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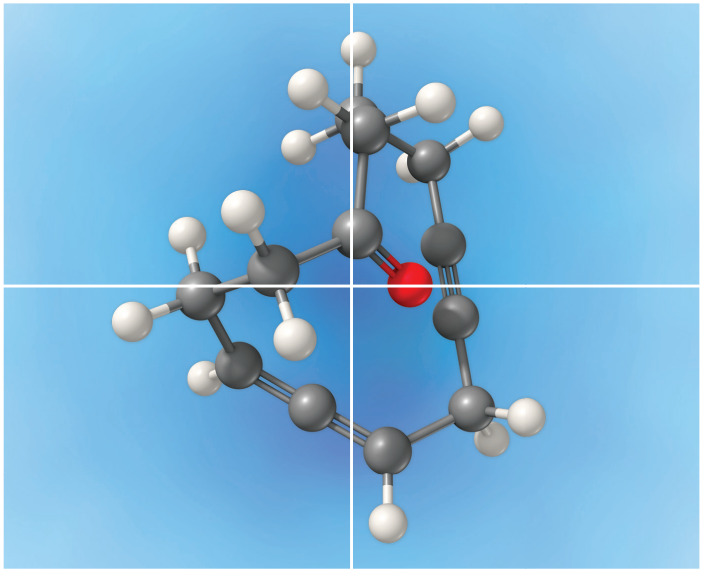

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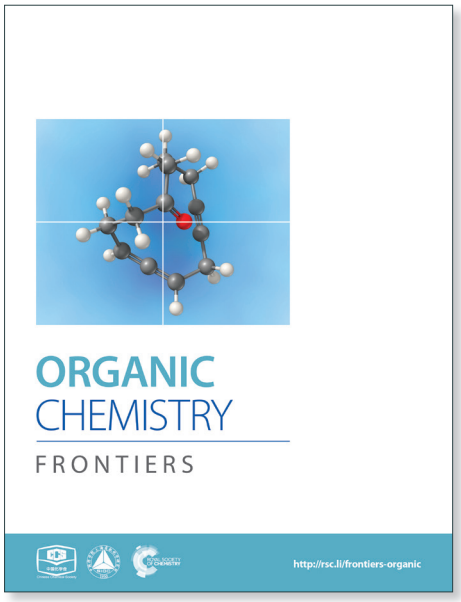

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ARTICLE

Concise synthesis of atorvastatin lactone under high-speed vibration milling conditions

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Verónica Estévez,[a] Mercedes Villacampa[a] and J. Carlos Menéndez[a]*

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The Hantzsch-type sequential three-component reaction under high-speed vibration milling conditions between 4-methyl-3-oxo-*N*-phenylpentanamide, *tert*-butyl 2-[(4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate and 1-(4-fluorophenyl)-2-iodo-2-phenylethanone in the presence of ytterbium triflate and silver nitrate, followed by hydrolytic deprotection/lactonization, afforded atorvastatin lactone in 38% overall yield, thus providing ready access to the top-selling antihyperlipidemic drug atorvastatin calcium.

Introduction

Mechanochemical synthesis is defined by the use of mechanical energy to induce chemical reactions.[1,2] While milling has been long employed in the pharmaceutical, chemical and metallurgical industries, mechanochemistry is still in a very early stage of development. However, it is increasingly considered as one of the most exciting additions to the synthetic repertoire as an environmentally friendly alternative to solution-based reactions because of the possibility of carrying out solvent-free chemical processes. Recently, analytical techniques such as the diffraction of high-energy synchrotron X-rays[3] and single-molecule force spectroscopy[4] have allowed the *in situ* study of model mechanochemical reactions, leading to the conclusion that they proceed with reaction rates comparable to or greater than those in solution. Among the various mechanochemical techniques, high-speed vibration milling (HSVM) is particularly well suited for work at the laboratory scale and is based on the vibratory movement of an arm that is attached to a vessel containing a ball made of inert material that falls over the material up to 30 times per second. In spite of the current interest in the development of solvent-free synthetic methodologies prompted by environmental concerns, this technique has found relatively little application in synthesis, especially in terms of the generation of carbon-heteroatom bonds.[5]

Multiple bond-forming transformations,[6] and in particular, multicomponent reactions,[7] have attracted much attention from the synthetic community in recent years because of the high efficiency due to the formation of several bonds in a single operation and also because the associated reduction in the number of isolation and purification steps is crucial for achieving a reduction of the use of organic solvents and chromatographic stationary phases, one of the main goals of green chemistry.[8] Nevertheless, the coupling of multicomponent reactions with other methodologies aimed at the reduction of reaction waste has received little attention.

