SUPORTING INFORMATION SECTION

The Total Synthesis of Calcium Atorvastatin

Luiz C. Dias\textsuperscript{a}, Adriano S. Vieira\textsuperscript{a} and Eliezer J. Barreiro\textsuperscript{b}

\textsuperscript{a}Instituto de Química, Universidade Estadual de Campinas, UNICAMP, P.O. Box 6154, 13084-971 Campinas, SP, Brazil

\textit{Tel.: +55 19 35213097; fax: +55 19 35213023.}

\textsuperscript{b}Laboratório de Avaliação e Síntese de Substâncias Bioativas, Universidade Federal do Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil.

\textit{Tel.: +55 21 25626644; fax: +55 21 25626478.}

Table of contents

<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- General Experimental</td>
<td>2</td>
</tr>
<tr>
<td>2- Preparation of aldehyde 3</td>
<td>2</td>
</tr>
<tr>
<td>3- Preparation of methyl ketone 4</td>
<td>5</td>
</tr>
<tr>
<td>4- Experimental</td>
<td>7</td>
</tr>
<tr>
<td>5- Appendix – Copies of \textsuperscript{1}H and \textsuperscript{13}C NMR data</td>
<td>12</td>
</tr>
</tbody>
</table>
1. General Experimental

The air-sensitive and/or water-sensitive reactions were performed under nitrogen atmosphere with dry solvents under anhydrous conditions. Standard syringe techniques were applied for the transfer of dry solvents and air-sensitive reagents. The reactions were monitored by TLC performed on Merck silica gel (60 F254) using UV light as the visualizing agent and 5% vanillin in 10% H2SO4 and heat as developing agents. Merck silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Dry THF and Et2O were distilled from sodium/benzophenone under nitrogen prior to use. Some reagents and solvents were commercially available and were used without further purification. All of the yields were calculated as gross yields. 1H (250 and 500 MHz) and 13C (62.5 and 125 MHz) NMR spectra were recorded on Bruker DPX250 and INOVA 500 MHz spectrometers in CDCl3, acetone-d6, C6D6, MeOD or DMSO-d6 using tetramethylsilane (TMS) as internal standards.

2. Preparation of aldehyde 3

4-Methyl-3-oxo-N-phenylpentanamide (10) was prepared from the inexpensive and commercially available 4-methyl-3-oxo-methylpentanoate (9) and aniline (Scheme 1). Among the several reaction conditions tested, the best result was obtained using NaOH (2 mol%) as the catalyst in the absence of solvent followed by the removal of methanol at 135 °C (92% yield). N-phenylpentanamide (10) was obtained as a viscous yellow oil in a pure form.
Scheme 1. Preparation of 1,4-diketone (12).

In the next step, to obtain 2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11), 4-methyl-3-oxo-N-phenylpentanamide (10) was subjected to a reaction with benzaldehyde in the presence of acid catalysts in hexanes as the solvent (Scheme 1). Among the several reaction conditions evaluated, we obtained the best results using 4-aminophenol (20 mol%) and acetic acid (20 mol%) as catalysts in refluxing hexanes for 24 h. Under these conditions, Z+E-2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11) was obtained in 94% isolated yield. 2-Benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11) is a white solid and was purified by washing with hot hexanes (60 °C) to remove the remaining benzaldehyde, followed by washing with distilled water to remove catalyst residues.

The synthesis of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) was performed via the Stetter reaction, according to the work of Sagyan and coworkers (Scheme 1). N-phenylpentanamide (11) was subjected to a reaction with 4-fluorobenzaldehyde in the presence of triethylamine as the base and 3-ethyl-5-(2-hydroxyethyl)-4-methyl-3-thiazolium bromide as the catalyst (20 mol%) in anhydrous ethanol, according to the reported procedure. Using this protocol, 1,4-diketone (12) was obtained in only 39% yield after recrystallization. Considering this result, we decided to test the reaction in the absence of
solvent at 75 °C for 16 h. To our delight, these conditions afforded 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) in 85% isolated yield (Scheme 1).

