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Synthesis of Deuterium-Labeled Atorvastatin and Its Metabolites for Use as Internal Standards in A LC/MS/MS Method Developed for Quantitation of the Drug and Its Metabolites in Human Serum

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Summary

D_5-labeled isotopomers of atorvastatin, atorvastatin lactone and its hydroxy metabolites were synthesized as internal standards for use in a LC/MS/MS method developed for the simultaneous quantitative determination of atorvastatin and its hydroxy metabolites in human serum. d_5-Atorvastatin and d_5-atorvastatin lactone were prepared from d_5-aniline whereas their corresponding hydroxy metabolites were synthesized using d_5-benzaldehyde.

Keywords: atorvastatin, atorvastatin lactone, hydroxy metabolites, deuterium.

Introduction

Atorvastatin, a drug used for the treatment of high serum cholesterol, is a new synthetic inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Atorvastatin is administered as the calcium salt of the active hydroxy acid and has at least two active metabolites, 2-hydroxyatorvastatin and 4-hydroxy-atorvastatin [1,2]. An HMG-CoA reductase inhibition assay [3-5] and a

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radioimmunoassay [6,7] have been previously used for the quantitation of atorvastatin equivalent concentrations in post-dose plasma samples. In a project aiming at the development of a bioanalytical method based on high-performance liquid chromatography (LC) with electrospray tandem mass spectrometry (MS/MS) for the simultaneous quantitative determination of atorvastatin and its hydroxy metabolites in human serum [8], deuterium labeled atorvastatin and its hydroxy metabolites, as well as their lactones, were required. While stable isotope labeled compounds have the same solubility, extraction and chromatographic behavior as their non-labeled counterparts, their difference in molecular weights make them distinguishable in LC/MS/MS from the non-labeled counterparts. Therefore, stable isotope labeled compounds are ideal internal standards in LC/MS/MS assay used for the quantitation of drugs and metabolites in biological matrices.