In this context, we present here the first example of the application of mechanochemical techniques to a target-oriented synthesis having a multicomponent reaction as the key step. Our chosen target was atorvastatin (Figure 1),[9,10] the best known representative of the statins, which are the main group of cholesterol-lowering drugs in therapeutic use.[11] This compound was introduced in the market in 1997 as its calcium salt under the trade name Lipitor® and is the best-selling drug in history, having been at the top of the list of largest-selling branded pharmaceutical entities for almost a decade. The importance of atorvastatin has led to much interest in its synthesis, which has been the subject of several recent reviews and chapters.[12,13] All these routes are aimed at the preparation

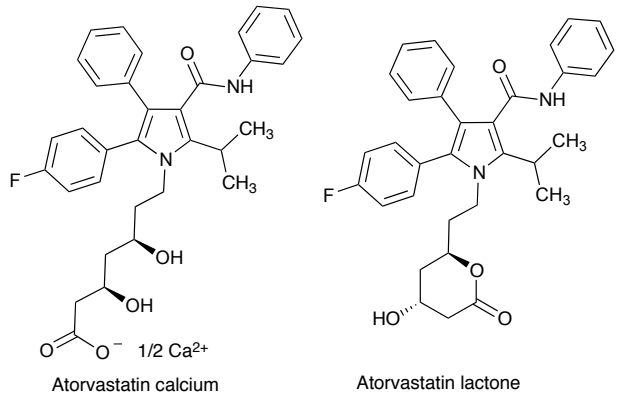

Figure 1. Structures of atorvastatin calcium and the atorvastatin lactone

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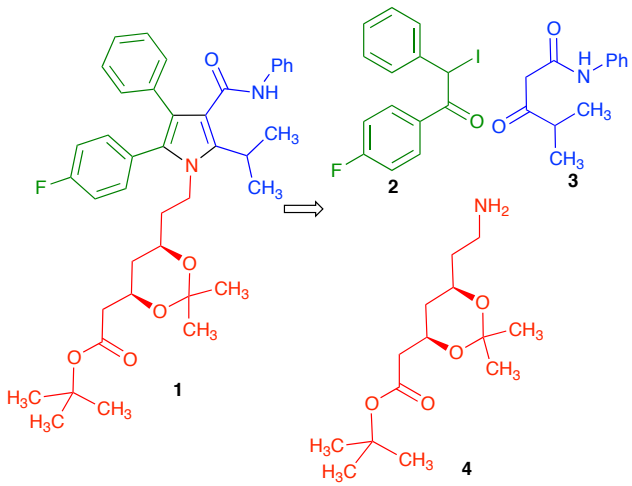
of the so-called atorvastatin lactone, which can be easily transformed into the final drug molecule by hydrolysis and salt formation.

Much effort has been directed towards the synthesis of the chiral side chain, and relatively little attention has been devoted to optimizing the construction of the atorvastatin pyrrole core. In published work, this has normally been achieved through linear sequences having as key steps the classical Paal-Knorr pyrrole synthesis or 1,3-dipolar cycloadditions.[14] We realized that our recent development of a generalized version of the Hantzsch pyrrole synthesis under mechanochemical conditions in the presence of cerium(IV) ammonium nitrate and silver nitrate[15] furnished an opportunity to develop a concise, convergent route to atorvastatin. Thus, the protected atorvastatin derivative **1** should be accessible along the lines summarized in Scheme 1 from α-iodoketone **2**, β-ketoamide **3** and chiral amine **4**. This disconnection is interesting in that, in spite of its name reaction status, the Hantzsch pyrrole synthesis has found little use in the literature because of its lack of generality, especially for the preparation of pentasubstituted pyrroles. The present paper describes the successful conclusion of this project.

