3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 7.[1] Modification of the Hexahydronaphthalene Moiety of Simvastatin: 5-Oxygenated and 5-Oxa Derivatives

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Modification of the hexahydronaphthalene ring 5-position in simvastatin **2a** via oxygenation and oxa replacement afforded two series of derivatives which were evaluated in vitro for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and acutely in vivo for oral effectiveness as inhibitors of cholesterogenesis in the rat. Of the compounds selected for further biological evaluation, the 6β-methyl-5-oxa **10** and 5α-hydroxy **16** derivatives of 3,4,4a,5-tetrahydro **2a**, as well as, the 6β-epimer **14** of **16** proved orally active as hypocholesterolemic agents in cholestyramine-primed dogs. Subsequent acute oral metabolism studies in dogs demonstrated that compounds **14** and **16** evoke lower peak plasma drug activity and area-under-the-curve values than does compound **10** and led to the selection of **14** and **16** for toxicological evaluation.

Introduction

Lovastatin (**1a**),[2] a fungal metabolite isolated from cultures of *Aspergillus terreus*, and simvastatin (**2a**),[3] a synthetic derivative of **1a**, are lactone prodrugs and have been shown to be effective hypocholesterolemic agents in both experimental animals and humans. The dihydroxy carboxylic acid forms of lactones **1a** and **2a** are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme which catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonic acid in the biosynthesis of cholesterol. Prodrugs **1a** and **2a** are shunted on first pass more efficiently into the liver, the major site of cholesterol biosynthesis, than are the corresponding dihydroxy carboxylic acids. The favorable toxicological consequences resulting from diminished peripheral exposure to active inhibitors render this prodrug choice attractive.[2a]

As part of a continuing effort to discover inhibitors that maintain potency and display novel metabolic profiles and low plasma drug activity levels, structural modifications of the hexahydronaphthalene portion of simvastatin (**2a**) were undertaken. It was anticipated that chemical modification at the hexahydronaphthalene ring 5- and 6-positions would produce novel compounds possessing unique pharmacological profiles since the 6-position of **1a** and **2a** is a primary site of metabolism by both rat and human liver microsomes.[7] In this report we describe the preparation and biological evaluation of 5-oxygenated A[5] and 5-oxa B[6] derivatives of **2a** (Figure 1).

Chemistry

The synthetic strategy used to construct 5-oxa analogues with geminal substitution at C-6 is depicted in Scheme I. Selective reduction of the disubstituted olefin of **2a** was accomplished with Wilkinson's catalyst in ethanol/toluene under a hydrogen atmosphere to furnish olefin **3** in 80% yield.[8] Ozonolysis of **3** in methanol at −78 °C followed by reduction of the ozonide with Zn/HOAc and the resulting keto aldehyde **3a** with $NaBH_4$ in aqueous THF gave triol **4** (62%) as a single stereoisomer. The expected axial addition of hydride to the ketone was confirmed through decoupling experiments that revealed a coupling constant for H_{4a}, H_{5a} of 10 Hz. The selenide **6** was obtained in 64% yield via a two step sequence by first treating triol **4** with Ph_3P/imidazole/iodine in CH_3CN to yield the 1′-iodide **5** followed by treatment of **5** with $NaBH_4$/*o*-$O_2NPhSeCN$ in DMF.[9] Oxidative elimination of the selenide **6** with H_2O_2/THF furnished olefin **7** in 79% yield. Cyclization of **7** was then effected by iodine in CH_2Cl_2 to afford iodides