Then, pyrrolic aldehyde (3) was prepared by a Pall-Knorr reaction.¹ᵇ,⁵ This process is composed of the reaction between 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) (previously prepared) with 3-aminopropan-1-ol and the subsequent oxidation of the resulting pyrrolic alcohol (13) (Scheme 2). For this purpose, 1,4-diketone (12) was treated with 1.5 equiv of 3-aminopropan-1-ol under pivalic acid catalysis in a mixture of toluene-heptane-tetrahydrofuran (1:4:1) under reflux with azeotropic removal of water for 24 h. Thus, 5-(4-fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (13) was obtained as a pale yellow solid in 73% isolated yield after purification by passing through a plug of silica gel. In the next step, pyrrolic alcohol (13) was subjected to oxidation under Swern conditions¹⁶ to give the corresponding pyrrolic aldehyde (3) in 84% yield, which was used in the next step without further purification.¹ᵇ

![Scheme 2. Preparation of pyrrolic aldehyde (3)](image)

3. Preparation of methylketone 4

The preparation of (S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (4) was easily performed in four steps from inexpensive L-(S)-malic acid (14), according to the procedure described in the literature¹⁷ (Scheme 3). In the first step, L-(S)-malic acid (14) was converted to its corresponding methyl ester (15) by a Fischer esterification reaction with methanol in the presence of catalytic amounts of sulfuric acid. Importantly, the product (S)-dimethylmalate (15) does not require
purification and can be used directly in the next step. In the next step, (S)-dimethyl malate (15) was converted to acetonide methyl ester (17) via Moriwake’s regioselective reduction reaction employing BH$_3$.SMe$_2$ and NaBH$_4$ (78% isolated yield). In this reaction, the intermediate 1,2-diol ester (16) was not isolated and was submitted directly to the ketalization reaction with 2,2-dimethoxy propane in the presence of catalytic amounts of p-TsOH (Scheme 3).

![Scheme 3. Synthesis of methyl ketone (4) from L-(S)-malic acid (14)](image)
4. Experimental

4-methyl-3-oxo-N-phenylpentanamide (10). To a mixture of 4-methyl-3-oxo methyl pentanoate (9) (100.0 g, 700 mmol) and NaOH (0.5 g) was added aniline (68.4 g, 730.5 mmol) at 135 °C, with simultaneous removal of methanol over 2 h. The reaction mixture was maintained for another 12 h at 135 °C and was monitored by thin layer chromatography. The reaction was cooled to room temperature and was slowly added to a 0 °C 5% aqueous HCl solution (until pH = 6) followed by water (300 mL). The reaction mixture was extracted with ethyl acetate (3 x 300 mL), and the organic phase was washed with water (3 x 300 mL). The organic phase was dried with anhydrous magnesium sulfate and then concentrated under vacuum to provide 4-methyl-3-oxo-N-phenylpentanamide (10) as a viscous yellow oil in 92% yield (130.5 g) in pure form (bp 262-263 °C).

1H NMR (250 MHz, DMSO-d6) δ 1.03 (d, J = 7.0 Hz, 6H), 2.77-2.83 (m, 1H), 3.61 (s, 2H); 7.04 (t, J = 8.1 Hz, 1H), 7.30 (t, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H); 10.07 (s, 1H).

13C NMR (62.5 MHz, DMSO-d6) δ 17.5, 40.3, 49.4, 118.9, 123.3, 128.6, 138.8, 165.1, 208.2. IR (KBr, cm⁻¹): 3298, 3044, 1729, 1658.