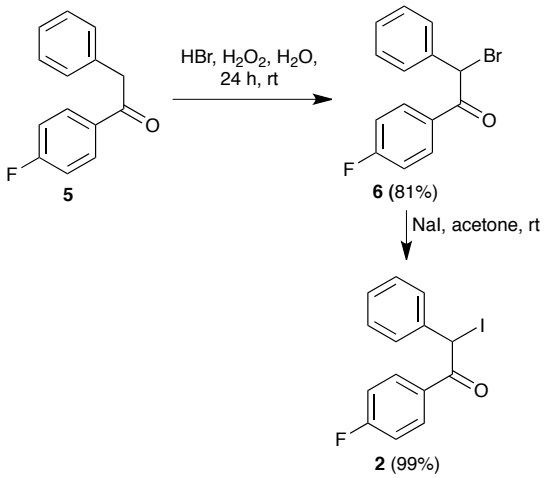


Scheme 1. Our plan for the synthesis of a protected atorvastatin precursor (compound **1**)

Results and discussion

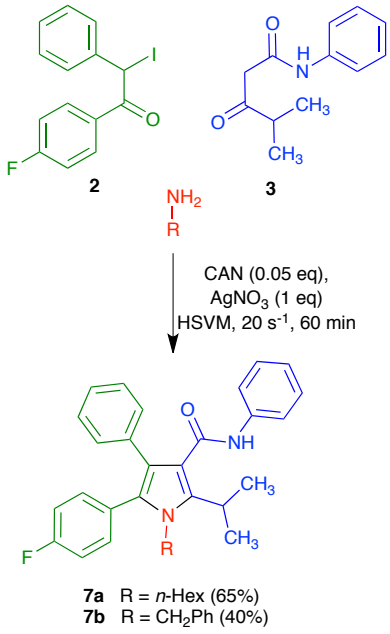
Regarding the synthesis of the required precursors, ketoamide **3** is known in the literature[16] and amine **4** is commercially available. Compound **2** was prepared from the known[17] acetophenone derivative **5** by α-bromination with hydrogen bromide in the presence of hydrogen peroxide,[18] followed by halogen exchange with sodium iodide (Scheme 2).

We recognized that the structural features of atorvastatin took our Hantzsch-like reaction to its limits because it represents an unfavorable case for several of the substituents involved, including an amide function and a branched substituent in the β-dicarbonyl component, two aryl substituents in the α-haloketone and a complex primary amine component. For this reason, before committing the valuable chiral material **4**, we



Scheme 2. Synthesis of the α-iodoketone component (compound **2**)

decided to optimize the conditions for the pyrrole synthesis using hexylamine as a model primary amine. In the event, we found that addition of a mixture of compound **3**, CAN and hexylamine to iodoketone **2** and silver nitrate followed by high-speed vibration at 20 Hz for 1 h afforded the atorvastatin analog **7a** in 65% yield. A similar experiment using benzylamine as a more hindered model primary amine furnished compound **7b** in 40% yield (Scheme 3). Compound **7b** was known in the literature,[19] but it had been obtained as a 1:1 mixture with its 4-(*p*-fluorophenyl)-5-phenyl regioisomer *via* 1,3-dipolar cycloaddition chemistry.



Scheme 3. Model reactions leading to atorvastatin analogues **7**

Unfortunately, when we applied the conditions established for the model compounds to the desired reaction between **2**, **3** and **4**, we obtained only complex mixtures instead of the target pyrrole derivative. We reasoned that this different behaviour of amine **4** with respect to the models could be associated to the

