The aldehyde **4** can be obtained from D-glucose.

Rosuvastatin has evoked much interest as a synthetic target by many research groups.[2] Watanabe and co-workers[3] were the first to report a synthesis of rosuvastatin calcium (Scheme 2). Their synthesis involved coupling the substituted pyrimidine[3] **6** with the resonance-stabilized phosphonium ylide[4] **7** under Wittig olefination conditions. The coupling resulted in the formation of key rosuvastatin precursor **8**. The precursor was converted into rosuvastatin calcium in four synthetic operations, including a step that involved diastereoselective reduction[5] of a carbonyl group using diethylmethoxyborane and sodium borohydride at –78 °C. The ylide **7** was synthesized from diethyl 3-hydroxy-



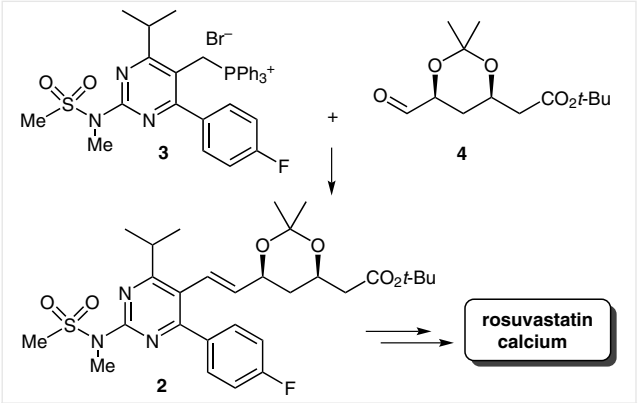
Scheme 1 Retrosynthetic analysis of rosuvastatin calcium

glutarate in nine steps. The synthesis required stereoselective desymmetrization of a prochiral anhydride intermediate with the lithium salt of benzyl (*R*)-mandelate at –78 °C.



Scheme 2 The first reported synthesis of rosuvastatin calcium[3]

An alternative synthetic strategy[6] (Scheme 3) involved Wittig olefination between the phosphonium ylide **3**[6b] and the fully functionalized aliphatic hexanoic ester **4**. The reaction resulted in the formation of the rosuvastatin precursor **2**, which was subsequently converted into rosuvastatin calcium following well-established synthetic operations.[7] The hexanoic ester **4** was prepared[8] from L-malic acid in nine steps, including a step that involved diastereoselective reduction using triethylborane and sodium borohydride.



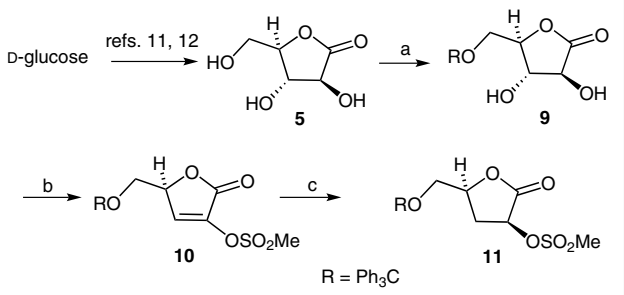
Scheme 3 An alternative synthetic strategy for the synthesis of rosuvastatin calcium[6]

The notable difference between both synthetic strategies lies in the way the 1,3-dihydroxyheptanoic acid side chain is installed in the molecule. The second strategy offers an additional advantage because the aldehyde **4** has the potential to be used for generating the side chain of other statins. For this reason, we embarked upon an investigation of the second synthetic strategy to synthesize rosuvastatin calcium.

From the point of view of industrial operations, the second synthetic strategy demands the development of a practical synthesis of the aldehyde **4**. Many synthetic strategies for the synthesis of this aldehyde[8,9] have been reported. We have developed an alternative, practical route for the manufacture of this aldehyde. The notable features of this route are that it uses a cheap starting material, avoids the Narasaka reduction[5] and the use of reagents such as *n*-butyllithium and sodium bis(trimethylsilyl)amide. D-Glucose, which is cheap and readily available in 100% optical purity, was used as the starting material in our route. It was carried through reliable synthetic operations using readily available reagents to furnish the required aldehyde **4**.

Our synthesis[10] commenced with the preparation of a tritylated lactone (Scheme 4). D-Arabino lactone **5**, which was prepared[11,12] on a commercial scale in excellent yield from D-glucose, was treated with trityl chloride and pyridine to furnish the tritylated lactone **9** in 96% yield.

