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Synthesis of one of the Major Mouse Metabolites of Lovastatin and Simvastatin

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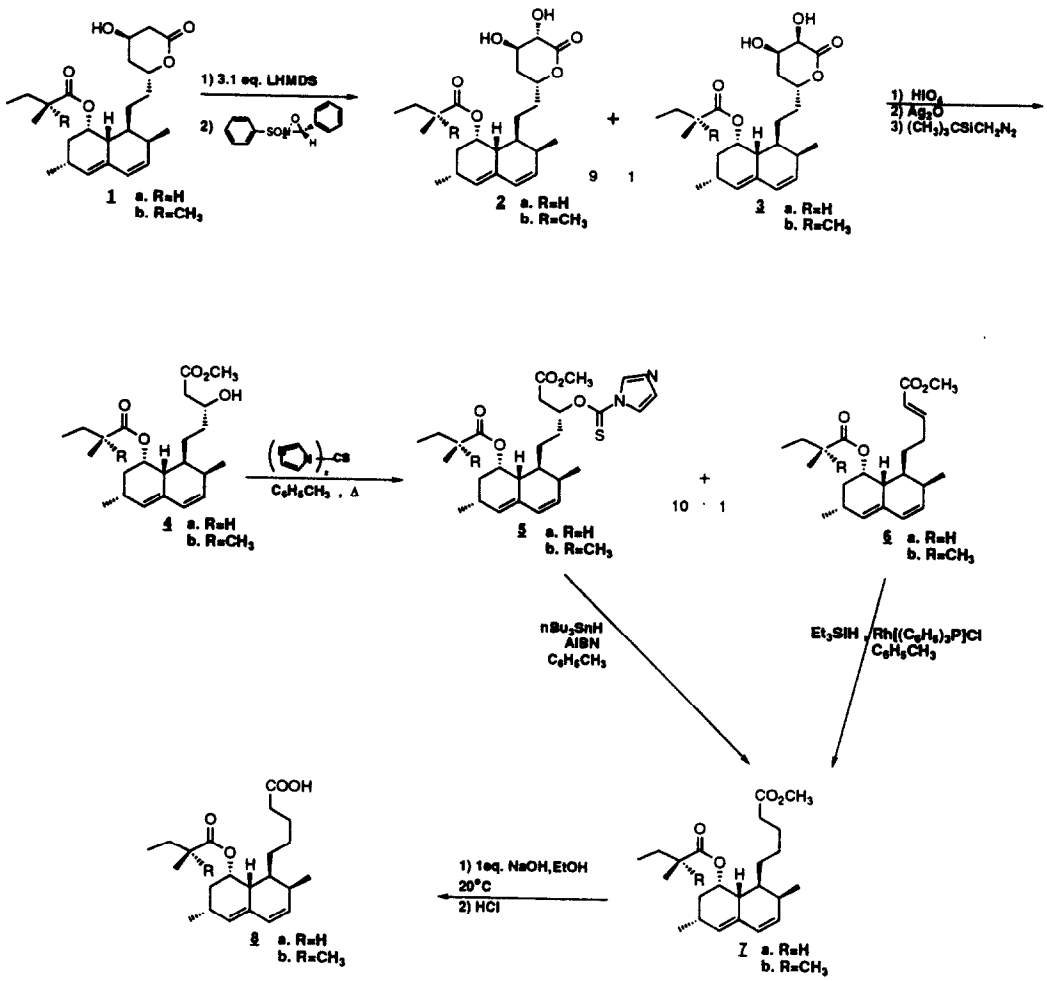
Abstract: An unequivocal synthesis of the mouse liver metabolites of lovastatin and simvastatin resulting from β-oxidation of the lactone portion is described.

Lovastatin (**1a**) and simvastatin (**1b**) are orally active cholesterol-lowering agents in animals[1] and man.[2] Upon hydrolysis of the lactone ring, **Ia** and **Ib** are converted to the β, δ-dihydroxy acid derivatives that are potent competitive inhibitors of HMG-CoA reductase, the enzyme catalyzing the rate-limiting step of cholesterol biosynthesis. Recently, it has been reported that the major metabolites of the dihydroxy acid form of **1** present in mouse livers are pentanoic acids **8**[3,4] formed via a putative β-oxidation pathway. This communication describes synthesis of acid **8a** and methyl esters **7a** and **7b** thus confirming the pentanoic acid structure assigned to the metabolites.

We began our investigation into the synthesis of pentanoic acids **8** by employing a pseudo-β-oxidation[5] as the key step (cf. Scheme 1). Oxidation of the dianion of **1** (generated with lithium hexamethyldisilazine (LHMDS)) by 2-(phenylsulfonyl) oxaziridine[6] provided a mixture of 3S, 4R (**2**) and 3R, 4R (**3**) diols in 35-45% yield. The use of other strong bases, such as LDA, NaHMDS or KHMDS, provided a much lower yield of the diols. Substitution of the 2-(phenylsulfonyl)oxaziridine by either (+)-(2R,8aS) or (-)-2S,8aR) (camphorylsulfonyl)oxaziridines[7] produced the same results while use of MoOPH[8] gave comparable yields, but with **3** as the major product. Metaperiodate oxidation[9] of either diol (**2** or **3**) followed by silver oxide oxidation[10] and subsequent esterification provided hydroxy pentanoic ester **4** in 40-45% yield from the diol lactone. The use of Tollen's reagent for the oxidation of the aldehyde to the acid[11] was not as efficient. Conversion of **4** to deoxygenated ester **7** was accomplished via formation of thiocarbamate **5** (75%) with thiocarbonyldiimidazole and subsequent radical reduction[12] (45-55%). The formation of **5** was accompanied by some dehydration to Δ^2 ester **6** which was conjugatively reduced with