2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11). A mixture of 4-methyl-3-oxo-N-phenylpentanamide (10) (100.0 g, 480 mmol), 4-aminophenol (10.4 g, 96.0 mmol), benzaldehyde (53.0 g, 504.0 mmol) and acetic acid (5.7 g, 96.0 mmol) in hexanes (1 L) was refluxed for 24 h with azeotropic removal of water. The remaining solid was filtered, washed with hexanes (1 L) followed by distilled water (1.5 L) and dried under high vacuum (12 h) to give 2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11) in 94% yield (131.0 g) as a white solid, mp 191-192 °C. 1H NMR (250 MHz, DMSO-d6) δ 1.12 (d, J = 7.1 Hz, 6H), 3.30-3.47 (m, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.30-7.41 (m, 5H), 7.66-7.70 (m, 5H), 9.61 (s, 1H). 13C NMR (62.5 MHz, DMSO-d6) δ 18.3, 36.0, 121.1, 124.2, 128.3, 129.5, 130.3, 132.7, 135.1, 136.0, 137.3, 140.2, 165.3, 202.8. IR (KBr, cm⁻¹): 3312, 3049, 1728, 1663.

2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (diketone of Atorvastatin) (12). A mixture of 2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (11) (130.0 g, 443.1 mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methyl-3-thiazolium bromide (22.3 g, 88.6 mmol), triethylamine (135.8 mL, 974.8 mmol) and 4-fluorobenzaldehyde (60.5 g, 487.4 mmol) was heated at 75 °C under argon atmosphere with vigorous stirring for 16 h. The reaction
was monitored by thin layer chromatography (TLC) until consumption of N-phenylpentanamide (11) was achieved. Isopropyl alcohol (650 mL) was added, and the reaction mixture was maintained at 25 °C for 4 h under stirring. The remaining solid was vacuum filtered and washed with 700 mL of water followed by 500 mL of isopropyl alcohol. The product 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) was dried under high vacuum for 4 h, affording a white crystalline solid (mp 205-209 °C, Lit. 206-209 °C) in 85% yield (167.2 g). 

\[
{^1}H \text{ NMR (250 MHz, DMSO-d}_6) \delta 0.92 (d, J = 6.5 \text{ Hz, 3H}), 1.15 (d, J = 7.5 \text{ Hz, 3H}), 2.83-2.94 (m, 1H), 4.87 (d, J = 11.0 \text{ Hz, 1H}), 5.42 (d, J = 11.0 \text{ Hz, 1H}), 6.97-7.40 (m, 12H), 8.13 (d, J = 8.2 \text{ Hz, 2H}), 10.18 (s, 1H).
\]

\[
{^{13}}C \text{ NMR (62.5 MHz, DMSO-d}_6) \delta 18.1, 18.6, 40.9, 54.1, 64.1, 115.6 (d, J_{C-F} = 22.0 \text{ Hz}), 120.6, 124.7, 128.0, 128.6, 129.4, 131.5, 131.6 (d, J_{C-F} = 9.4 \text{ Hz}), 132.2 (d, J_{C-F} = 2.5 \text{ Hz}), 135.2, 136.7, 165.5, 165.6 (d, J_{C-F} = 255.3 \text{ Hz}), 196.4, 209.6. \]

IR (KBr, cm\textsuperscript{-1}): 3296, 1720, 1684, 1598.

5-(4-fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (13). To a solution of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) (140.0 g, 335.3 mmol) and 3-aminopropan-1-ol (37.8 g, 502.9 mmol) in toluene-heptane-tetrahydrofuran (1:4:1) (1 L) was added pivalic acid (6.8 g, 67.0 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 24 h with azeotropically removal of water, monitored by thin layer chromatography (TLC), cooled to room temperature and extracted with ethyl acetate (3 x 700 mL). The organic phase was washed with brine (500 mL). The solvent was removed under vacuum, and pyrrolic alcohol (13) was obtained as a pale yellow solid in 73% yield (113.8 g, 251.4 mmol) after purification by passing through a plug of silica. Alternatively, pyrrolic alcohol (13) can be purified by recrystallization from hexane-isopropyl alcohol. Mp 175-178 °C. 