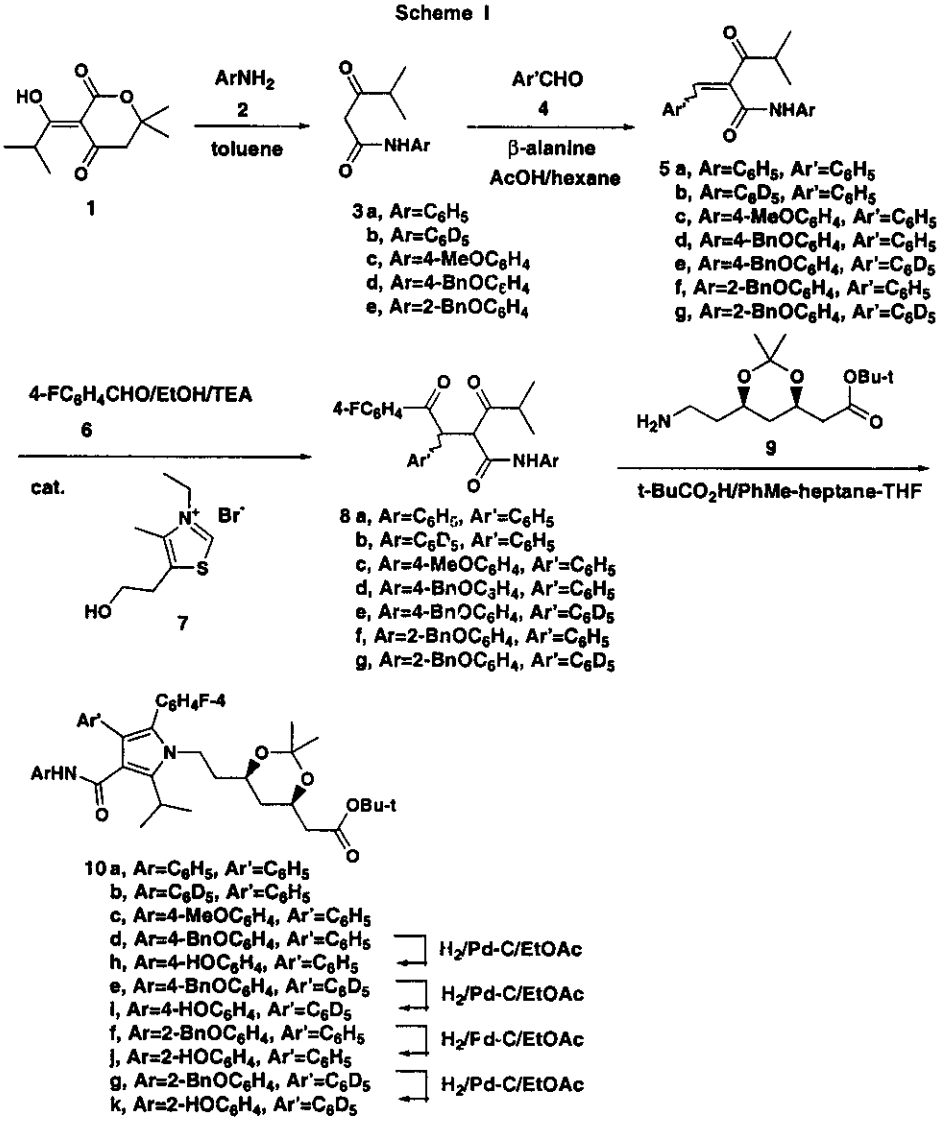
Results and Discussion

The phenyl amide site of atorvastatin appears to be appropriate for labeling with deuterium because of the ready availability of d_5-aniline. While the previously reported procedures for the synthesis of atorvastatin [9] could be adapted, significant modifications were needed and new procedures were developed for the preparation of the deuterated intermediates and atorvastatin lactones (Schemes I-II). A similar synthetic strategy was used for the preparation of deuterated atorvastatin hydroxy metabolites. The site for labeling, however, was changed from the N-aryl amide site to the 4-phenyl group on the pyrrole ring, in view of the difficulty of preparing O-protected deuterium labeled 2- and 4-hydroxyanilines.

Thus, treatment of isobutyryl Meldrum's acid **1** with anilines **2** in refluxing toluene gave N-aryl isobutyrylacetamides **3** [10]. Condensation of **3** with benzaldehyde or d_5-benzaldehyde **4** in the presence of a catalytic amount of β-alanine provided **5** [9]. Treatment of **5** with 4-fluorobenzaldehyde **6** in the presence of a catalytic amount of **7** gave **8**. Pyrrole ester **10a** formation was initially performed using 0.2 equivalents of pivalic acid and the desired product was obtained in <5% yield. However, it was found by using 2 equivalents of pivalic acid, a 56% yield of **10a** was obtained. Under similar reaction conditions, pyrrole esters **10b-g** were