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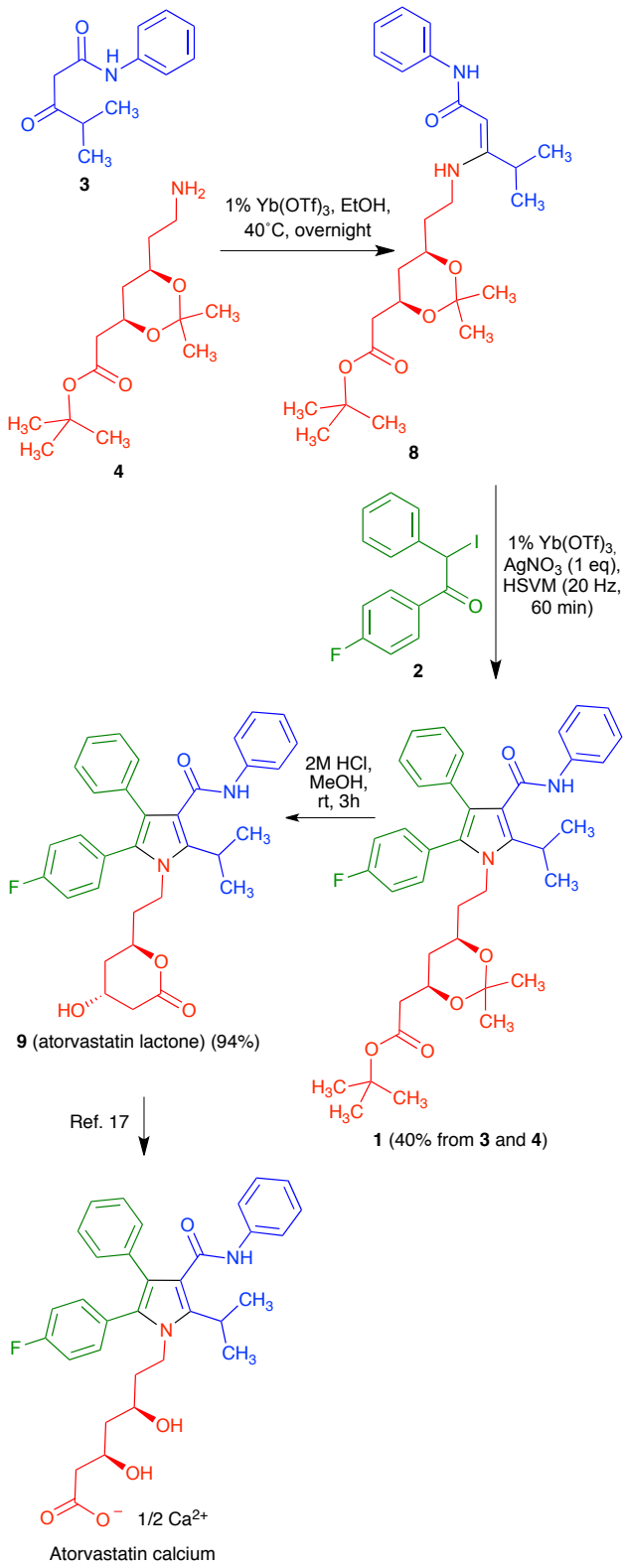
fact that CAN is known to promote the hydrolysis of acetals[20] and might therefore be affecting the acetonide protection. For this reason, a change in the Lewis acid was considered necessary and, after some experimentation, we discovered that



Scheme 4. Synthesis of the atorvastatin lactone

ytterbium triflate was a suitable catalyst for the desired process. As a relatively minor downside, the generation of the intermediate β-enaminone involved in the mechanism of the Hantzsch reaction was slower than in the presence of CAN and required a mild heating of β-ketoamide **3** and amine **4** in the presence of 1% ytterbium triflate. The pure enaminone **8** thus obtained was mixed with compound **2**, 1% ytterbium triflate and an equimolecular amount of silver nitrate, which was necessary to prevent reductive dehalogenation of **2** by the iodide anion liberated during the reaction.[15] This mixture was submitted to high-speed vibration milling at 20 Hz for 1 h, leading to compound **1** in 40% overall yield. A final hydrolytic deprotection followed by acid-promoted spontaneous lactonization afforded atorvastatin lactone in 94% yield (Scheme 4). The transformation of compound **9** into atorvastatin calcium can be regarded as trivial.[18,21]