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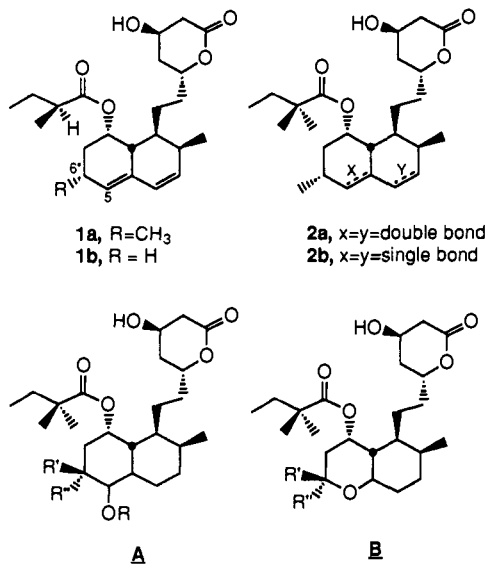
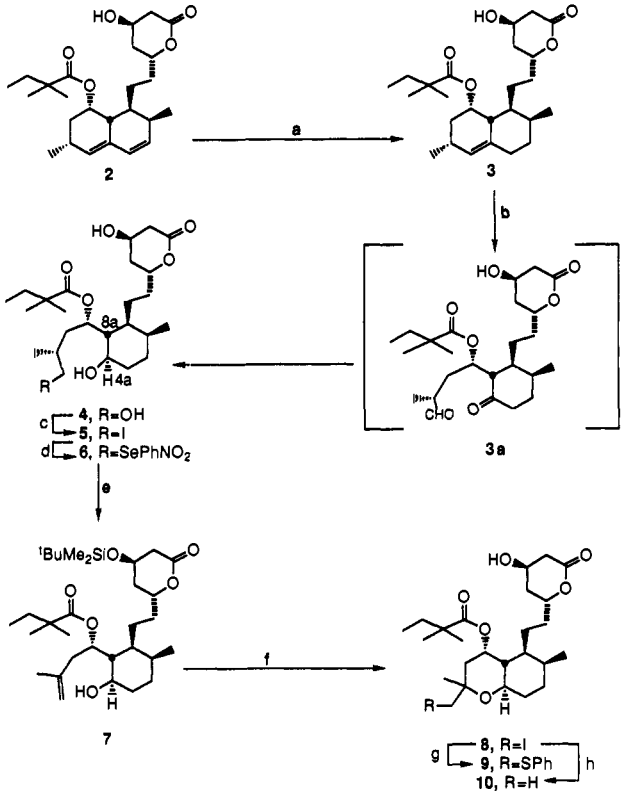


Figure 1.

Scheme I. Synthesis of 5-Oxa Analogues

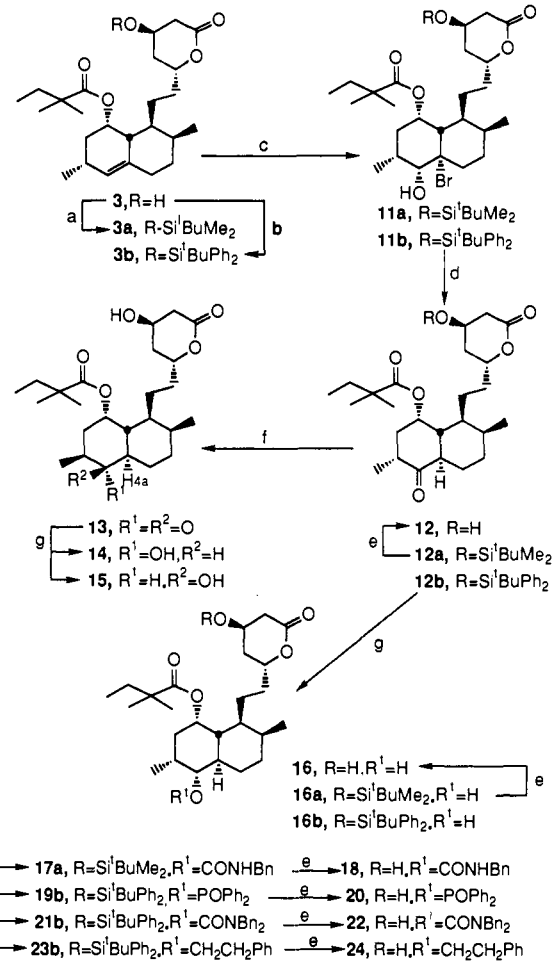


[a] (a) $(Ph_3P)_3RhCl$, H_2, toluene/ethanol; (b) O_3, CH_3OH, -78 °C, and then Zn/HOAc, and then $NaBH_4$, THF/H_2O; (c) Ph_3P, imidazole, I_2, CH_3CN; (d) $NaBH_4$, o-$O_2NPhSeCN$ DMF; (e) H_2O_2, THF; (f) I_2, $NaHCO_3$, CH_2Cl_2; (g) DBU, DMF, PhSH; (h) Bu_3SnH, AIBN, toluene.

8 (63%) as a 1:1 mixture of epimers at C-6.

The mixture of epimeric iodides 8 was converted, by either nucleophilic or free radical reactions, to a variety of 5-oxa analogues. For example, nucleophilic attack of 8 with thiophenol in DMF in the presence of DBU furnished the chromatographically separable sulfides 9α and 9β in 98% combined yield. The configuration at the C-6 stereogenic center of 9α and 9β was elucidated through qualitative NOE experiments focusing on peak enhancements from the C-6 substituents to H_{4a}. Alternatively, treatment of 8 with *n*-Bu_3SnH/AIBN in toluene at 80 °C produced the 6,6-dimethyl analogue **10** in 84% yield.