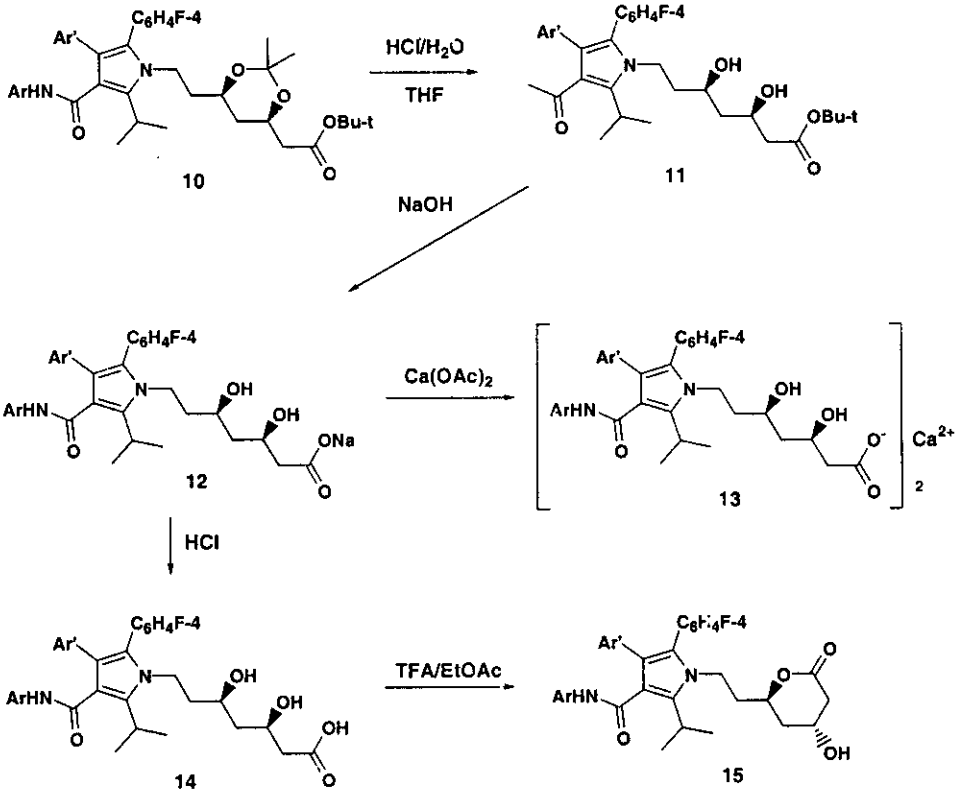
obtained. The benzyl protecting group in **10d-g** was then removed via hydrogenation to give **10h-k** respectively. It should be pointed out that the initial plan of using the more readily available 4-methoxyaniline **2c** instead of 4-benzyloxyaniline **2d** for the preparation of **10h** failed in this deprotection step. Under usual reaction conditions for deprotecting a methoxy group, decomposition of the starting material **10c** was observed.

Scheme I



Deprotection of **10a**, **10b** and **10h-k** with dilute HCl gave dihydroxy esters **11**, which were hydrolyzed with sodium hydroxide to give **12** (Scheme II). The calcium salts **13** were then obtained by cation exchange of **12** using calcium acetate. For the preparation of the corresponding atorvastatin lactones **15**, the sodium salts **12** were neutralized with HCl to give acids **14** which were then converted to lactones **15** using TFA in ethyl acetate.

Scheme II



10 11 12 13 14 15

a, Ar=C_6H_5, Ar'=C_6H_5; b, Ar=C_6D_5, Ar'=C_6H_5; h, Ar=4-HOC_6H_4, Ar'=C_6H_5
l, Ar=4-HOC_6H_4, Ar'=C_6D_5; j, Ar=2-HOC_6H_4, Ar'=C_6H_5; k, Ar=2-HOC_6H_4, Ar'=C_6D_5

Experimental

Isobutyryl Meldrum's acid **1** [11] and the amino ester **9** [9] were prepared according to literature procedures. 2-Benzyloxyaniline **2e** was prepared in 67% yield

by reduction of 2-benzyloxynitrobenzene using sodium dithionite in methanol. d_5-Aniline (99+ atom % D) and d_5-benzaldehyde (99 atom % D) were purchased from Aldrich Company. ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker ARX-400 instrument using tetramethylsilane as internal standard. The reactions were monitored by HPLC using a Shimadzu LC-10AS system. LC/MS analyses were conducted using a Hewlett-Packard 1090L HPLC system and a Finigan TSQ-7000 triple quadruple mass spectrometer [8].

Preparation of N-aryl isobutyrylacetamides 3. In a 1L round bottomed flask equipped with a condenser and a magnetic stirrer was placed isobutyryl Meldrum's acid (**1**, 26.19 g), d_5-aniline (10.0 g) and toluene (200 mL). The reaction mixture was stirred to give a solution under nitrogen, heated to 80°C and stirred for 4 h. The reaction mixture was cooled and washed with 18% HCl (2x100 mL), sat. K_2CO_3 (100 mL) and brine (100 mL) and dried over anhydrous $MgSO_4$. Removal of $MgSO_4$ and solvent afforded N-d_5-phenyl isobutyrylacetamide **3b** (20.78 g) in 97% yield which was used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J=6.8 Hz, 6H), 2.80 (m, 1H), 3.60 (s, 2H), 9.25 (s, 1H).

