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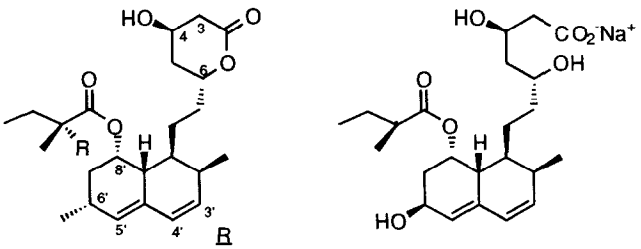
SYNTHESIS OF THE 3'(S)-HYDROXY DERIVATIVE OF SIMVASTATIN

G. E. Stokker
Department of Medicinal Chemistry, Merck Research Laboratories
West Point, Pennsylvania 19486

Abstract: A simple two step synthesis of the 3'(S)-hydroxylated derivative of simvastatin isolated from rat and mice liver microsomes along with the 3'(R) epimer and a two step preparation of the 3'(S)-5'(S)-dihydroxylated compound is described.

Lovastatin (**1**), simvastatin (**2**) and pravastatin (**3**) are potent orally active competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-determining enzyme of cholesterol biosynthesis. Recent reports from these and other laboratories have described the isolation and determination of the structure of the metabolites of lovastatin[1,2] simvastatin[3,4] and pravastatin[5,6,7] resulting from hydroxylation of the hexahydronaphthalene moiety of the substrate. In addition to these, a study of auto-oxidation of simvastatin resulting in similar ring hydroxylations has also recently appeared.[8] The present paper describes the synthesis and structure of the mono and dihydroxy hexahydronaphthalene derivatives of simvastatin for comparison to the hydroxylated compounds isolated from incubation of simvastatin with rat and mouse liver microsomes and confirm their identities. The 3'-hydroxy derivative is not thought to be a metabolite per se but is formed by a rearrangement of the 6'-hydroxy metabolite. This rearrangement has been observed in acetonitrile with aqueous acetic acid by proton NMR.[9]