Scheme II. Synthesis of 5-Oxygenated Analogues



16a → 17a, R=Si^{t}BuMe$_2$,R^1=CONHBn → 18, R=H,R^1=CONHBn
16b → 19b, R=Si^{t}BuPh$_2$,R^1=POPh$_2$ → 20, R=H,R^1=POPh$_2$
16b → 21b, R=Si^{t}BuPh$_2$,R^1=CONBn$_2$ → 22, R=H,R^1=CONBn$_2$
16b → 23b, R=Si^{t}BuPh$_2$,R^1=CH$_2$CH$_2$Ph → 24, R=H,R^1=CH$_2$CH$_2$Ph

[a] (a) ^{t}BuMe$_2$SiCl, imidazole, DMF; (b) ^{t}BuPh$_2$SiCl, imidazole DMF; (c) NBS, THF, DMSO, H_2O; (d) PCC, CH_2Cl_2, and then Zn, HOAC, THF; (e) Bu_4NF, HOAc, THF; (f) DBU, CH_3CN; (g) $NaBH_4$, THF, H_2O; (h) CuCl, DMF, BnNCO; (i) Ph_2POCl, DMAP, CH_2Cl_2; (j) CH_2Cl_2, $COCl_2$, NEt_3, and then Bn_2NH; (k) PhCH=CHOCH$_3$, CSA, CH_2Cl_2 and then Pd/C, EtOAc, H_2.

The olefin 3 also was employed to prepare 5-oxygenated analogues of 2a (Scheme II). Silylation of the hydroxyl function of 3 with either *tert*-butyldimethylsilyl chloride or *tert*-butyldiphenylsilyl chloride under standard conditions gave the silyl ethers 3a and 3b, respectively. Treatment of olefin 3a in DMSO/H_2O/THF at 0 °C with *N*-bromosuccinimide gave the bromohydrin 11a in 61% yield. This intermediate was oxidized with PCC and the resulting α-bromo ketone was immediately reduced with Zn/HOAc in THF to furnish the ketone 12a in 79% yield. Stereoelectronic requirements directed protonation of the intermediate enol from the α-face to afford the *trans*-decalin 12a exclusively. The *tert*-butyldiphenylsilyl ether 12b also was obtained through this reaction sequence. Deprotection of the silyl ether 12a with *n*-Bu_4NF/HOAc furnished ketone 12 in 79% yield.

The ketone 12 was crucial for constructing 5-oxygenated analogues in which the C-6 methyl substituent was β-oriented. Treatment of ketone 12 at 50 °C in acetonitrile with DBU furnished exclusively the thermodynamically more stable 6-β-methyl ketone 13 in 65%. Reduction of 13 with BH_3-THF at -15 °C afforded a chromatographically separable mixture of alcohols 14 (69%) and 15 (19%). Proton decoupling studies confirmed the assignment of stereochemistry at both C-5 and C-6 in compounds 14 and 15.

Table I. In Vitro Results for 5-Oxygenated and 5-Oxa Derivatives

	recryst solvent	mp, °C	molecular formula[a]	IC_{50}, nM	relative potency[b]
1a				18.0	158
2a				12.1	235
2b				13	138
4	ether	128–130	$C_{25}H_{44}O_7$	2800	0.5
7		oil	$C_{25}H_{42}O_6 \cdot 0.5H_2O$	1700	0.9
9α		oil	$C_{31}H_{46}O_6S$	6.6	258
9β		oil	$C_{31}H_{46}O_6S$	6	280
10	ether/hexane	119–120	$C_{25}H_{42}O_6$	35	70
12	EtOAc/hexane	159–160	$C_{25}H_{40}O_6$	34	125
13	EtOAc/hexane	137–137	$C_{25}H_{40}O_6$	59	63
14	EtOAc/hexane	107–108	$C_{25}H_{42}O_6$	48.6	61
15		oil	$C_{25}H_{42}O_6$	269	11.1
16	EtOAc/hexane	129–131	$C_{25}H_{42}O_6$	40.8	73
18		oil	$C_{33}H_{49}O_7N \cdot 1.5H_2O$	5	360
20		oil	$C_{37}H_{51}O_7P \cdot 0.5H_2O$	6	300
22		oil	$C_{40}H_{55}O_7N \cdot 0.5H_2O$	16	94
24		oil	$C_{33}H_{50}O_6$	6	300

[a] All new compounds exhibited satisfactory microanalyses: C, H, N ±0.4%. [b] For estimation of relative inhibitory potencies, compactin (1b) was assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin.