Experimental

General experimental information. All reagents and solvents were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel and fluorescent indicator. Separations by flash chromatography were performed on silica gel. Mechanochemical reactions were carried out in a Retsch MM200 mixer ball mill at a frequency of 20 Hz using a 25 mL zirconium oxide grinding jar and a single zirconium oxide ball 20 mm in diameter. Melting points were measured with a Kofler-type heating platine microscope from Reichert, 723 Model, and are uncorrected. The optical rotation measurements were determined at 20 °C, on a 1 ml cell measuring 10 cm, using a Perkin Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp (589 nm); the concentration *c* is given in g/100 mL. Infrared spectra were recorded with a Perkin-Elmer FTIR Paragon-1000 spectrophotometer as thin films on NaCl disks; wavenumbers are given in cm^{-1}. NMR spectroscopic data were recorded using spectrometers maintained by the CAI de Resonancia Magnética, UCM, operating at 250 or 500 MHz for ^{1}H NMR, 235 MHz for ^{19}F and 63 or 125 MHz for ^{13}C NMR; chemical shifts are given in (δ) parts per million and coupling constants (*J*) in hertz. High-resolution mass spectra (HRMS) were recorded by the CAI de Espectrometría de Masas, UCM, on a Bruker FTMS APEX QIV mass spectrometer. Elemental analyses were determined by the CAI de Microanálisis, Universidad Complutense, using a Leco CHNS-932 combustion microanalyzer.

2-Bromo-1-(*p*-fluorophenyl)-2-phenylethanone (6). To a round-bottomed flask, protected from light with aluminium foil, a suspension of 1-(*p*-fluorophenyl)-2-phenylethanone (2.13 g, 10 mmol) in water (5 mL), a 48% aqueous solution of HBr (0.56 mL, 5 mmol) and a stirring bar were added. After stirring the reaction mixture at room temperature for 5 minutes, a 33% aqueous solution of H_2O_2 (0.51 mL, 5 mmol) was added. The additions of HBr and H_2O_2 were repeated twice within intervals

Organic Chemistry Frontiers Accepted Manuscript

of 2-3 h while the mixture was stirred. After 24 h, ethyl acetate (10 mL) was added and the organic layer was washed with a 10% solution of $Na_2S_2O_3$ (5 mL) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure and purification of the residue by column chromatography on silica gel, eluting with petroleum ether-ethyl ether (99:1), gave the desired bromide **6** as a yellow oil (2.365 g, 81%). IR (NaCl, neat) 1693, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.07-8.02 (m, 2H), 7.54 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.41-7.38 (m, 3H), 7.18-7.11 (m, 2H), 6.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 189.5 (C), 165.8 (d, *J* = 257.1 Hz, C), 135.6 (C), 131.8 (d, *J* = 9.5 Hz, C), 130.3 (d, *J* = 3.0 Hz, CH), 129.2 (CH), 129.0 (2 CH), 116.0 (d, *J* = 22.0 Hz, CH), 50.8 (CH); ^{19}F NMR ($CDCl_3$, 235 MHz) δ (-103.81) to (-103.93) (m). Anal. Calcd. for $C_{14}H_{10}BrFO$: C, 57.36; H, 3.44. Found: C, 57.31; H, 3.39.

2-Iodo-1-(*p*-fluorophenyl)-2-phenylethanone (2). A solution of sodium iodide (1.50 g, 10 mmol) in anhydrous acetone (10 mL) was added to a solution of compound **6** (2.64 g, 9 mmol) in the same solvent (20 mL). The formation of a white precipitate of sodium bromide was observed instantly. The reaction was stirred at room temperature for 10 min and was then filtered. Removal of the solvent under reduced pressure afforded the expected iodoketone as a reddish viscous liquid (3.03 g, 99%). IR (NaCl, neat) 1681 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.11-8.03 (m, 2H), 7.63 (dd, *J* = 8.2, 1.7 Hz, 2H), 7.41-7.23 (m, 3H), 7.16 (t, *J* = 8.2 Hz, 2H), 6.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ = 190.7 (C), 165.8 (d, *J* = 256.8 Hz, C), 137.1 (C), 131.7 (d, *J* = 9.5 Hz, CH), 129.8 (d, *J* = 3.0 Hz, C), 129.4 (CH), 128.9 (CH), 128.7 (CH), 116.0 (d, *J* = 22.1 Hz, CH), 27.6 (CH); ^{19}F NMR ($CDCl_3$, 235 MHz) δ (-104.12) to (-104.24) (m). Anal. Calcd. for $C_{14}H_{10}FIO$: C, 49.44; H, 2.96. Found: C, 49.38; H, 3.02.