N-Phenyl isobutyrylacetamide 3a. prepared similarly from **2a**, 96% yield. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J=6.8 Hz, 6H), 2.80 (m, 1H), 3.60 (s, 2H), 7.00-7.75 (m, 5H), 9.25 (s, 1H).

N-4-Methoxyphenyl isobutyrylacetamide 3c. prepared similarly from **2c**, 99% yield. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J=6.9 Hz, 6H), 2.73 (m, 1H), 3.60 (s, 2H), 3.75 (s, 3H), 6.80 (d, J=7.7 Hz, 2H), 7.39 (d, J=7.7 Hz, 2H), 9.15 (s, 1H).

N-4-Benzyloxyphenyl isobutyrylacetamide 3d. prepared similarly from **2d**, 82% yield. ^{1}H NMR (DMSO-d_6) δ 1.06 (d, J=7.0 Hz, 6H), 2.75 (m, 1H), 3.28 (s, 2H), 5.02 (s, 2H), 6.90 (d, J=7.7 Hz, 2H), 7.15-7.65 (m, 7H), 9.90 (s, 1H).

N-2-Benzyloxyphenyl isobutyrylacetamide 3e. prepared similarly from **2e**, 76% yield. ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J=6.8 Hz, 6H), 2.72 (m, 1H), 3.58 (s, 2H), 5.12 (s, 2H), 6.85-8.34 (m, 9H), 9.50 (s, 1H).

Preparation of pyrrole esters 10a-g. In a 500mL round bottomed flask equipped with a mechanical stirrer, a Dean-Stark trap and a condenser was placed N-d_5-phenyl isobutyrylacetamide (**3b**, 20.5 g), benzaldehyde (9.4 g) and hexanes (320

mL). The reaction mixture was stirred under nitrogen, and β-alanine (1.6 g) and glacial acetic acid (3 mL) were added. The reaction mixture was heated to reflux and stirred for 25 h. After cooling to room temperature, the solvent was decanted. The solid was slurried with anhydrous ether (50 mL), filtered and washed with anhydrous ether (5x20 mL). The cake was then slurried in deionized water (100 mL) for 1 h. The slurry was filtered, washed with deionized water (5x20 mL) and dried in a vacuum oven for 18 h to give **5b** (15.26 g) which was used in the next step without further purification.

In a 250mL round bottomed flask equipped with a mechanical stirrer, a Dean-Stark trap and a condenser was placed 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**7**, 2.46 g) and absolute ethanol (60 mL). The mixture was heated to reflux and about 56mL of ethanol was distilled off. After cooling the pot to 45-50°C, **5b** (14.24 g), triethylamine (6.7 mL) and 4-fluorobenzaldehyde (5.6 mL) were added. The mixture was heated to 75-80°C and stirred for 21 h. The solvent was removed. The residue was dissolved with ether (300 mL), washed with deionized water (2x50 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. After removal of $MgSO_4$ and the solvent, the residue was crystallized with isopropanol (60 mL) to give **8b** (4.7 g).

In a 250mL round bottomed flask equipped a condenser and magnetic stirrer was placed **8b** (4.7 g), the amino ester (**9**, 4.10 g), pivalic acid (2.25 g), THF (26 mL), toluene (26 mL) and heptane (104 mL). The reaction flask was wrapped with aluminum foil. The mixture was heated to reflux under nitrogen and stirred for 24 h. The solvent was removed and the residue was purified by silica flash chromatography using ether and hexane as eluent to give d_5-pyrrole ester **10b** (4.07 g) as a foam in 8% overall yield from **3b** in three steps. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.45 (s, 9H), 1.50 (d, J=7.0 Hz, 6H), 1.00-1.80 (m, 4H), 2.20-2.46 (m, 2H), 3.48-4.35 (m, 5H), 6.80-7.40 (m, 9H).