\[
{^1}H \text{ NMR (500 MHz, CDCl}_3) \delta 1.53 (d, J = 7.0 \text{ Hz, 6H}), 1.71-1.82 (m, 2H), 3.46-3.61 (m, 3H), 3.99 (t, J = 7.7 \text{ Hz, 2H}), 6.87 (s, 1H), 6.95-7.21 (m, 14H). \]

\[
{^{13}}C \text{ NMR (125 MHz, CDCl}_3) \delta 21.7 (2C), 26.1, 34.3, 41.7, 59.8, 115.4 (d, J_{C-F} = 21.3 \text{ Hz}), 119.6, 121.8, 123.5, 126.5, 128.2 (d, J_{C-F} = 2.5 \text{ Hz}), 128.3, 128.6, 128.8, 130.4, 133.1 (d, J_{C-F} = 8.8 \text{ Hz}), 133.2, 134.6, 138.3, 141.4, 162.2 (d, J_{C-F} = 247.6 \text{ Hz}), 164.8. \]

IR (KBr, cm\textsuperscript{-1}): 3335, 3367, 1669.
5-(4-fluorophenyl)-2-isopropyl-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide (3). To a solution of oxalyl chloride (33.3 g, 262.8 mmol) in CH₂Cl₂ (800 mL) under an atmosphere of dry argon at −50 °C was added DMSO (34.2 g, 438 mmol) over 30 min. After 20 min at −50 °C, pyrrolic alcohol (13) (100.0 g, 219.0 mmol) dissolved in CH₂Cl₂ (200 mL) was slowly added over 30 min. The reaction mixture was maintained at −50 °C for 1 h, and Et₃N was added (88.4 g, 876 mmol, 4.0 eq.). The reaction was continued for 1 h at room temperature and was extracted with ethyl acetate (3 x 500 mL).

Pyrrolic aldehyde (3) was purified by passing through a plug of silica and eluted with hexane/acetate (9:1 mixture) to obtain a pale yellow solid in 84% yield (84.2 g, 186.1 mmol). Mp 160-163 °C. Lit.¹b mp 164-165 °C.

¹H NMR (500 MHz, CDCl₃) δ 1.51 (d, J = 7.0 Hz, 6H), 2.67 (t, J = 7.5 Hz, 2H), 3.61 (quint, J = 7.0 Hz, 1H), 4.25 (t, J = 7.5 Hz, 2H), 6.85 (s, 1H), 6.95-7.21 (m, 14H), 9.58 (s, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 21.6 (2C), 25.9, 37.6, 45.2, 115.7 (d, J_C-F = 21.4 Hz), 119.5, 122.1, 123.5, 126.7, 127.6, 127.7 (d, J_C-F = 3.8 Hz), 128.5, 128.6, 130.5, 133.0 (d, J_C-F = 7.3 Hz), 133.4, 134.7, 138.5, 141.5, 162.3 (d, J_C-F = 248.8 Hz), 164.4, 198.5. IR (KBr, cm⁻¹): 3402, 2965, 1722, 1674, 1596, 1510.

(S)-dimethylmalate (15). To a mixture of L-(S)-malic acid (14) (100.0 g, 745.7 mmol) in anhydrous methanol (600 mL) was added sulfuric acid (3.65 g, 2 mL), and the resulting mixture was refluxed for 12 h. Methanol was distilled off to obtain a final volume of approximately 100 mL. To the mixture was added a saturated aqueous NaHCO₃ solution until reaching pH = 8.0 (100 mL). The reaction was extracted with ethyl acetate (3 x 500 mL), and the organic phase was collected and dried with anhydrous Na₂SO₄. The solvent was removed in a rotary evaporator (40 °C/100 mmHg), and the remaining solvent was removed under high vacuum (1 mmHg) for 5 h. (S)-Dimethyl malate (15) was obtained in 94% yield (113.9 g) as a pale yellow oil and was used in the next step without purification. ¹H NMR (250 MHz, CDCl₃) δ 2.67 (dd, J = 15.1 Hz, 7.4 Hz, 1H), 2.71 (s, 1H), 2.78 (dd, J = 15.1 Hz, 7.4 Hz, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.50 (t, J = 7.3 Hz, 1H). ¹³C NMR (62.5 MHz, CDCl₃) δ 38.2, 51.6, 51.8, 68.9, 172.1, 172.3. IR (thin film, cm⁻¹): 3368, 2964, 1740.