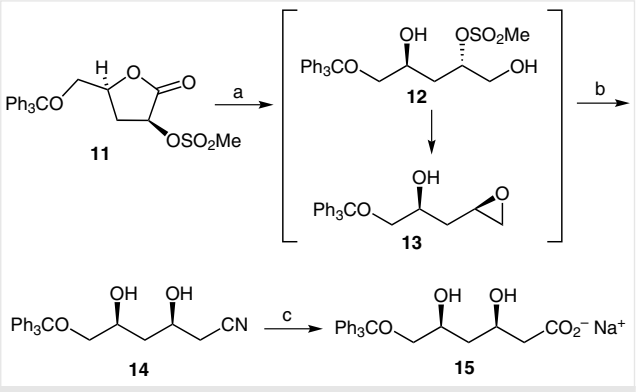
The lactone **9** was treated with methanesulfonyl chloride and pyridine triggering β-elimination[13] of the hydroxy group and generated a double bond in the molecule. The α,β-unsaturated lactone **10** thus formed was subsequently reduced by catalytic hydrogenation in ethyl acetate at 110 psi using 5% palladium over charcoal (10% w/w, Pd/C) as the catalyst. The saturated lactone **11** was obtained in 90% yield. The reduction, as predicted, was highly diastereose-



Scheme 4 *Reagents and conditions:* (a) trityl chloride, pyridine, –10 °C to r.t., 22 h, 96%; (b) MsCl, pyridine, N_2, –14 °C to –8 °C, 8 h, 60%; (c) 5% Pd/C, EtOAc, H_2, 110 psi, 15 °C, 24 h, 90%.

lective; the undesired diastereoisomer could not be detected. The steric hindrance stemming from the bulk of the trityl protecting group dictated effectively the facial selectivity of the hydrogenation, forcing hydrogen to approach preferentially the surface of the double bond from the less hindered side. The relative stereochemistry of the chiral center bearing the methanesulfonyl group was determined unequivocally by NOESY NMR spectroscopy.

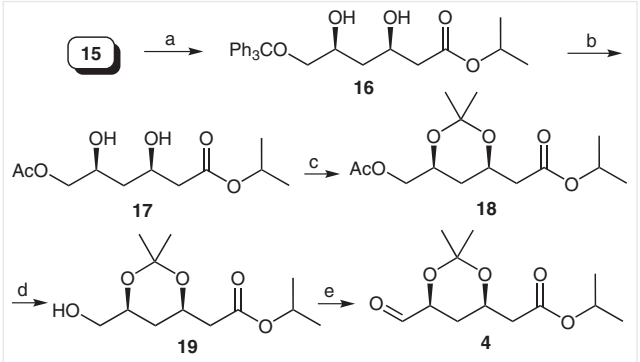
The lactone **11** was reduced using one equivalent of sodium borohydride in a mixture of methanol and dichloromethane (2:3 v/v) (Scheme 5). Under the mildly basic conditions of reduction, the primary hydroxy group acted as a nucleophile and displaced the neighboring mesyl group in an S_N2 fashion, providing the epoxide **13**. The epoxide was not isolated but was treated in situ with sodium cyanide. The reaction opened up the epoxide ring[14] to provide an elongated carbon skeleton, attaching a nitrile functional group at the site of opening. The ring-opening seemed to occur exclusively from the primary carbon side of the epoxide, as evidenced from the fact that the other regioisomer could not be detected.



Scheme 5 *Reagents and conditions:* (a) $NaBH_4$, CH_2Cl_2/MeOH, r.t., 20 h; (b) NaCN, H_2O, 0 °C to r.t., 48 h; (c) NaOH, H_2O, MeOH, 70 °C, 15 h; 68% overall yield in 4 steps.

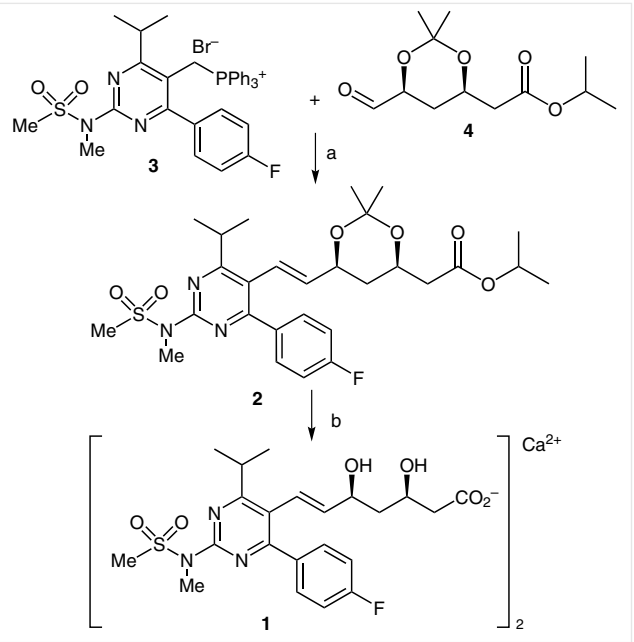
The cyano compound **14** precipitated out from the reaction mixture on cooling. It was filtered off and carried over to the following step as a wet mass. The wet mass was refluxed in methanol with an aq solution of sodium hydroxide at 70 °C for 15 hours to give the acid **15** as its sodium salt. The salt **15** precipitated out from the reaction mixture during concentration. The precipitate was filtered off, dried and carried over to the following step without further purification. The overall yield of the salt **15** over four steps was 68%.