The 5-oxygenated analogues retaining the axial α-methyl at C-6 and were prepared from either **12a** or **12b**. As expected, $NaBH_4$ delivered a hydride axially to ketone **12a** to furnish **16a** (88%). Desilylation of **16a** with *n*-Bu_4NF/HOAc gave the diol **16** in 77% yield. By using technology developed in this laboratory, the alcohol **16a** was treated with benzyl isocyanate in DMF at 25 °C in the presence of CuCl to furnish the benzylcarbamate **17a** (74%).[10] Desilylation of **17a** afforded alcohol **18** in 82% yield. The phosphinate **20** was prepared to good yield by treatment of **16b** with diphenylphosphonic chloride/DMAP followed by desilylation. Sequential treatment of the alcohol **16b** with NEt_3, phosgene, and dibenzylamine in dichloromethane, followed by desilylation, afforded the dibenzyl carbamate **22** in 27% yield. The 2-phenethyl ether **24** was prepared by a three-step sequence. Treatment of alcohol **16b** with (±)-camphorsulfonic acid (CSA) in the presence of β-methoxy styrene gave an unstable enol ether which was immediately reduced by treatment with 10% Pd/C under a hydrogen atmosphere to give **23b** in 39% overall yield. Desilylation of **23b** then furnished **24** quantitatively.

Results and Discussion

The compounds displayed in Table I were evaluated as the sodium salts of their dihydroxy carboxylate forms for their ability to inhibit solubilized, partially purified, rat liver HMG-CoA reductase by using the in vitro procedure reported earlier.[11,13] In the 5-oxa series, the two ring-opened intermediates **4** and **7** exhibited very weak activity, indicating the necessity of a rigid lipophilic anchor for potency. The 6,6-dimethyl derivative **10** was half as active as the *trans*-decalin **2b**. However, potency comparable to that of **2a** could be recovered in this series by substituting either the 6α- or β-methyl group with a lipophilic moiety such as thiophenol, as shown in compounds **9α** and **9β**.[12]

Table II. Acute Inhibition of Cholesterol Synthesis in the Rat

compd	% change of [^{14}C]cholesterol (±5%)[a]
9α	−34
9β	0
10	−67
12	−56
13	−68
14	−54
16	−37
18	−27
20	−27
22	−4
24	−39

[a] Percent change of [^{14}C]cholesterol for 1a varied from −50 to −60% and for 2a varied from −60 to −70%.

Table III. Effect of 1a, 10, 14, and 16 (4 mg/kg per day) on Cholesterol in Cholestyramine-Primed Dogs

dog	compd	plasma cholesterol: % change[a]
1	10	20
	1a	25
2	14	34
	1a	38
3	16	19
	1a	25

[a] Percent cholesterol change from the resin-treated dog.

Potency in the 5-oxygenated series was influenced both by C-5 and C-6 stereochemistry and by the hydrophobic nature of the C-5 hydroxyl substituent. Although the 6α-methyl ketone **12** was 2-fold more potent than the 6β-epimer **13**, the 5α-hydroxy analogues bearing either a 6β- or 6α-methyl group (**14** and **16**, respectively) were essentially equipotent. Interestingly, the 5β-hydroxy derivative **15**, in which the alcohol is axially disposed, exhibits a 6-fold decrease in potency relative to **14** and **16**. Conversion of alcohol **16** to the corresponding benzylcarbamate **18**, diphenylphosphonate **20** and the 2-phenethyl ether **24** derivatives provides compounds that exhibit 4- to 5-fold increases in potency. These potency increases may suggest that a new hydrophobic binding domain within the enzyme has been located. However, the dibenzylcarbamate **22** prepared from alcohol **16**, displayed only a modest increase in potency relative to **16**, a result which suggests that the hydrophobic pocket boundary may have been reached. The C-6 thiophenol moiety in 5-oxa analogues **9α** and **9β** also may interact with this hydrophobic binding site.