SCHEME 1


1) 3.1 eq. LHMDS
2)
1 a. R=H b. R=CH3
2 a. R=H b. R=CH3
9 1
3 a. R=H b. R=CH3
1) HIO4
2) Ag2O
3) (CH3)3CSiCH2N2
4 a. R=H b. R=CH3
C6H5CH3 , Δ
5 a. R=H b. R=CH3
10 1
6 a. R=H b. R=CH3
nBu3SnH
AIBN
C6H5CH3
Et3SiH, Rh[(C6H5)3P]Cl
C6H5CH3
1) 1eq. NaOH,EtOH
20°C
2) HCl
8 a. R=H b. R=CH3
7 a. R=H b. R=CH3

triethyl silane catalyzed by Wilkinson's catalyst[13] to afford **7** in high yield. Mild basic hydrolysis of **7a** gave a moderate yield of pentanoic acid **8a**[14] which proved to be identical (PMR & HPLC) with the isolated metabolite.

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14. TLC and diagnostic NMR data for **2a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 ($C_5\underline{H}$, m), 2.14 ($C_5\underline{H}$, dd, J ~ 11, 9Hz), 3.98 ($C_4\underline{H}$, dt, J ~ 8, 8, 2Hz), 4.32 ($C_3\underline{H}$, d, J ~ 7Hz), 4.49 ($C_6\underline{H}$, m); TLC:SiO_2, $CHCl_3$/acetone (3:1), Rf ~ 0.21 vs 0.50 for **1a**.

2b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 ($C_5\underline{H}$, m), 2.13 ($C_5\underline{H}$, dd, J ~ 9, 11Hz), 3.98 ($C_4\underline{H}$, dt, J ~ 8, 8, 2Hz), 4.32 ($C_3\underline{H}$, d, J ~ 7Hz), 4.48 ($C_6\underline{H}$, m); TLC:SiO_2, $CHCl_3$/acetone (3:1), R_f ~ 0.27 vs 0.53 for **1b**.
3b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 ($C_5\underline{H}$, m), 2.24 ($C_5\underline{H}$, m), 4.09 ($C_3\underline{H}$, d, J ~ 3 Hz), 4.33 ($C_4\underline{H}$, m), 4.70 ($C_6\underline{H}$, m); NoE between 4.09 and 1.81 ppm; TLC:SiO_2, $CHCl_3$/acetone (3:1), R_f ~ 0.38 vs 0.53 for **1b**.
4a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 ($C_2\underline{H}$, dd, J ~ 17, 8Hz), 2.51 ($C_2\underline{H}$, dd, J ~ 17, 4Hz), 3.72 ($CO_2C\underline{H}_3$, s), 3.94 ($C_3\underline{H}$, m); TLC:SiO_2, $CHCl_3$/acetone (20:1), Rf ~ 0.33; MS (m/z) 392.
4b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 ($C_2\underline{H}$, dd, J ~ 17, 8Hz), 2.51 ($C_2\underline{H}$, dd, J ~ 17, 4Hz), 3.71 ($CO_2C\underline{H}_3$,s), 3.94 ($C_3\underline{H}$, m); TLC:SiO_2, $CHCl_3$/acetone (40:1), Rf ~ 0.15; TLC of precursor acid: SiO_2, $CHCl_3$/acetone/acetic acid (400:100:5), R_f ~ 0.33.
5a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.78 ($C_2\underline{H}$, dd, J ~ 15, 6Hz), 2.88 ($C_2\underline{H}$, dd, J ~ 17, 7Hz), 3.69 ($CO_2C\underline{H}_3$, s), 5.81 ($C_3\underline{H}$, m); TLC:SiO_2, Hexane/EtOAc (2:1), Rf ~ 0.18 vs 0.35 for **4a**.
5b: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.79 ($C_2\underline{H}$, dd, J ~ 15, 6Hz), 2.88 ($C_2\underline{H}$, dd, J ~ 17, 7Hz), 3.70 ($CO_2C\underline{H}_3$, s), 5.80 ($C_3\underline{H}$, m); TLC:SiO_2, Hexane/EtOAc (2:1), R_f ~ 0.31.
6a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 ($CO_2C\underline{H}_3$, s), 5.80 ($C_2\underline{H}$, dt, J ~ 16, 1Hz), 6.91 ($C_3\underline{H}$, dt, J ~ 16, 7 Hz); TLC:SiO_2, Hexane/EtOAc (2:1), Rf ~ 0.76 vs 0.35 for **4a**.
6b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 ($CO_2C\underline{H}_3$, s), 5.81 ($C_2\underline{H}$, dt, J ~ 16, 1Hz), 6.92 (C3H, dt, J ~ 16, 7 Hz); TLC:SiO_2, Hexane/EtOAc (2:1), Rf ~ 0.80.
7a: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.29 ($C_2\underline{H}_2$, t, J ~ 7Hz), 3.66 ($CO_2C\underline{H}_3$, s); TLC:SiO_2, Hexane/EtOAc (4:1). Rf ~ 0.62 vs 0.60 for **6a**; MS (m/z) 376.
7b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 ($C_2\underline{H}_2$, t, J ~ 7Hz), 3.66 ($CO_2C\underline{H}_3$, s); TLC:SiO_2, Hexane/EtOAc (10:1), R_f ~ 0.23; MS (m/z) 390.
8a: ^{1}H NMR ($CDCl_3$, 360 MHz), δ 1.15 ($C_4\underline{H}_2$, m), 1.63 ($C_3\underline{H}_2$, m), 2.36 ($C_2\underline{H}_2$, m); MS (m/z) 362.