General procedure for the CAN-catalyzed synthesis of pyrroles. To a ball mill vessel was added a-iodoketone **2** (340 mg, 1 mmol), along with a zirconium oxide ball. Then, a mixture of the suitable amine (1.95 mmol), β-ketoamide **3** (308 mg, 1.5 mmol) and cerium ammonium nitrate (CAN, 27 mg, 0.05 eq), previously stirred together at room temperature during 30 min, and silver nitrate (169 mg, 1 mmol) were added. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 Hz for 60 min at room temperature. The reaction vessel was cleansed with ethyl acetate (5 mL) and the suspension thus obtained was filtered to remove silver iodide. The organic layer was washed with water (2 mL) and dried over anhydrous sodium sulphate, and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel eluting with a petroleum ether-ethyl acetate mixture (9:1) afforded the desired pyrroles.

5-(4-Fluorophenyl)-1-hexyl-2-isopropyl-4-phenylpyrrole-3-(*N*-phenyl)carboxamide (7a). Prepared from compound **2** (340 mg, 1 mmol), hexylamine (197 mg, 1.95 mmol) and *N*-phenyl-4-methyl-3-oxopentanamide (307 mg, 1.5 mmol): yellow viscous oil (314 mg, 65%). IR (NaCl, neat) 3323, 1681, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.24-7.17 (m, 9H), 7.10-6.97 (m, 5H), 6.89 (br s, 1H), 3.85-3.78 (m, 2H), 3.60-3.47 (m, 1H) 1.61-1.55 (m, 2H), 1.56 (d, *J* = 7.1 Hz, 6H), 1.36-1.17 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8 (C), 162.2 (d, *J* = 246.1 Hz, C), 141.4 (C), 138.4 (C), 134.7 (C), 133.1 (d, *J* = 8.1 Hz, CH), 130.5 (CH), 128.8 (C), 128.6 (CH), 128.4 (d, *J* = 3.5 Hz, C), 128.3 (CH), 126.5 (CH), 123.4 (CH), 121.6 (C), 119.5 (CH), 115.2 (d, *J* = 21.5 Hz, CH), 115.1 (C), 44.6 (CH_2), 31.5 (CH_2), 31.0 (CH_2), 26.3 (CH_2), 26.2 (CH), 22.3 (CH_2), 21.6 (CH_3), 13.8 (CH_3); ^{19}F NMR ($CDCl_3$, 235 MHz) δ (-114.17) to (-114.31) (m). Anal. Calcd. for $C_{32}H_{35}FN_2O$: C, 79.63; H, 7.31; N, 5.80. Found: C, 79.58; H, 7.26; N, 5.74.

1-Benzyl-5-(4-fluorophenyl)-2-isopropyl-4-phenylpyrrole-3-(*N*-phenyl)carboxamide (7b). Prepared from compound **2** (340 mg, 1 mmol), benzylamine (160 mg, 1.5 mmol) and compound **3** (307 mg, 1.5 mmol): white solid (195 mg, 40%); mp 225-228 ºC (lit.[14] 218-220 ºC). IR (NaCl, neat) 3410, 1668, 1527, 1239, 1157; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34-6.82 (m, 20H), 5.11 (s, 2H), 3.36-3.24 (m, 1H), 1.43 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7 (C), 162.2 (d, *J* = 246.2 Hz, C), 142.0 (C), 138.5 (C), 138.3 (C), 134.5 (C), 132.9 (d, *J* = 8.1 Hz, CH), 130.5 (CH), 129.4 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 127.7 (d, *J* = 3.4 Hz, C), 127.3 (CH), 126.6 (CH), 125.4 (CH), 123.5 (CH), 121.8 (C), 119.6 (CH), 115.8 (C), 115.1 (d, *J* = 21.3 Hz, CH), 48.0 (CH_2), 26.6 (CH), 21.3 (CH_3); ^{19}F NMR ($CDCl_3$, 235 MHz) δ (-114.06) to (-114.18) (m); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{33}H_{29}FN_2ONa$ 511.2122, found 511.2155. Anal. Calcd for $C_{33}H_{29}FN_2O$: C, 81.12; H, 5.98; N, 5.73. Found: C, 81.06; H, 5.92; N, 5.73.