An initial assessment for oral in vivo efficacy was achieved in a rat model. In this model, cholesterol synthesis from [^{14}C]acetate was measured at a fixed time after a single oral dose of 0.45 mg/kg for each test compound.[13] The results are displayed in Table II as the percent change in [^{14}C]cholesterol. In the 5-oxa series, compounds **9α** and **9β** exhibited in vitro potencies 4-fold greater than **10**; nevertheless, they were less active than **10**, in vivo. In fact, the 6β-epimer **9β** displayed no effect on cholesterol biosynthesis at the dose tested in this model. The activity of compound **10** was comparable to that of lovastatin.

In vivo effectiveness of compounds in the 5-oxygenated series in the rat model also varied greatly from the in vitro results. The epimeric ketones **12** and **13** exhibited in vivo

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(12) 9α = 6α-$PhSCH_2$- and 9β = 6β-$PhSCH_2$-.

(13) For experimental see: Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. Mevinolin: A Highly Potent Competitive Inhibitor of Hydroxymethylglutaryl-Coenzyme A Reductase and A Cholesterol-lowering Agent. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957–3961.

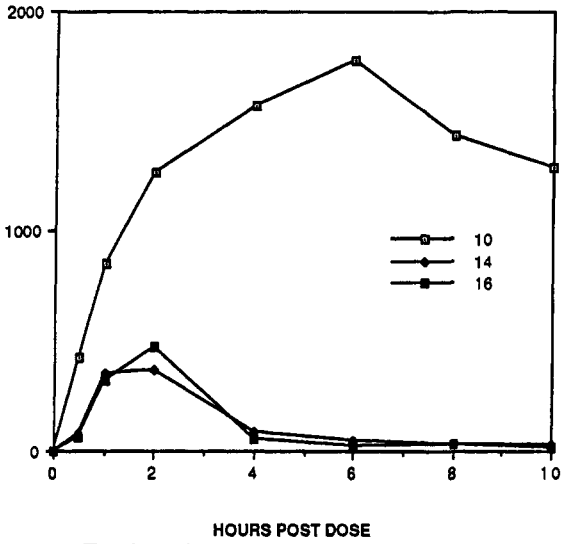

Figure 2. Total inhibitors in plasma.

potencies similar to that of **1a**. In contrast to the results presented for **9α** and **9β** vide supra, the 6β-methyl epimer **14** was more effective than the 6α-methyl epimer **16** and as effective as **1a** in inhibiting cholesterol biosynthesis. Although compounds **18**, **20**, and **24** were the most potent analogues in this series in vitro, they were demonstrably less effective than lovastatin in vivo. Derivative **24**, the most potent in vivo of the three, was equipotent to the parent 5α-hydroxy compound **16**.

Since compounds **10**, **14**, and **16** also displayed oral activity in the dog model utilizing lovastatin **1a** as a control (see Table III), their plasma drug activity levels, in dogs, were determined.[14] Compounds that exhibit low peripheral plasma drug activity levels may display minimal, pharmacologically related side effects since the major site of cholesterol biosynthesis is the liver. Mean plasma concentrations of inhibitory equivalents for compounds **10**, **14**, and **16** from 0 to 10 h are post dose, displayed graphically in Figure 2. Peak inhibitory concentration (PIC) and area-under-the-curve (AUC) values were much greater for the 6-methyl-5-oxa derivative **10** than for the 5α-hydroxy derivatives **14** and **16**. Although compounds **14** and **16** are epimeric at C-6, their PIC and AUC values are quite similar.

In contrast, the metabolic profiles of these three compounds were quite different. Plasma samples were base treated, to convert any remaining lactone to the active dihydroxy carboxylic acid, and then fractionated on a reverse-phase column. Fractions were collected at a rate of 4 per minute, neutralized, and assayed for HMG-CoA reductase inhibitory activity.[14] For compound **10**, only one peak of inhibitory activity was evident in a plasma sample taken 4 h post dose. The retention time of this peak was identical with that of the dihydroxy carboxylic acid form of **10**. It appears that disubstitution at C-6, a major site of metabolism in simvastatin, can block this event in the 5-oxa series.

The 5α-hydroxy derivatives **14** and **16** displayed disparate metabolic profiles. Plasma taken 2 h after dosing with the 6α-methyl epimer **16**, which possesses the same stereochemistry at C-6 as lovastatin and simvastatin, contained a single major active metabolite along with a small amount of unchanged drug. However, in the case of the 6β-methyl epimer **14**, unchanged **14** (or the corresponding ring-opened form) was the major prodrug (or active) compound in the plasma 2 h post dose; in addition, a small amount of a faster eluting metabolite was present. The absolute concentration of these metabolites was not determined since their structures were not known. This data demonstrates that in dogs the profile of pharmacologically active metabolites of **14** and **16** in plasma is a function of C-6 stereochemistry.