Pyrrole ester 10a: prepared similarly from **3a**, 6% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.45 (s, 9H), 1.50 (d, J=7.0 Hz, 6H), 1.00-1.80 (m, 4H), 2.20-2.46 (m, 2H), 3.48-4.35 (m, 5H), 6.80-7.40 (m, 14H).

4-Methoxypyrrole ester 10c: prepared similarly from **3c**, 8% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.45 (s, 9H), 1.50 (d, J=7.0 Hz, 6H), 1.00-1.80 (m, 4H), 2.20-2.46 (m, 2H), 3.75 (s, 3H), 3.48-4.20 (m, 5H), 6.70-7.30 (m, 13H).

4-Benzyloxypyrrole ester 10d: prepared similarly from **3d**, 9% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.43 (s, 9H), 1.48 (d, J=7.3 Hz, 6H), 1.00-1.80 (m, 4H), 2.18-2.45 (m, 2H), 3.48-4.20 (m, 5H), 4.98 (s, 2H), 6.70-7.55 (m, 18H).

d_5-4-Benzyloxypyrrole ester 10e: prepared similarly from **3d** and d_5-benzaldehyde, 9% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.52 (d, J=7.3 Hz, 6H), 1.00-1.72 (m, 4H), 2.18-2.42 (m, 2H), 3.50-4.20 (m, 5H), 4.99 (s, 2H), 6.73-7.42 (m, 13H).

2-Benzyloxypyrrole ester 10f: prepared similarly from **3e**, 15% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.35 (s, 3H), 1.45 (s, 9H), 1.50 (d, J=7.2 Hz, 6H), 1.00-1.80 (m, 4H), 2.18-2.45 (m, 2H), 3.48-4.20 (m, 5H), 4.78 (s, 2H), 6.70-7.55 (m, 18H).

d_5-2-Benzyloxypyrrole ester 10g: prepared similarly from **3e** and d_5-benzaldehyde, 17% overall yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.43 (s, 9H), 1.49 (d, J=7.23 Hz, 6H), 1.60-1.80 (m, 2H), 2.20-2.40 (m, 2H), 3.41-4.18 (m, 5H), 4.76 (s, 2H), 6.68-7.35 (m, 12H), 7.67 (s, 1H), 8.53 (d, 1H).

Preparation of hydroxypyrrole esters 10h-k: In a 1L hydrogenation flask was placed 4-benzyloxypyrrole ester **10d** (13.8 g), ethyl acetate (200 mL), palladium on carbon (4.0 g, 10%) and acetic acid (2.0 mL). The reaction flask was wrapped with aluminum foil and hydrogenated at 50psi H_2 for 34 h. The reaction mixture was filtered through of a pad of silica gel (15 g) and the pad washed with ethyl acetate (3x30 mL). The filtrate was washed with sat. $NaHCO_3$ (200 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. After removal of $MgSO_4$ and the solvent, the residue was purified by flash column using MTBE/hexane as the eluent to give 4-hydroxypyrrole ester **10h** (10.3 g) in 85% yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.45 (s, 9H), 1.50 (d, J=7.1 Hz, 6H), 1.00-1.80 (m, 4H), 2.20-2.45 (m, 2H), 3.45-4.25 (m, 5H), 6.10 (s, 1H), 6.55-7.35 (m, 13H).

d_5-4-Hydroxypyrrole ester 10i: prepared similarly from **10e**, 93% yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.44 (s, 9H), 1.51 (d, J=7.1 Hz, 6H), 1.00-1.77 (m, 4H), 2.20-2.45 (m, 2H), 3.45-4.22 (m, 5H), 6.60-7.22 (m, 9H).