***tert*-Butyl 2-{(4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1)**. To a solution of commercially available *tert*-butyl-[6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]acetate **4** (191 mg, 0.7 mmol) and compound **3** (143 mg, 0.7 mmol) in ethanol (0.5 mL) was added ytterbium triflate (4 mg, 0.007 mmol) and the reaction mixture was stirred at 40 ºC overnight. Afterwards, the ethanol was removed and the oily residue was dissolved in ethyl acetate (5 mL) and washed with water (2 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to yield 296 mg of a yellow oil, identified as the intermediate β-enaminone **8**. After verifying the identity of this material (see characterization data below), it was employed without further purification.

Compound **2** (102 mg, 0.3 mmol) was added to a ball mill vessel, followed by ytterbium triflate (2 mg, 0.003 mmol) and silver nitrate (85 mg, 0.5 mmol). Then, a solution of the intermediate β-enaminone **8** (230 mg, 0.5 mmol) in ethanol (0.5 mL) was also added to the reaction vessel and the solvent was evaporated under a stream of argon. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the

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other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 Hz for 60 min. After extracting the reaction mixture from the ball mill vessel with ethyl acetate (5 mL), the suspension obtained was filtered and the organic layer was washed with water (2 mL) and dried over anhydrous sodium sulphate. Finally, the solvent was evaporated under reduced pressure. Purification was achieved through silica gel column chromatography, using a mixture of petroleum ether-ethyl acetate (8:2) as eluent to yield compound **1** as a yellow solid (79 mg, 40%).

Data for **8**: $[\alpha]_D^{20}$ + 12.8 (*c* 1.2, $CHCl_3$); IR (NaCl, neat) 3331, 1726, 1677, 1596, 1254 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 9.37 (br s, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.72 (br s, 1H), 4.47 (s, 1H), 4.33-4.22 (m, 1H), 4.07-3.96 (m, 1H), 3.74 (q, *J* = 7.0 Hz, 2H), 3.42-3.29 (m, 2H), 2.75-2.69 (m, 1H), 2.38 (qd, *J* = 15.0, 7.0 Hz, 2H), 1.72 (q, *J* = 6.0 Hz, 2H), 1.39 (s, 9H), 1.27 (s, 6H), 1.16 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.3 (C), 170.1 (C), 169.6 (C), 139.3 (C), 128.7 (CH), 122.5 (CH), 119.5 (CH), 98.7 (C), 80.6 (C), 79.8 (CH), 66.1 (CH), 65.7 (CH), 42.6 (CH_2), 37.7 (CH_2), 37.2 (CH_2), 36.4 (CH_2), 28.4 (CH), 28.0 (CH_3), 21.5 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{26}H_{40}N_2O_5Na$ 483.2835; found 483.2125.

Data for **1**: mp 72-74 ºC; $[\alpha]_D^{20}$ + 5.5 (*c* 1.5, $CHCl_3$); IR (NaCl, neat) 3315, 1724, 1667, 1599, 1231, 1158 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.24-6.94 (m, 14H), 6.88 (br s, 1H), 4.24-4.04 (m, 2H), 3.93-3.81 (m, 1H), 3.77-3.69 (m, 1H), 3.60-3.54 (m, 1H), 2.42 (dd, *J* = 15.3, 6.2 Hz, 1H), 2.26 (dd, *J* = 15.3, 6.2 Hz, 1H), 1.73-1.65 (m, 2H), 1.55 (d, *J* = 7.1 Hz, 6H), 1.46 (s, 9H), 1.39 (s, 3H), 1.32 (s, 3H), 0.86 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.2 (C), 164.8 (C), 162.2 (d, *J* = 246.2 Hz, C), 141.5 (C), 138.3 (C), 134.6 (C), 133.1 (d, *J* = 8.1 Hz, CH), 130.5 (CH), 128.7 (C), 128.6 (CH), 128.3 (CH), 128.2 (d, *J* = 3.4 Hz, C), 126.5 (CH), 123.5 (CH), 121.7 (C), 119.5 (CH), 115.3 (d, *J* = 21.3 Hz, CH), 115.2 (C), 98.6 (C), 80.7 (C), 66.4 (CH), 65.8 (CH), 42.4 (CH_2), 40.8 (CH_2), 38.0 (CH_2), 35.9 (CH_2), 28.0 (CH_3), 26.0 (CH), 21.7 (CH_3), 21.5 (CH_3), 19.6 (CH_3); ^{19}F NMR ($CDCl_3$, 235 MHz) δ (-114.08) to (-114.18) (m). Anal. Calcd. for $C_{40}H_{47}FN_2O_5$ C, 73.37; H, 7.23; N, 4.28. Found: C, 73.31; H, 7.19; N, 4.24.