In summary, two series of compounds, 5-oxygenated and 5-oxa derivatives, were prepared from simvastatin and evaluated in vitro for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and acutely in vivo for oral effectiveness as inhibitors of cholesterogenesis in the rat. Of the compounds selected for further biological evaluation, the 6β-methyl-5-oxa **10** and 5α-hydroxy **16** derivatives of simvastatin, as well as, the 6β-epimer **14** of **16** proved orally active as hypocholesterolemic agents in cholestyramine-primed dogs. Subsequent acute, oral metabolism studies in dogs demonstrated that compounds **14** and **16** evoke lower peak plasma drug activity and area-under-the-curve values than does compound **10** and led to the selection of **14** and **16** for toxicological evaluation. In addition, the disparate metabolic profiles of these analogues was dictated by the stereochemistry or substitution at C-6.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded in $CDCl_3$, unless noted otherwise, on a Varian EM360 spectrometer. Chemical shifts are reported in parts per million relative to TMS as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise. All starting materials were commercially available, unless indicated otherwise.

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-1,2,3,4,6,7,8,8a(*R*)-octahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (3). Nitrogen was bubbled through a solution of 50% toluene in absolute ethanol (300 mL) for 5 min. Wilkinson's catalyst (5.0 g, 33% wt) was added to the solvent and the mixture reduced at room temperature under 50 psi H_2 for 1 h. Simvastatin **2** (15 g, 36 mmol) was added and the resulting pale yellow solution reduced at room temperature under H_2 (60 psi) for 40 h. The mixture was concentrated and the residue heated in toluene (700 mL) at 60 °C in the presence of thiourea (5.0 g, 64 mmol) for 1.5 h. The mixture was cooled to 0 °C (ice bath), filtered, and concentrated. The residue was diluted with 50% EtOAc/hexanes and passed through a pad of silica to give **3** (12.0 g, 80%) as a beige solid: mp 128–129 °C (ethyl acetate/hexanes); TLC R_f = 0.65 (EtOAc); ^1H NMR ($CDCl_3$) δ 5.36 (bs, 1 H), 5.30 (m, 1 H), 4.58 (m, 1 H), 4.33 (m, 1 H), 2.68 (dd, J = 17 and 5 Hz, 1 H), 2.68 (m, 1 H), 2.59 (dd, J = 17 and 4 Hz, 1 H), 2.20–1.20 (m), 1.13 (s, 3 H), 1.12 (s, 3 H), 1.05 (d, J = 7 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[6(*R*)-[1(*S*)-[(2,2-Dimethylbutyryl)oxy]-4-hydroxy-3(*R*)-methylbutyl]-2(*S*)-methyl-5(*R*)-hydroxycyclohexyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (4). Ozone was bubbled through a bright red solution of olefin **3** (10 g, 23 mmol), Sudan III (10 mg), and methanol (200 mL) at −78 °C until the red color dissipated (20 min), followed immediately by bubbling argon through the solution for 2 min to remove excess ozone. Addition of zinc (3 g) and HOAc (6 mL), followed by removal of the cooling bath, produced the aldehyde/ketone after 20 min. TLC (EtOAc): ozonide R_f = 0.58; aldehyde/ketone R_f = 0.53). The reaction mixture was filtered to remove excess zinc and most of the solvent from the filtrate was evaporated. The residue was diluted with EtOAc, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Residual HOAc was removed azeotropically with toluene (200 mL). The aldehyde/ketone was then dissolved in THF/H_2O (10:1, 220 mL) and cooled to 0 °C (ice bath). $NaBH_4$ (2.0 g, 53 mmol) was added to the mixture in four portions at 15-min intervals. After

(14) Personal communication from Stubbs, R. J.; Schwartz, M. S., Merck Sharp and Dohme Research Laboratories, West Point, PA.