(S)-methyl 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (17). To a solution of (S)-dimethyl malate (15) (110.0 g, 678.7 mmol) in anhydrous THF (1.0 L) at 20 °C under argon atmosphere was added BH₃·SMe₂ (10 M) (60.5 mL, 605.0 mmol) over 40 min. The solution was stirred for...
30 min at 20 °C until the hydrogen evolution ceased. The reaction temperature was reduced to 10 °C, and the solution was maintained for 10 min at this temperature. Then, NaBH₄ was added in portions (0.23 g in 5 portions) (1.15 g, 28.6 mmol) over 50 min. The reaction mixture was maintained under intense agitation for 1 h at 20 °C. The reaction was monitored by thin layer chromatography until total consumption of (S)-dimethyl malate (15) was achieved. Next, anhydrous methanol (500 mL) was slowly added to the reaction at 0 °C, and the mixture was stirred for 30 min at 20 °C. The solvent was removed completely on a rotary evaporator and then under high vacuum for 4 h. The viscous oil residue containing 16 was dissolved in a mixture of acetone (600 mL) and 2,2-dimethoxypropane (200 mL). To this mixture was added p-TsOH (4.95 g), and the reaction was stirred for 4 h at 20 °C. The mixture was extracted with ethyl acetate (3 x 500 mL), and the residue was subjected to distillation under reduced pressure (bp 74-75 °C/6 mbar). The product (17) was obtained as a colorless liquid in 78% yield (92.2 g, 529.3 mmol). ¹H NMR (250 MHz, CDCl₃) δ 1.35 (s, 3H), 1.41 (s, 3H), 2.52 (dd, J = 15.0 Hz, 7.5 Hz, 1H); 2.72 (dd, J = 15.0 Hz, 7.5 Hz, 1H), 3.65 (dd, J = 10.0 Hz, 7.5 Hz, 1H), 3.70 (s, 3H); 4.15 (dd, J = 8.7 Hz, 7.5 Hz, 1H), 4.47 (quint, J = 7.5 Hz, 1H). ¹³C NMR (62.5 MHz, CDCl₃) δ 25.4, 26.8, 38.7, 51.7, 69.1, 72.0, 109.2, 171.0. IR (thin film, cm⁻¹): 2966, 1738, 1230.

(S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (4). To a slurry of (S)-methyl 2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetate (17) (90.0 g, 516.7 mmol) and CH₃(OCH₃)NH.HCl (57.6 g, 593.8 mmol) in anhydrous THF (1.0 L) at −10 °C was slowly added a solution of CH₃MgCl (3.0 M in THF) (689.0 mL, 2.06 mol) over 1 h. After 1 h at −5 °C, the reaction mixture was warmed to 25 °C over 1 h, aged for 8 h then quenched into 1 M HCl (pH = 7.0). The layers were separated, and the THF solution was concentrated to 100 mL. The crude mixture was extracted with ethyl acetate (3 x 400 mL) and washed with brine (300 mL), and the residue was subjected to distillation under reduced pressure (bp 68-69 °C/7 mmHg). The product (S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (4) was obtained as a light yellow liquid in 92% yield (75.2 g, 475.3 mmol). ¹H NMR (250 MHz, CDCl₃) δ 1.34 (s, 3H), 1.40 (s, 3H), 2.19 (s, 3H), 2.60 (dd, J = 17.5 Hz, 7.0 Hz, 1H), 2.89 (dd, J = 17.5 Hz, 6.0 Hz, 1H), 3.53 (dd, J = 7.5 Hz, 6.7 Hz, 1H); 4.17 (dd, J = 7.5 Hz, 6.7 Hz, 1H), 4.45 (quint, J = 6.7 Hz, 1H). ¹³C NMR (62.5 MHz, CDCl₃) δ 25.3, 26.8, 30.5, 47.7, 69.3, 71.6, 108.7, 206.2. IR (thin film, cm⁻¹): 2960, 1732, 1235.
5. Appendix – Copies of $^1$H and $^{13}$C NMR data