2-Hydroxypyrrole ester 10j: prepared similarly from **10f**, 35% yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.42 (s, 9H), 1.50 (d, J=7.2 Hz, 6H), 1.00-1.80 (m, 4H), 2.20-2.45 (m, 2H), 3.48-4.25 (m, 5H), 6.55-7.35 (m, 13H), 10.02 (s, 1H).

d_5-2-Hydroxypyrrole ester 10k: prepared similarly from **10g**, 81% yield. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.37 (s, 3H), 1.42 (s, 9H), 1.53 (d, J=7.24 Hz, 6H), 1.65-1.80 (m, 3H), 2.20-2.45 (m, 2H), 3.51-4.20 (m, 5H), 5.63 (d, 1H), 6.55-7.20 (m, 8H), 10.02 (s, 1H).

Preparation of atorvastatins 13. In a 500mL round bottomed flask equipped with a magnetic stirrer was placed d_5-pyrrole ester **10b** (4.0 g) and THF (180 mL). The mixture was stirred to give a solution. After wrapping the flask with aluminum foil, 10% HCl (13.8 mL) was added and the reaction was stirred under nitrogen at room temperature for 23 h. Sodium hydroxide (3.3 g) was added and the reaction was stirred at room temperature for 64 h. Deionized water (135 mL) and hexane (80 mL) were added. The phases were separated. Calcium acetate monohydrate (0.534 g) was added to the aqueous layer containing **12b** and the mixture was stirred for 0.5 h. The pH of the reaction mixture was adjusted to 6.37 using 18% HCl. The reaction mixture was concentrated on a rotary evaporator to a volume of 190 mL. The resulted slurry was cooled with ice-water bath and stirred for 0.5 h. The slurry was filtered and washed with cold deionized water (3x20 mL) and dried to give d_5-atorvastatin **13b** (2.88 g) in 82% yield. ^{1}H NMR (DMSO-d_6) δ 1.00-1.68 (m, 4H), 1.35 (d, J=7.2 Hz, 6H), 1.90-2.15 (m, 2H), 3.18-4.10 (m, 7H), 6.95-7.30 (m, 9H), 9.82 (s, 1H). $[M+H]^+$ (free acid)=564.

Atorvastatin 13a: prepared similarly from **10a**, 60% yield. ^{1}H NMR (DMSO-d_6) δ 1.20-1.68 (m, 4H), 1.35 (d, J=7.2 Hz, 6H), 1.75-2.10 (m, 2H), 3.18-4.10 (m, 7H), 6.85-7.60 (m, 14H), 9.82 (s, 1H). $[M+H]^+$ (free acid)=559.

4-Hydroxyatorvastatin 13h: prepared similarly from **10h**, 51% yield. ^{1}H NMR (DMSO-d_6) δ 1.20-1.68 (m, 4H), 1.36 (d, J=7.2 Hz, 6H), 1.90-2.18 (m, 2H), 3.10-4.10 (m, 8H), 6.55-7.45 (m, 13H), 9.50 (s, 1H). $[M+H]^+$ (free acid)=575.

d_5-4-Hydroxyatorvastatin 13i: prepared similarly from **10i**, 45% yield. ^{1}H NMR (DMSO-d_6) δ 1.20-1.68 (m, 4H), 1.37 (d, J=7.2 Hz, 6H), 2.10-2.38 (m, 2H), 3.15-4.10 (m, 8H), 6.55-7.30 (m, 8H), 9.55 (s, 1H). $[M+H]^+$ (free acid)=580.

2-Hydroxyatorvastatin 13j: prepared similarly from **10j**, 48% yield. ^{1}H NMR (DMSO-d_6) δ 1.10-1.72 (m, 4H), 1.35 (d, J=7.1 Hz, 6H), 1.94-2.20 (m, 2H), 3.10-4.10 (m, 8H), 6.60-7.70 (m, 13H), 8.65 (s, 1H). $[M+H]^+$ (free acid)=575.

d_5-2-Hydroxyatorvastatin 13k: prepared similarly from **10k**, 33% yield. ^{1}H NMR (DMSO-d_6) δ 1.16-1.60 (m, 4H), 1.39 (t, J=6.8 Hz, 6H), 1.98-2.11 (m, 2H), 3.25-4.00 (m, 8H), 6.66-7.60 (m, 8H), 8.98 (s, 1H). $[M+H]^+$ (free acid)=580.