an additional 15 min, the reaction mixture was diluted with EtOAc, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, EtOAc) gave 4 (6.5 g, 14 mmol) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.55 (m, 1 H), 4.72 (m, 1 H), 4.38 (m, 1 H), 3.61 (dd, J = 11 and 4 Hz, 1 H), 3.44 (dd, J = 11 and 5 Hz, 1 H), 3.39 (m, 1 H), 2.73 (dd, J = 11 and 4 Hz, 1 H), 2.63 (m, 1 H), 2.01–1.20 (m), 1.15 (s, 6 H), 0.96 (d, J = 4 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[6(*R*)-[1(*S*)-[(2,2-Dimethylbutyryl)oxy]-3(*R*)-methyl-4-iodobutyl]-2(*S*)-methyl-5(*R*)-hydroxycyclohexyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5). A stirred mixture of the triol 4 (3.5 g, 7.7 mmol), triphenylphosphine (2.2 g, 8.5 mmol), imidazole (0.8 g, 11.6 mmol), and dry acetonitrile (77 mL) at 0 °C (ice bath) was treated in one portion with iodine (2.2 g, 8.5 mmol). After 10 min the cooling bath was removed and the orange solution stirred for 16 h. The reaction mixture was diluted with ether, washed sequentially with 10% Na_2SO_3, H_2O (2×), and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave the iodide 5 (3.5 g, 81%) as a colorless oil: TLC R_f = 0.54 (EtOAc); ^1H NMR ($CDCl_3$), δ 5.44 (m, 1 H), 4.68 (m, 1 H), 4.37 (m, 1 H), 3.40 (m, 1 H), 3.32 (dd, J = 15 and 5 Hz, 1 H), 3.25 (dd, J = 15 and 3 Hz, 1 H), 2.70 (dd, J = 17 and 4 Hz, 1 H), 2.61 (m, 1 H), 2.00–1.28 (m), 1.13 (s, 6 H), 0.98 (d, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[6(*R*)-[1(*S*)-[(2,2-Dimethylbutyryl)oxy]-3(*R*)-methyl-4-[(*o*-nitrophenyl)seleno]butyl]-2(*S*)-methyl-5-(*R*)-hydroxycyclohexyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6). A stirred solution of iodide 5 (4.2 g, 7.3 mmol), (*o*-nitrophenyl) selenocyanate (2.6 g, 11.4 mmol), and dry DMF (30 mL) was purged (3×) with argon after evacuation via the water aspirator. The solution was then cooled to 0 °C (ice bath) and treated in one portion with $NaBH_4$ (440 mg, 11.4 mmol). After 5 min the cooling bath was removed and the bright red reaction mixture stirred for 1.5 h. The reaction mixture was then recooled to 0 °C, diluted with EtOAc and H_2O, and stirred for 5 min. The organic portion was separated in an addition funnel, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 8% acetone/CH_2Cl_2) gave the selenide 6 (3.8 g, 79%) as a yellow oil: TLC R_f = 0.50 (EtOAc); ^1H NMR ($CDCl_3$) δ 8.23 (m, 1 H), 7.54 (m, 2 H), 7.28 (m, 1 H), 5.60 (m, 1 H), 4.67 (m, 1 H), 4.38 (m, 1 H), 3.35 (m, 1 H), 3.05 (dd, J = 15 and 5 Hz, 1 H), 2.80 (dd, J = 15 and 6 Hz, 1 H), 2.73 (dd, J = 17 and 5 Hz, 1 H), 2.61 (m, 1 H), 2.00–1.30 (m), 1.55 (s, 3 H), 1.54 (d, J = 7 Hz, 3 H), 0.81 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[6(*R*)-[1(*S*)-[(2,2-Dimethylbutyryl)oxy]-3-methyl-3-butenyl]-2(*S*)-methyl-5(*R*)-hydroxycyclohexyl-1-(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (7). A stirred solution of selenide 6 (3.8 g, 5.8 mmol), THF (50 mL), and 30% hydrogen peroxide (1.8 mL), 17.5 mmol) was heated at 45 °C for 4 h. The cooled reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 25% to 30% acetone/hexane) furnished olefin 7 (2.0 g, 79%) as a beige oil: TLC R_f = 0.60 (5% CH_3OH/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.48 (m, 1 H), 4.78 (d, J = 5 Hz, 2 H), 4.70 (m, 1 H), 4.40 (m, 1 H), 3.43 (m, 1 H), 2.74 (dd, J = 16 and 5 Hz, 1 H), 2.64 (m, 1 H), 2.55–2.27 (m, 2 H), 2.05–1.24 (m), 1.15 (s, 6 H), 0.86 (d, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5-oxa-6(*S*)-(iodomethyl)-1,2,3,4,4a(*R*),7,8,8a(*R*)-octahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one and 6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-5-oxa-6(*R*)-(iodomethyl)-1,2,3,4,4a(*R*),7,8,8a(*R*)-octahydronaphthyl-1(*S*)]-ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (8). A stirred heterogeneous mixture of olefin 7 (550 mg, 1.3 mmol), $NaHCO_3$ (430 mg, 5.0 mmol), and dry dichloromethane (10 mL) at 0 °C was treated with iodine (640 mg, 2.5 mmol) in one portion. After 30 min the reaction mixture was diluted with ether, washed with 10% Na_2SO_3, H_2O, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 10% acetone/CH_2Cl_2) afforded a 1:1 mixture of iodides 8 (450 mg, 63%) as a colorless oil: TLC R_f = 0.48, 0.44 (5% 2-propanol/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.20 (m, 1 H), 4.58 (m, 1 H), 4.35 (m, 1 H), 3.79 (d, J = 9 Hz, 0.5 H), 3.61 (m, 0.5 H), 3.34 (d, J = 9 Hz, 0.5 H), 3.20 (d, J = 11 Hz, 0.5 H), 3.15 (d, J = 11 Hz, 0.5 H), 2.71 (dd, J = 17 and 5 Hz, 1 H), 2.59 (m, 1 H), 2.30–1.1 (m), 0.84 (m, 6 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5-oxa-6(*S*)-[(phenylthio)methyl]-1,2,3,4,4a-(*R*),7,8,8a(*R*)-octahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9a) and 6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-5oxa-6(*R*)-[(phenylthio)methyl]-1,2,3,4,4a(*R*),7,8,8a(*R*)-octahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9b). A degassed solution of iodides 8 (120 mg, 0.21 mmol), thiophenol (110 mL, 1.0 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (150 mL, 1.0 mmol), and dry DMF was heated at 80 °C for 4.0 h. The cooled reaction mixture was diluted with ether, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 80% EtOAc/hexane) gave a 1:1 mixture of epimers as a colorless oil. Separation of the epimers was accomplished by preparative-plate chromatography (0.5 mm silica, 65% EtOAc/benzene) to furnish the faster moving 6α-(phenylthio)methyl epimer 9a (60 mg, 49%) and the slower moving epimer 9b (60 mg, 49%).