$^1$H NMR spectrum of 4-methyl-3-oxo-N-phenylpentanamide (10) in DMSO-d$_6$ at 250 MHz

Current Data Parameters
NAME         out28asvH1
EXPNO                 1
PROCNO                1
F2 - Acquisition Parameters
Date_          20091028
Time              12.57
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG            zg30
TD                32768
SOLVENT            DMSO
NS                   16
DS                    0
SWH           5175.983 Hz
FIDRES         0.157958 Hz
AQ            3.1653888 sec
RG                228.1
DN                96.000 sec
TE                30.000 sec
DS                    0
TD0                   1
======== CHANNEL f1 ========
NUC1                 1H
P1                13.00 usec
PL1               -6.00 dB
SFO1        250.1315447 MHz

13C NMR spectrum of 4-methyl-3-oxo-N-phenylpentanamide (10) in DMSO-d$_6$ at 62.5 MHz

Current Data Parameters
NAME          out29asvC
EXPNO                 1
PROCNO                1
F2 - Acquisition Parameters
Date_          20091029
Time              19.25
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                16384
SOLVENT            DMSO
NS                   67
DS                    0
SWH           15060.241 Hz
FIDRES         0.919204 Hz
AQ            0.5439488 sec
RG                406.4
DW               33.200 usec
DE                 6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                   1
SFO1         62.9015280 MHz
NUC1                 13C
P1                10.00 usec
PLW1        -1.00000000 W
SFO2        250.1310005 MHz
NUC2                 1H
CPDPRG[2        waltz16
PCPD2            100.00 usec
PLW2        -1.00000000 W
PLW12       -1.00000000 W
PLW13       -1.00000000 W

F2 - Processing parameters
SI                32768
SF           62.8952390 MHz
WDW                  EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 1.40
$^1$H NMR spectrum of (Z)-2-benzylidene-4-methyl-3-oxo-\(N\)-phenylpentanamide (11) in acetone-\(d_6\) at 250 MHz

$^{13}$C NMR spectrum of (Z)-2-benzylidene-4-methyl-3-oxo-\(N\)-phenylpentanamide (11) in acetone-\(d_6\) at 62.5 MHz
$^1$H NMR spectrum of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) in CDCl$_3$ at 250 MHz

$^{13}$C NMR spectrum of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-N-phenylpentanamide (12) in CDCl$_3$ at 62.5 MHz
$^1$H NMR spectrum of [5-(4-fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (13) in CDCl$_3$ at 500 MHz.

$^{13}$C NMR spectrum of [5-(4-fluorophenyl)-1-(3-hydroxypropyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (13) in CDCl$_3$ at 125 MHz.
$^1$H NMR spectrum of 5-(4-fluorophenyl)-2-isopropyl-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrole-3-carboxamide (3) in CDCl$_3$ at 500 MHz

$^{13}$C NMR spectrum of 5-(4-fluorophenyl)-2-isopropyl-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrole-3-carboxamide (3) in CDCl$_3$ at 125 MHz.
1H NMR spectrum of (S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (4) in CDCl₃ at 250 MHz

\[
\text{H}_3C
\text{O}\text{O} \text{H}_3C
\text{CH}_3
\]