In the next step, the sodium salt **15** was treated with 2-bromopropane in dimethylformamide to provide the isopropyl ester **16** in 78% yield. With the ester **16** in hand, our research was then directed toward finding appropriate reagents and conditions to deprotect the trityl group. The removal of the trityl group, which had served so well not only in controlling the facial selectivity of the hydrogenation but also facilitating the isolation of the intermediates, proved challenging. A host of reagents known for removing trityl groups were utilized. Amongst all these reagents, ferric chloride[15] was the best, cleanly removing the trityl group in dichloromethane at –10 °C to provide the desired triol. The triol was not isolated from the reaction mixture, but was instead treated in situ with acetyl chloride and pyridine at –78 °C. The reaction resulted in selective acetylation of the primary hydroxy group to furnish the acetate **17** in 67% yield. The acetate **17** was then treated with 2,2-dimethoxypropane, acetone and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[16] to protect both the hydroxy groups. The isopropylidene derivative **18** thus obtained was subjected to Zemplén saponification[17] with methanol and a catalytic amount of sodium methoxide to furnish alcohol **19**. The alcohol **19** was oxidized using sodium hypochlorite, potassium bromide and a catalytic amount of TEMPO[18] in a biphasic reaction medium of water and dichloromethane. The oxidation provided the aldehyde **4** in 81% yield (Scheme 6).



Scheme 6 *Reagents and conditions:* (a) 2-bromopropane, DMF, 65 °C, 78%; (b) (i) $FeCl_3·6H_2O$, CH_2Cl_2, –10 °C, 3 h, $MgSO_4$; (ii) AcCl, pyridine, –78 °C, N_2, 4 h, 67% (2 steps); (c) acetone, 2,2-dimethoxypropane, PPTS, 15 h, 80%; (d) NaOMe, MeOH, –10 °C, 2 h, 98%; (e) TEMPO, NaOCl, KBr, H_2O, CH_2Cl_2, –5 °C, 81%.

The aldehyde **4** was then coupled with the triphenylphosphonium salt of the pyrimidine moiety **3** under Wittig olefination conditions (Scheme 7) in dimethyl sulfoxide at 70 °C under the influence of potassium carbonate. The coupling provided the ester **2** in 62% yield. The ester was converted into rosuvastatin calcium following a well-established procedure.[7] The diastereomeric excess of rosuvastatin calcium was found to be >99% de. The melting point of rosuvastatin calcium salt was found to be 147–154 °C (Lit.[7f] 145–150 °C).



Scheme 7 *Reagents and conditions:* (a) K_2CO_3, DMSO, N_2, 70 °C, 4 h, 62%; (b) (i) HCl, MeCN, r.t., 5 h, *tert*-butylamine, –5 °C to r.t., 1 h, 70%; (ii) NaOH, 40 °C, 1 h, $Ca(OAc)_2$, H_2O, r.t., 1 h, 85%.

In conclusion, we have reported the synthesis of rosuvastatin calcium (**1**) in 3.5% overall yield and a total of 14 steps. A novel asymmetric synthesis of (3*R*,5*S*)-dihydroxyhexanoic ester **4** starting from D-glucose, and subsequent coupling with the phosphonium ylide **3**[6b] under Wittig olefination conditions gave appropriately functionalized precursor **2**. This precursor was converted into rosuvastatin calcium following the literature procedure.[7] The synthesis has the potential to be scaled up and adopted for the industrial production of rosuvastatin.

All reactions were carried out in oven- or flame-dried glassware under a moisture-free atmosphere. Pyridine was distilled prior to use. All other reagents were used as supplied. CH_2Cl_2, EtOAc, MeOH, acetone, hexane, DMF, toluene, DMSO and *i*-PrOH were obtained from commercial sources and used as supplied without distillation. LR grade MeCN was used. Unless otherwise noted, reactions were mechanically stirred and monitored by thin-layer chromatography (TLC) using Merck aluminum coated silica gel 60 F_{254} plates. Yields refer to crude compounds unless otherwise noted. Specific optical rotations were recorded on a Rodolph Autopol V Polarimeter. Melting points were obtained using an SRS Optimelt MPA 100 melting point apparatus. Infrared spectra were recorded on an FT IR Bruker Alpha T spectrometer using OPUS software. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded using Bruker and Varian spectrometers and $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0) or DMSO-d_6 [^{1}H, δ 2.50 (quin, J_{H-D} = 1.9 Hz); ^{13}C, δ 39.5]. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, sept = septet, m = multiplet, br = broad), coupling constant, integration. Mass spectra were obtained using an Agilent 6400 Series Triple Quad LC/MS system version B.06.00. HRMS (ESI)$^+$ spectra were obtained with an Agilent 6250 Q-TOF instrument. The diastereomeric ratio of the final product was determined by HPLC.