5-(4-Fluorophenyl)-1-[2-((2*R*,4*R*))-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-(*N*-phenyl)carboxamide 9 (atorvastatin lactone). To a solution of compound **1** (79 mg, 0.12 mmol) in methanol (1 mL), 2M hydrochloric acid (0.15 mL) was added and the mixture was stirred for 2 hours, followed by the addition of an additional amount of 0.15 mL of 2M HCl and the stirring was maintained for another hour. Then, 0.6M NaOH (2 mL) was added and after 2 hours, the methanol was removed. Ethyl ether (5 mL) and water (5 mL) were added to the residue and the aqueous layer was extracted with a mixture of ethyl acetate and hexane (1:1, 6 mL). Thereafter, 2M aqueous HCl was added to the aqueous layer until its pH was neutral and it was then extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to give atorvastatin lactone **9** as a white solid (63 mg, 94%); mp 150-153 ºC; $[\alpha]_D^{20}$ + 24.4 (*c* 1.0, $CHCl_3$) [lit.[22] + 25.5 (*c* 0.2, $CHCl_3$); lit.[23] + 26.05 (*c* 1.0, $CHCl_3$)]; IR (NaCl, neat) 3406, 1715, 1651, 1596, 1248, 1157 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.24-6.96 (m, 14H), 6.91 (br s, 1H), 4.20-3.90 (m, 1H), 4.25-4.09 (m, 3H), 3.61-3.55 (m, 1H), 2.67-2.62 (m, 2H), 2.35 (br s, 1H), 1.78-1.54 (m, 4H), 1.67-1.57 (m, 6H); ^{13}C-NMR ($CDCl_3$, 63 MHz) δ 169.4 (C), 163.1 (C), 162.5 (d, *J* = 246.6 Hz, C), 141.3 (C), 138.2 (C), 134.3 (C), 133.1 (d, *J* = 8.1 Hz, CH), 133.0 (C), 130.4 (CH), 128.7 (CH and C), 128.4 (CH), 128.3 (d, *J* = 3.9 Hz, C), 126.6 (CH), 123.7 (CH), 119.6 (CH and C), 115.7 (d, *J* = 21.7 Hz, CH), 115.6 (C), 73.0 (CH), 65.5 (CH), 42.4 (CH_2), 40.7 (CH_2), 38.5 (CH_2), 37.1 (CH_2), 35.6 (CH_2), 26.1 (CH), 22.0 (CH_3), 21.7 (CH_3). HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{33}H_{33}FN_2O_4Na$ 563.2322, found 563.2318. Anal. Calcd. for $C_{33}H_{33}FN_2O_4$: C, 73.31; H, 6.15; N, 5.18. Found: C, 73.28; H, 6.12; N, 5.22.

Conclusions

In conclusion, we have developed a very short, convergent synthesis of atorvastatin lactone based on a mechanochemical Hantzsch-like pyrrole synthesis in the presence of ytterbium triflate and silver nitrate. Our method provides the target compound in 38% overall yield from precursors that are either commercially available or can be prepared in very high yield from commercial materials. This synthesis illustrates the power of the mechanochemical approach by providing the first example of a target-oriented synthesis using as the key step a reaction employing high-speed vibration milling as the only source of energy.

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Notes and references

[a] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain. E-mail: josecm@farm.ucm.es.

Electronic Supplementary Information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR (including DEPT-135) and ^{19}F-NMR spectra. See DOI: 10.1039/b000000x/

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