Preparation of atorvastatin lactones 15: After the aqueous layer containing **12b** was obtained as described in the preparation of **13b**, the pH was adjusted to 1 using 18% HCl. The product was extracted with ethyl acetate (2x200 mL). The combined organic extracts were washed with deionized water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Removal of Na_2SO_4 and solvent gave an oil which was dissolved with ethyl acetate (120 mL). TFA (1.2 mL) was added and the solution was heated to 50°C and stirred for 16 h. The solvent was removed and the product was purified using flash chromatography with ethyl acetate and hexane as eluent to give d_5-atorvastatin lactone **15b** (2.0 g) in 62% yield. ^{1}H NMR ($CDCl_3$) δ 1.45-1.94 (m, 4H), 1.53 (t, J=6.4 Hz, 6H), 2.48-2.62 (m, 2H), 3.10 (s, 1H), 3.47-3.60 (m, 1H), 3.95-4.25 (m, 3H), 4.48-4.58 (m, 1H), 6.90-7.25 (m, 9H). $[M+H]^+$=546.

4-Hydroxyatorvastatin lactone 15h: prepared similarly from **10h**, 72% yield. ^{1}H NMR (DMSO-d_6) δ 1.42 (d, J=7.2 Hz, 6H), 1.52-1.90 (m, 4H), 2.32-2.70 (m, 2H), 3.17-3.30 (m, 1H), 3.90-4.13 (m, 3H), 4.48-4.59 (m, 1H), 5.24 (s, 1H), 6.65-7.40 (m, 13H), 9.18 (s, 1H), 9.50 (s, 1H). $[M+H]^+$=557.

d_5-4-Hydroxyatorvastatin lactone 15i: prepared similarly from **10i**, 62% yield. ^{1}H NMR (DMSO-d_6) δ 1.35 (d, J=7.2 Hz, 6H), 1.50-1.85 (m, 2H), 2.30-2.65 (m, 2H), 3.17-3.28 (m, 1H), 3.85-4.10 (m, 4H), 4.42-4.52 (m, 1H), 5.20 (s, 1H), 6.60-7.30 (m, 8H), 9.12 (s, 1H), 9.56 (s, 1H). $[M+H]^+$=562.

2-Hydroxyatorvastatin lactone 15j: prepared similarly from **10j**, 55% yield. ^{1}H NMR (DMSO-d_6) δ 1.50 (d, J=7.1 Hz, 6H), 1.40-1.98 (m, 4H), 2.50-2.70 (m, 2H), 3.37 (s, 1H), 5.50-3.65 (m, 1H), 4.00-4.35 (m, 3H), 4.53-4.67 (m, 1H), 6.90 (d, 1H), 6.65-7.45 (m, 13H), 9.98 (s, 1H). $[M+H]^+$=557.

d_5-2-Hydroxyatorvastatin lactone 15k: prepared similarly from **10k**, 68% yield. ^{1}H NMR (DMSO-d_6) δ 1.41 (d, J=7.1 Hz, 3H), 1.42 (d, J=6.7 Hz, 3H), 1.53-1.63 (m, 2H), 1.72-1.83 (m, 2H), 2.31-2.35 (m, 1H), 2.57-2.62 (m, 1H), 3.31-3.33 (m,

1H), 3.85-4.05 (m, 2H), 4.47-4.49 (m, 1H), 5.17 (d, J=2.7 Hz, 1H), 6.69-7.62 (m, 8H), 8.60 (s, 1H), 9.68 (s, 1H). $[M+H]^+$=562.

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