5-*O*-(Triphenylmethyl)-3-deoxy-2-*O*-(methanesulfonyl)-D-*glycero*-pent-2-enono-1,4-lactone (10)

Methanesulfonyl chloride (4.6 kg, 40.15 mol) was added dropwise to a cold solution of the tritylated lactone **9** (6.85 kg, 17.56 mol) in pyridine (9.71 kg, 122.76 mol) over a period of 8 h under nitrogen. During the addition, the temperature of the mixture was maintained between –14 °C and –8 °C. After completion of the addition, the mixture was stirred at this temperature for 5 h. The mixture was poured onto crushed ice (15 kg) and stirred for 0.5 h. The precipitated solid was filtered off and washed thoroughly with H_2O. To purify further, the solid was slurried with *i*-PrOH and filtered. This process was repeated one more time. The solid thus obtained was air dried to furnish the crude α,β-unsaturated lactone **10** (6 kg). The crude material (6 kg) was dissolved in EtOAc (60 L) and the solution was heated to reflux. Activated charcoal (2.4 kg) was then added to the solution at this temperature. After 1 h at reflux, the hot solution was filtered through a pad of Celite and the pad washed with hot EtOAc (3 L). The washings were combined with the filtrate, concentrated to a volume of approximately 40 L and cooled to r.t. The precipitated solid was filtered and dried to give the desired α,β-unsaturated lactone **10** (4.74 kg, 60%) as a white solid.

$[\alpha]_D^{25}$ –42.3 (*c* 0.5, $CHCl_3$); mp 182.5–184.7 °C; R_f = 0.33 (hexane/EtOAc, 7:3).

IR (KBr): 3134, 2930, 1783, 1594, 1400, 1334, 1257, 1212, 1181, 1114, 1073, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 6 H), 7.39–7.30 (m, 6 H), 7.30–7.25 (m, 3 H), 7.10 (d, *J* = 2.0 Hz, 1 H), 5.12–5.04 (m, 1 H), 3.54 (dd, *J* = 4.4, 10.4 Hz, 1 H), 3.43 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 165.9, 143.0, 137.7, 135.2, 128.5, 128.0, 127.4, 87.2, 78.0, 63.0, 39.5.

MS: *m*/*z* = 449 [M – H]$^-$.

HRMS: *m*/*z* (M – H)$^-$ calcd for $C_{25}H_{21}O_6S$: 449.1054; found: 449.3904.

5-*O*-(Triphenylmethyl)-3-deoxy-2-*O*-(methanesulfonyl)-D-*threo*-pentono-1,4-lactone (11)

The α,β-unsaturated lactone **10** (120 g, 266.4 mmol) was dissolved in EtOAc (1200 mL) at 70 °C. After complete dissolution, the mixture was allowed to cool to 35 °C and charged into an autoclave. 5% Pd/C (12 g) was added to the solution under nitrogen. The mixture was cooled to 15 °C and stirred at this temperature under a hydrogen pressure of 110 psi until the reaction was complete as indicated by TLC. The mixture was filtered through a pad of Celite. The Celite pad was washed

with EtOAc (100 mL). The washings were combined with the filtrate and concentrated under reduced pressure at 40 °C. The saturated lactone **11** (109 g, 90%) was obtained as a white solid.

$[\alpha]_D^{25}$ –7.9 (*c* 0.5, $CHCl_3$); mp 129.5–130.8 °C; R_f = 0.25 (hexane/EtOAc, 7:3).

IR (KBr): 3135, 2933, 1782, 1594, 1489, 1400, 1257, 1215, 1172 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 6 H), 7.37–7.28 (m, 6 H), 7.28–7.22 (m, 3 H), 5.40–5.35 (dd, *J* = 9.2, 10.0 Hz, 1 H), 4.60–4.50 (m, 1 H), 3.44 (dd, *J* = 3.6, 10.8 Hz, 1 H), 3.28 (s, 3 H), 3.26 (dd, *J* = 5.2, 10.8 Hz, 1 H), 2.80–2.60 (m, 1 H), 2.50–2.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 170.9, 143.0, 128.5, 128.0, 127.0, 86.9, 76.0, 73.8, 64.0, 39.6, 31.0.

MS: *m*/*z* = 451 $[M - H]^-$.

HRMS: *m*/*z* $(M - H)^-$ calcd for $C_{25}H_{23}O_6S$: 451.1212; found: 451.3105.

(3*S*,5*S*)-3,5-Dihydroxy-6-(trityloxy)hexanenitrile (14)

$NaBH_4$ (25.5 g, 674.0 mmol) was added to a solution of the saturated lactone **11** (305 g, 674.0 mmol) in a mixture of CH_2Cl_2 (915 mL) and MeOH (610 mL) at –10 °C over a period of 0.5 h. After completion of the addition, the mixture was stirred for 1 h at –5 °C, allowed to warm to r.t. and stirred at this temperature for 20 h. The mixture was filtered and the residue washed with MeOH (200 mL). The washing was combined with the filtrate and the combined organic layer concentrated under reduced pressure at 35 °C to recover CH_2Cl_2. To the concentrated mixture thus obtained, MeOH (915 mL) was added and the mixture was cooled to 0 °C. An aq solution of NaCN (82.66 g, 1.68 mol dissolved in 610 mL of H_2O) was added and the mixture was allowed to warm to r.t. and stirred for 48 h at this temperature. The mixture was cooled to 0 °C, H_2O (610 mL) was added and the mixture was stirred for 0.5 h. The precipitated material was filtered off and washed with cold H_2O (100 mL) to furnish the cyano compound **14** (260 g) as a white gummy solid. The material was carried over to the next step without drying or further purification.