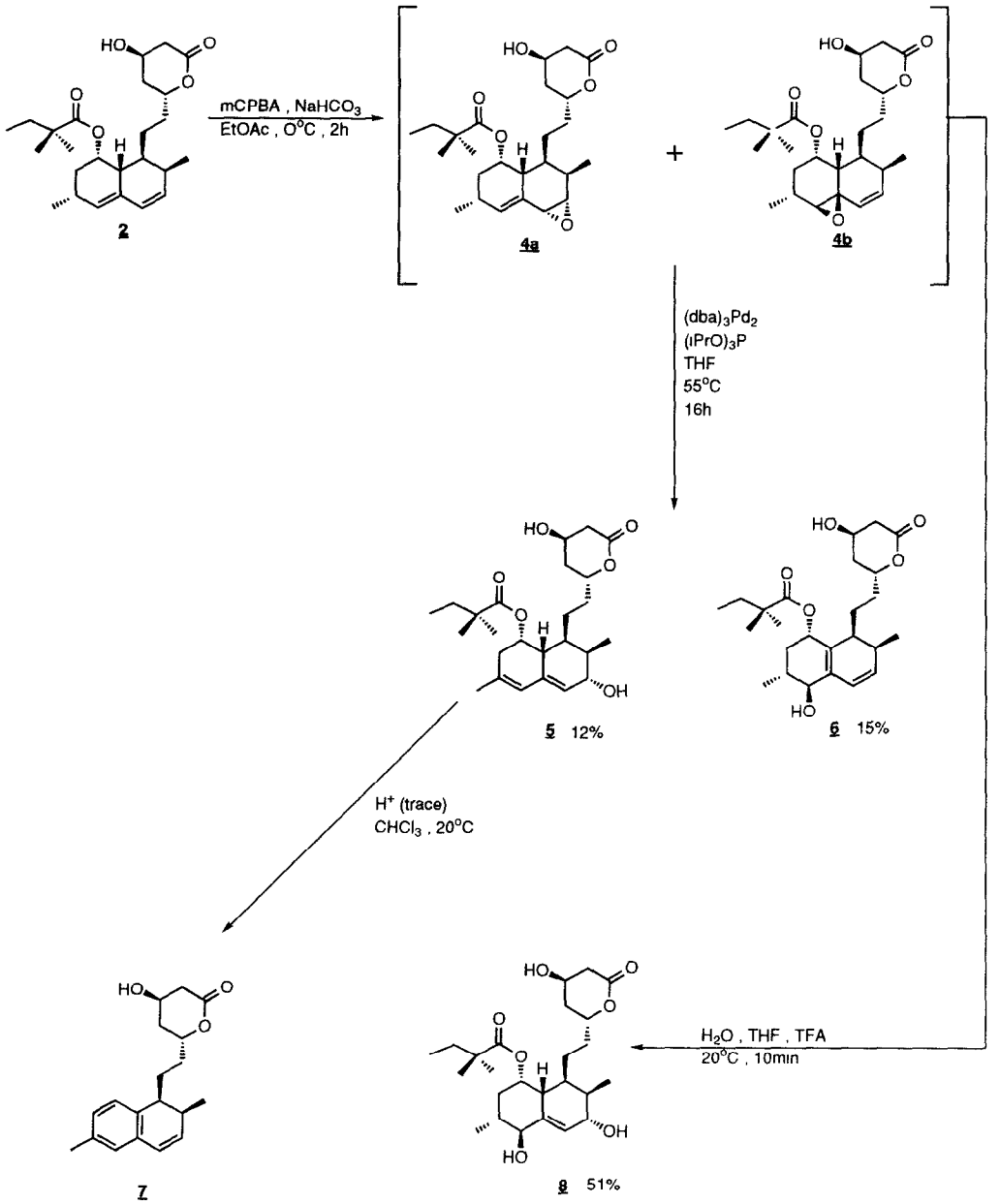
	R
1	H
2	CH_3

3

FIGURE 1

Scheme 1 summarizes the preparation of the ring hydroxylated derivatives. We began our investigation with a 3-chloroperbenzoic acid oxidation of **2** to give a nearly inseparable mixture of epoxides **4a** and **4b**.[10] This epoxide mixture was rearranged under mild palladium (0)[11] catalysis to give the chromatographically separable dienols **5** and **6**. Dienol **5** was shown by mass spectral and ^1H NMR analysis to be identical to the 3'-hydroxylated rearranged metabolite of Simvastatin.[3]

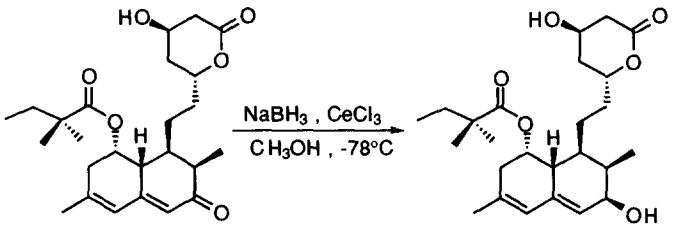
SCHEME 1


mCPBA , NaHCO3
EtOAc , 0°C , 2h
2
4a
4b
(dba)3Pd2
(iPrO)3P
THF
55°C
16h
5 12%
6 15%
H+ (trace)
CHCl3 , 20°C
7
8 51%
H2O , THF , TFA
20°C , 10min

Dienol **5** is acid labile as demonstrated by its dehydration and subsequent aromatization to tetrahydronapthalene derivative **7** when left in chloroform at room temperature overnight. In contrast dienols **6** and **10** (Scheme 2) are stable under identical conditions even after several days. Dienol **6** has yet to be isolated and identified as a metabolite or rearrangement product, but it has been found as an auto-oxidation product.[8]

When the epoxide mixture was treated with trifluoroacetic acid in aqueous tetrahydrofuran at room temperature only the 3'(S)-5'(S) diol (**8**) was isolated which has been shown by ^{1}H NMR analysis to be identical to the hexahydronapthalene portion of the cytochrome P450 3A catalyzed metabolite of lovastatin from rat and human liver microsomes[2] and similar to one of the metabolites of pravastatin.[7]

SCHEME 2



9 **10**

Scheme 2 delineates the cerium (III) chloride mediated borohydride reduction[12] of dienone **9**[13] to give **10** the expected 3'(R) epimer of **5**. The structures of 3' epimeric dienols **5** and **10** were confirmed by careful 1 and 2D NMR analysis. The hydroxylated compounds described herein were evaluated as their ring-opened sodium dihydroxy carboxylate forms for their ability to inhibit recombinant HMG-CoA reductase. The 3',5'-dihydroxy (**8**) and 5'-hydroxy (**6**) derivatives were inactive while the 3'(S)derivative (**5**) was thirteen fold less active and the 3'(R) derivative (**10**) was thirty three fold less active than **2**.[14]