13C NMR spectrum of (S)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one (4) in CDCl₃ at 62.5 MHz

\[
\text{H}_3C
\text{O}\text{O} \text{H}_3C
\text{CH}_3
\]
$^1$H NMR spectrum of 1-[(R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-5-oxohexyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (5) in C$_6$D$_6$ at 250 MHz

$^{13}$C NMR spectrum of 1-[(R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-5-oxohexyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (5) in C$_6$D$_6$ at 125 MHz
$^1$H NMR spectrum of 1-[(3R,5R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,5-dihydroxyhexyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrrole-3-carboxamide (6) in C$_6$D$_6$ at 500 MHz

$^{13}$C NMR spectrum of 1-[(3R,5R)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,5-dihydroxyhexyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrrole-3-carboxamide (6) in C$_6$D$_6$ at 125 MHz
$^1$H-NMR spectrum of 5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1-[(3R,5R,7S)-3,5,7,8-tetrahydroxyoctyl]-1$H$-$pyrrole-3-carboxamide (2) in MeOD at 500 MHz

$^{13}$C NMR spectrum of 5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1-[(3R,5R,7S)-3,5,7,8-tetrahydroxyoctyl]-1$H$-$pyrrole-3-carboxamide (2) in MeOD at 125 MHz
$^1$H NMR spectrum of 1-[2-((2R,4R)-4,6-dihydroxytetrahydro-2H-pyran-2-yl)ethyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (7) in CDCl$_3$ at 500 MHz

$^{13}$C NMR spectrum of 1-[2-((2R,4R)-4,6-dihydroxytetrahydro-2H-pyran-2-yl)ethyl]-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (7) in CDCl$_3$ at 125 MHz
$^1$H NMR spectrum of 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-2H-pyran-2-yl)ethyl]-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (8) in CDCl$_3$ at 250 MHz

$^{13}$C NMR spectrum of 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-2H-pyran-2-yl)ethyl]-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (8) in CDCl$_3$ at 62.5 MHz
1H NMR spectrum of Calcium Atorvastatin (1) in DMSO-d$_6$ at 500 MHz

13C NMR spectrum of Calcium Atorvastatin (1) in DMSO-d$_6$ at 125 MHz
Amorphous Calcium Atorvastatin (1) XR Diffractogram

Measurement Condition

X-ray tube

- target = Cu
- voltage = 40.0 (kV)
- current = 20.0 (mA)

Slits

- divergence slit = 1.00000 (deg)
- scatter slit = 1.00000 (deg)
- receiving slit = 0.30000 (mm)

Scanning

- drive axis = Theta-2Theta
- scan range = 2.000 - 37.000
- scan mode = Continuous Scan
- scan speed = 2.0000 (deg/min)
- sampling pitch = 0.0200 (deg)
- preset time = 0.60 (sec)
ASV79B_2 4 (0.085) AM (Cen, 5, 80.00, Ht, 5000.0, 0.00, 1.00); Sm (Mn, 3x2.00); Cm (3.24)

615.3235

ASV79B_1101 (0.034) Is (1.00, 1.00) C37H44FN2O5

615.3234

M = 644.3156 - Teórico

M + H = 615.3234 - Teórico

616.3267
Sample Name: atorvastatina

Acq. Operator: ricardo
Acq. Instrument: Instrument 1
Injection Date: 9/28/2011 11:04:01 AM
Inj Volume: 20.0 µl

Method: C:\CHEM32\1\METHODS\ATORVASTATINA-ADRIANO.M

Wavelength=240 nm (ADRIANO-ATORVASTATINAAMOSTRA 1.0)

Area Percent Report

Signal 1: WVD1 A, Wavelength=240 nm

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] [mAU] %
---|------|-------|-----------|-----------|-------|
1  3.024 VB 0.2259 2177.05591 133.777722 100.0000

Totals: 2177.05591 133.777722

*** End of Report ***