$[\alpha]_D^{25}$ +15.9 (*c* 0.5, $CHCl_3$); R_f = 0.16 (hexane/EtOAc, 6:4).

IR (KBr): 3136, 2932, 1593, 1487, 1400, 1321, 1219, 1111, 1070 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.60–7.40 (m, 6 H), 7.40–7.20 (m, 9 H), 5.30 (d, *J* = 3.9 Hz, 1 H), 5.00 (d, *J* = 4.5 Hz, 1 H), 4.00–3.80 (m, 2 H), 3.20–3.00 (m, 1 H), 3.00–2.80 (m, 1 H), 2.70–2.50 (m, 2 H), 1.90–1.70 (m, 1 H), 1.70–1.60 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 143.9, 128.0, 127.8, 126.9, 119.0, 85.7, 67.6, 66.7, 64.0, 40.4, 25.1.

MS: *m*/*z* = 388 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{25}NO_3Na$: 410.1724; found: 410.1746.

Isopropyl (3*R*,5*S*)-3,5-Dihydroxy-6-(trityloxy)hexanoate (16)

An aq solution of NaOH (53.74 g, 1.34 mol, in 1.3 L of H_2O) was added to a stirred solution of the cyano compound **14** (260 g, 671.0 mmol) in MeOH (1.3 L) at r.t. The mixture was heated to 70 °C and maintained at this temperature for 15 h when the reaction was complete as indicated by TLC. The mixture was allowed to cool to r.t., concentrated under reduced pressure at 40 °C and cooled to 0 °C when a gummy solid precipitated out of the reaction mixture. The aq layer was decanted off and H_2O (930 mL) and EtOAc (930 mL) were added to the gummy residue in succession at r.t. The mixture was stirred for 0.5 h at this temperature during which time the layers separated. The organic layer was separated and the aq layer extracted with EtOAc (3 × 400 mL). The aq layer was concentrated under reduced pressure at 70 °C to furnish a gummy solid. Toluene (300 mL) was added to the gummy compound and the mixture was concentrated under vacuum at 70 °C. This process was repeated to furnish the sodium salt of the tritylated acid **15** (196 g, 68% in 4 steps) as a white solid.

The salt **15** (196 g, 457.4 mmol) was suspended in DMF (588 mL) and 2-bromopropane (128 mL, 1.37 mol) was added to the stirred suspension at r.t. The mixture was heated to 65 °C and maintained at this temperature for 15 h after which time another batch of 2-bromopropane (85.66 mL, 914.8 mmol) was added. After 7 h at this temperature, a third batch of 2-bromopropane (85.66 mL, 914.8 mmol) was added and the mixture was maintained at this temperature until the reaction was complete (approximately 15 h) as indicated by TLC. The reaction mixture was concentrated, first at atmospheric pressure at 60 °C to recover unreacted 2-bromopropane, and then under reduced pressure at 60 °C to remove DMF. The resulting oil was dissolved in EtOAc (588 mL), and the organic layer was washed with H_2O (500 mL), 10% aq $NaHCO_3$ solution (2 × 200 mL), H_2O (2 × 250 mL) and brine (500 mL), then dried over Na_2SO_4 and concentrated under reduced pressure at 40 °C. The isopropyl ester **16** (160 g, 78%) was obtained as a colorless syrup.

$[\alpha]_D^{25}$ –1.2 (*c* 0.5, $CHCl_3$); R_f = 0.55 (hexane/EtOAc, 7:3).

IR (KBr): 3137, 1723, 1594, 1400, 1327, 1109, 1071, 991 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 15 H), 5.10 (sept, *J* = 6.3 Hz, 1 H), 4.30–4.20 (m, 1 H), 4.10–4.00 (m, 1 H), 3.90–3.70 (m, 1 H), 3.40–3.20 (m, 1 H), 3.20–3.10 (m, 2 H), 2.60–2.40 (m, 2 H), 1.80–1.50 (m, 2 H), 1.25 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 171.0, 143.0, 128.0, 127.9, 127.8, 127.2, 127.1, 86.0, 71.0, 68.3, 68.2, 67.0, 41.0, 39.0, 21.0.

MS: *m*/*z* = 449 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{32}O_5Na$: 471.2142; found: 471.2153.