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10. When the tert-butyldiphenylsilyl ether derivative of **2** was epoxidized, the corresponding epoxides could be separated by chromatography: TLC:SiO_2, Hexane/EtOAc (2:1), R_f ~ 0.50 for α epoxide vs 0.59 for β epoxide.
11. The use of tetrakis(triphenylphosphine)palladium (0) as in the case of Suzuki, M.; Oda, Y.; Noyori, R. *J. Am.Chem.Soc.*, **1979,** 101, 1623 gave inconsistent results as did replacement of the triisopropyl phosphite with 1,3-bis(diphenylphosphine)propane.
12. Gamal, A. L.; Luche, J. -L. *J. Am. Chem. Soc.*, **1981**, *103*, 5454.
13. The synthesis of **9** will be published elsewhere.
14. Schwartz, M. S. private communication and represent ratios of IC_{50}'s.
15. TLC data for **4a** and **4b**:SiO_2, $CHCl_3$/acetone (2:1), R_f ~ 0.62 for mixture vs 0.67 for **2**. Hexane/EtOAc (1:2), R_f ~ 0.33 for mixture vs 0.47 for **2**.
5: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75 (CH_3C_6', s), 2.62 (C_3H, ddd, J ~ 1.5, 3.7, 17 Hz), 2.75 (C_3H, dd, J ~ 5, 17 Hz), 3.95 (C_3'H, d J ~ 3.8 Hz), 4.38 (C_4H, m), 4.66 (C_6H, m), 5.39 (C_8'H, m), 5.63 (C_4'H, d, J ~ 3.8 Hz), 5.90 (C_5'H, s); TLC:SiO_2, $CHCl_3$/acetone (3/2), R_f ~ 0.44.
6: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.595 (C_3H, ddd, J ~ 1.5, 3.7, 17 Hz), 2.697 (C_3H, dd, J ~ 5, 17 Hz), 3.75 (C_5'H, d, J ~ 6.9 Hz), 4.34 (C_4H, m), 4.58 (C_6H, m), 5.52 (C_8'H, obscure), 5.57 (C_4'H, d, J ~ 9.9 Hz), 6.18 (C_3'H, dd, J ~ 3.1, 9.9 Hz); TLC:SiO_2, $CHCl_3$/acetone (3/2), R_f ~ 0.35.
7: ^1H NMR ($CDCl_3$, 300 MHz), δ 2.31 (CH_3,C_6', s), 4.35 (C_4H, m), 4.65 (C_6H, m), 5.74 (C_3'H, dd, J ~ 3.2, 9.5 Hz), 6.36 (C_4'H, dd, J ~ 2.3, 9.5 Hz), 6.87 (C_5'H, d, J ~ 1.5 Hz), 6.93 (C_7'H, dd, J ~ 1.5, 6 Hz), 6.97 (C_8'H, d, J ~ 6 Hz); TLC:SiO_2, $CHCl_3$/acetone (3/2), R_f ~ 0.70).
8: ^1H NMR ($CDCl_3$, 300 MHz), δ 2.61 (C_3H, ddd, J ~ 1.5, 3.7, 17 Hz), 2.74 (C_3H, dd, J ~ 5, 17 Hz), 3.89 (C_3'H, dd, J 2 X ~ 4 Hz), 3.99 (C_5'H, d, J ~2.3 Hz), 4.37 (C_4H, m), 4.64 (C_6H, m), 5.35 (C_8'H, ddd, J 3 X ~ 3 Hz), 5.92 (C_4'H, dd, J ~ 1.8, ~ 4 Hz); TLC:SiO_2, $CHCl_3$/acetone (3/2), R_f ~ 0.14; MS (M+H) 451.
10: ^1H NMR ($CDCl_3$, 300 MHz); δ 1.75 (CH_3C_6',s), 2.62 (C_3H, ddd, J ~ 1.5, 3.7, 17 Hz), 2.75 (C_3H, dd, J ~ 5, 17Hz), 4.395 (C_4H, C_3'H, m), 4.66 (C_6H, m), 5.37 (C_4'H, C_8', m), 5.875 (C_5'H, m) TLC:SiO_2, $CHCl_3$/acetone (3/2), R_f ~ 0.39; $CHCl_3$/CH_3OH (8/1). R_f ~ 0.34 vs 0.38 for **5**.

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