Isopropyl (3*R*,5*S*)-6-Acetoxy-3,5-dihydroxyhexanoate (17)

Ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) (250 g, 928.0 mmol) was added to a solution of the isopropyl ester **16** (320 g, 713.4 mmol) in CH_2Cl_2 (3.84 L) at –10 °C under nitrogen. The mixture was stirred at this temperature for 3 h when the reaction was complete as indicated by TLC. $MgSO_4$ (640 g) was added and the mixture was stirred for 10 min at this temperature. Pyridine (172.6 mL, 2.14 mol) was then added and the mixture was stirred at this temperature for a further 10 min. The mixture was cooled to –78 °C and CH_3COCl (76.9 mL, 1.07 mol) was added at this temperature under nitrogen over a period of 1 h. The mixture was stirred under these conditions until the reaction was complete (approximately 4 h), as indicated by TLC. The mixture was allowed to warm to 10 °C after which H_2O (4 L) was added. The mixture was allowed to warm to r.t. and stirred for 20 min at this temperature. The separated organic layer was washed with 5% dilute HCl (750 mL), sat. $NaHCO_3$ solution (2 × 1 L), H_2O (1 L) and brine (2 L), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure at 40 °C to furnish a thick oil. MeOH (320 mL) was added to the oil. The mixture was cooled to –20 °C and stirred for 0.5 h at this temperature. The precipitated solid was filtered off and washed with MeOH (320 mL). The filtrate was concentrated under reduced pressure at 40 °C to furnish the acetate **17** (118 g, 67%) as a light yellow oil.

$[\alpha]_D^{25}$ –14 (*c* 0.5, $CHCl_3$); R_f = 0.33 ($CHCl_3$/MeOH, 9:1).

IR (KBr): 3137, 2984, 1728, 1594, 1399, 1259, 1108, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (sept, *J* = 6.4 Hz, 1 H), 4.30–4.20 (m, 1 H), 4.15–4.09 (m, 1 H), 4.10–4.05 (m, 1 H), 4.01 (dd, *J* = 6.2, 11.0 Hz, 1 H), 3.50–3.20 (br, 2 H), 2.46 (d, *J* = 6.0 Hz, 2 H), 2.00 (s, 3 H), 1.70–1.55 (m, 2 H), 1.23 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 172.0, 171.0, 69.7, 68.4, 68.3, 68.1, 41.7, 38.5, 21.77, 21.76, 20.89.

MS: *m*/*z* = 249 $[M + H]^+$, 271 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{20}O_6Na$: 271.1152; found: 271.1164.

Isopropyl 2-[(4*R*,6*S*)-6-(Acetoxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (18)

2,2-Dimethoxypropane (232 mL) was added to a solution of the acetate **17** (116 g, 467 mmol) in acetone (232 mL) at r.t. Next, PPTS (23.48 g, 93 mmol) was added to the mixture under nitrogen, and the mixture was stirred for 15 h at this temperature. After completion of reaction as indicated by TLC, the mixture was concentrated under reduced pressure at 38 °C, diluted with hexane (600 mL) and stirred for 0.5 h at r.t. The precipitated solid was filtered off and washed with hexane. The filtrate was washed with H_2O (2 × 500 mL) and brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure at 35 °C to give the acetonide **18** (108 g, 80%) as a light yellow oil.

$[\alpha]_D^{25}$= +16.4 (*c* 0.5 $CHCl_3$); R_f = 0.46 (hexane/EtOAc, 6:4).

IR (KBr): 3134, 2992, 2360, 1737, 1594, 1399, 1239, 1204, 1172 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (sept, *J* = 6.2 Hz, 1 H), 4.40–4.28 (m, 1 H), 4.20–4.08 (m, 1 H), 4.10–4.04 (m, 1 H), 4.02 (dd, *J* = 6.0, 11.2 Hz, 1 H), 2.50 (dd, *J* = 7.2, 15.2 Hz, 1 H), 2.35 (dd, *J* = 5.6, 15.2 Hz, 1 H), 2.08 (s, 3 H), 1.62–1.55 (m, 1 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.40–1.25 (m, 1 H), 1.23 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 170.9, 170.2, 99.0, 67.9, 67.1, 67.0, 65.6, 41.6, 32.5, 29.8, 21.7, 20.9, 19.5.

MS: *m*/*z* = 289 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{25}O_6$: 289.1646; found: 289.1656.

Isopropyl 2-[(4*R*,6*S*)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (19)

NaOMe (3.18 g, 58.9 mmol) was added to a solution of the acetonide **18** (85 g, 294.8 mmol) in MeOH (425 mL) at –10 °C under nitrogen, and the mixture was stirred for 2 h at this temperature. After completion of reaction as indicated by TLC, the mixture was neutralized with aq 10% citric acid solution (17 mL) and concentrated under reduced pressure at 35 °C to furnish a gummy residue. The residue was dissolved in EtOAc (400 mL). The organic layer was washed with H_2O (2 × 250 mL) and brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure at 40 °C. The alcohol **19** (71.0 g, 98%) was obtained as a light yellow oil.

$[\alpha]_D^{25}$ +16.2 (*c* 0.5, $CHCl_3$); R_f = 0.27 (hexane/EtOAc, 7:3).

IR (KBr): 3134, 2989, 2940, 1730, 1594, 1399, 1204, 1171, 1109 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (sept, *J* = 6.3 Hz, 1 H), 4.40–4.20 (m, 1 H), 4.10–3.90 (m, 1 H), 3.66–3.55 (m, 1 H), 3.55–3.45 (m, 1 H), 2.5.0 (dd, *J* = 7.0, 15.3 Hz, 1 H), 2.40 (dd, *J* = 6.0, 15.3 Hz, 1 H), 2.00 (t, *J* = 6.0 Hz, 1 H), 1.55–1.47 (m, 1 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.40–1.30 (m, 1 H), 1.24 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDC1_3$): δ = 170.0, 99.0, 69.0, 67.0, 65.8, 65.6, 41.0, 31.0, 30.0, 21.8, 19.7.

MS: *m*/*z* = 247 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{23}O_5$: 247.1539; found: 247.1553.

Isopropyl 2-[(4*R*,6*S*)-6-Formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (4)

A solution of the alcohol **19** (80 g, 324.8 mmol) in CH_2Cl_2 (400 mL) was added to a mixture of KBr (3.86 g, 32.48 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical) (507 mg, 3.248 mmol) in CH_2Cl_2 (400 mL) at –5 °C. An aq solution of 15% NaOCl (177 mL, 357.2 mmol; pH adjusted to 9.0–9.5 with a sat. solution of $NaHCO_3$) was added dropwise to the mixture over a period of 1 h at this temperature. On completion of the reaction as indicated by TLC, a 10% aq solution of $Na_2S_2O_3$ (300 mL) was added at this temperature. The aq phase was extracted with CH_2Cl_2 (150 mL) and the extract combined with the organic layer. The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4 and concentrated under vacuum at 40 °C to give the aldehyde **4** (64 g, 81%) as a light yellow oil. The crude material was carried over to the next step.

R_f = 0.30 (hexane/EtOAc, 7:3).

Isopropyl 2-[(4*R*,6*S*)-6-{(*E*)-2-[4-(4-Fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl]vinyl}-2,2-dimethyl-1,3-dioxan-4-yl]acetate (2)

A solution of the aldehyde **4** (64 g, 262.0 mmol) in DMSO (184 mL) was added to a solution of the triphenylphosphonium salt of the pyridinium moiety **3** (142.2 g, 209.6 mmol) in DMSO (200 mL) at r.t. under nitrogen. The mixture was heated to 70 °C and K_2CO_3 (27.15 g, 196.45 mmol) was added to the mixture. After 0.5 h at this temperature, another batch of K_2CO_3 (27.15 g, 196.45 mmol) was added under nitrogen and the mixture was maintained at this temperature for 3 h when the reaction was complete as indicated by TLC. The mixture was allowed to cool to r.t. and toluene (500 mL) was added. After 0.5 h at this temperature, H_2O (1 L) was added and the mixture was stirred for a further 0.5 h when the layers separated. The aq layer was extracted with toluene (200 mL) and the extract was combined with the organic layer. The combined organic layer was washed with H_2O (2 × 500 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated under vacuum at 50 °C to furnish crude ester **2**. *i*-PrOH (320 mL) was added to the crude residue and the mixture was stirred at r.t. for 1 h. The mixture was cooled to 0 °C to –5 °C and stirred for a further 1 h at this temperature to initiate precipitation of the solid. The precipitated solid was filtered, washed with *i*-PrOH (50 mL) and dried to furnish the ester **2** (92 g, 62%) as an off white solid.

$[\alpha]_D^{25}$ +10.2 (*c* 0.5, $CHCl_3$); mp 132.5–133.8 °C; R_f = 0.4 (hexane/EtOAc, 8:2).

IR (KBr): 3134, 2987, 1723, 1596, 1551, 1512, 1398, 1335, 1154, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 5.4 Hz, 1 H), 7.64 (d, *J* = 5.4 Hz, 1 H), 7.10 (d, *J* = 5.4 Hz, 1 H), 7.08 (d, *J* = 5.4 Hz, 1 H), 6.50 (d, *J* = 16.4 Hz, 1 H), 5.47 (dd, *J* = 5.6, 16.4 Hz, 1 H), 5.10 (sept, *J* = 6.4 Hz, 1 H), 4.50–4.40 (m, 1 H), 4.40–4.20 (m, 1 H), 3.57 (s, 3 H), 3.52 (s, 3 H), 3.38 (sept, *J* = 6.6 Hz, 1 H), 2.50 (dd, *J* = 6.8, 15.2 Hz, 1 H), 2.36 (dd, *J* = 5.6, 15.2 Hz, 1 H), 1.60–1.50 (m, 1 H), 1.49 (s, 3 H), 1.41 (s, 3 H), 1.25 (d, *J* = 6.6 Hz, 6 H), 1.23 (d, *J* = 6.4 Hz, 6 H), 1.20–1.10 (m, 1 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 174.0, 170.0, 163.4, 162.0 (d, J_{C-F} = 248 Hz), 157.0, 137.0, 134.0 (d, J_{C-F} = 3 Hz), 132.2 (d, J_{C-F} = 8.4 Hz), 123.0, 121.0, 115.0 (d, J_{C-F} = 22 Hz), 114.0, 99.0, 69.0, 67.9, 65.0, 42.0, 41.0, 35.9, 33.0, 31.9, 29.9, 21.80, 21.79, 21.7, 19.7.

MS: *m*/*z* = 564 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{39}FN_3O_6S$: 564.2538; found: 564.2559.

Rosuvastatin Calcium (1)

Dilute HCl (25 mL, 0.02 M) was added to a stirred solution of the ester **2** (13 g, 460 mmol) in MeCN (90 mL) at r.t. under nitrogen. The mixture was heated to 30 °C and maintained at this temperature for 5 h when the reaction was complete as indicated by TLC. The mixture was cooled to 25 °C and an aq solution of NaOH (25 mL, 1 M) was added. After 0.5 h at this temperature, NaCl (15 g) was added, the mixture was cooled to –5 °C and dilute HCl (1 M) was added until the pH attained 3.5. Another batch of NaCl (15 g) was added to the reaction mixture at which point the layers separated. The organic layer was diluted with MeCN (300 mL) and filtered through a pad of Celite. The Celite pad was washed with MeCN (16 mL). The washings were combined with the filtrate, cooled to –5 °C, and *tert*-butylamine (2.7 mL) was added at this temperature. The mixture was warmed to r.t., stirred for 1 h and again cooled to 0 °C. The mixture was maintained at this temperature for 0.5 h. The precipitated solid was filtered off, washed with cold MeCN and dried under vacuum at 27 °C to give the *tert*-butylamine salt of rosuvastatin (9.0 g, 70%).

A solution of NaOH (648 mg, 17.1 mmol) in demineralized H_2O (9 mL) was added to a solution of the *tert*-butylamine salt of rosuvastatin (9 g, 17.1 mmol) in demineralized H_2O (45 mL) at 27 °C and the mixture was heated to 40 °C. After 1 h at this temperature, the mixture was cooled to 30 °C and *tert*-butyl acetate (27 mL) was added. The mixture was stirred for 0.5 h to remove *tert*-butylamine and non-polar organic impurities. The process was repeated twice to ensure complete removal of non-polar impurities. Dilute HCl (1 M) was added to the mixture under nitrogen until the pH attained 9–9.5. The mixture was filtered through a filter paper (40 microns), and a solution of $Ca(OAc)_2$ (1.6 g, 10.2 mmol) in demineralized H_2O (9 mL) was added to the filtrate. The mixture was stirred for 1 h at 27 °C. The precipitated solid was filtered off, washed with deionized H_2O (2 × 18 mL) and dried under high vacuum at 27 °C for 24 h to furnish rosuvastatin calcium (**1**) (6.9 g, 85%) as a white powder.

$[\alpha]_D^{25}$ –2.3 (*c* 0.5, $CHCl_3$); mp 147–154 °C (Lit[7f] 145–150 °C).

IR (KBr): 3148, 1596, 1547, 1398, 1332, 1228, 1153, 1113, 1070, 965, 776 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 7.57 (t, *J* = 5.2, 7.6 Hz, 2 H), 6.96 (t, *J* = 8.4 Hz, 2 H), 6.49 (d, *J* = 15.2 Hz, 1 H), 5.39 (d, *J* = 15.2 Hz, 1 H), 4.30 (br, 1 H), 4.10 (br, 1 H), 3.60–3.40 (br, 1 H), 3.51 (s, 3 H), 3.46 (s, 3 H), 3.24 (m, 1 H), 2.33 (br, 2 H), 1.65–1.45 (br, 1 H), 1.53 (br, 1 H), 1.39 (br, 1 H), 1.15 (d, *J* = 5.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 164.0, 163.0, 161.0, 157.0, 139.0, 134.0, 132.0, 123.0, 120.0, 114.9, 114.7, 76.0, 71.0, 42.0, 33.0, 32.0, 21.0.

MS: *m*/*z* = 482 [acid, M + H]$^+$, 504 [acid, M + Na]$^+$.

HRMS: *m*/*z* [acid, M + H]$^+$ calcd for $C_{22}H_{29}FN_3O_6S$: 482.1753; found: 482.1767.

Diastereomeric excess: >99% [column: ID CHIRALPAK IB-3 (4.6 × 250 mm) 3 µ; mobile phase: *n*-hexane/EtOH/IPA/TFA = 90:5:5:0.3; flow rate = 1 mL/min; *T* = 25 °C].

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Supporting Information

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