9a: ^1H NMR ($CDCl_3$) δ 7.40–7.10 (m, 5 H), 5.23 (bs, 1 H), 4.56 (m, 1 H), 4.34 (m, 1 H), 3.62 (m, 1 H), 3.06 (d, 1 H, J = 13 Hz), 2.95 (d, 1 H, J = 13 Hz), 2.70 (dd, 1 H, J = 15 and 5 Hz), 2.58 (dd, 1 H, J = 15 and 2 Hz), 2.14 (m, 1 H), 2.00–1.14 (m), 1.40 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H), 0.84 (d, 3 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz).

9b: ^1H NMR ($CDCl_3$) δ 7.40–7.10 (m, 5 H), 5.20 (m, 1 H), 4.56 (m, 1 H), 4.33 (m, 1 H), 3.64 (d, 1 H, J = 12 Hz), 3.48 (m, 1 H), 3.04 (d, 1 H, J = 12 Hz), 2.70 (dd, 1 H, J = 15 and 5 Hz), 2.58 (m, 1 H), 2.22–1.10 (m), 1.29 (s, 3 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 0.83 (d, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = Hz).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6,6-trimethyl-5-oxa-1,2,3,4,4a(*R*)-octahydronaphthyl-1(*S*)]-ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10). A stirred mixture of the iodides 8 (1.3 g, 2.3 mmol), tributyltin hydride (2.4 mL, 9.0 mmol), AIBN (10 mg), and deoxygenated dry toluene (11 mL) was heated at 85 °C for 2 h. The cooled reaction mixture was concentrated to dryness. The residue was then dissolved in acetonitrile and washed with hexane (4×) to remove tin products. Concentration and flash chromatography (silica, 17% acetone/hexane) gave the pyran 10 (0.84 g, 84%) as a crystalline solid: mp = 119–120 °C (ethyl acetate/hexane); TLC R_f = 0.29 (30% acetone/hexane); ^1H NMR ($CDCl_3$) δ 5.20 (m, 1 H), 4.59 (m, 1 H), 4.37 (m, 1 H), 3.63 (m, 1 H), 2.73 (dd, J = 17 and 5 Hz, 1 H), 2.61 (m, 1 H), 2.00–1.15 (m), 1.32 (s, 3 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 0.87 (d, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-1,2,3,4,6,7,8,8a(*R*)-octahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (3a). To a stirred solution of alcohol 3 (5.0 g, 11.9 mmol), imidazole (1.8 g, 26.2 mmol), and dry DMF (30 mL) at 25 °C was added *tert*-butyldimethylsilyl chloride (2.0 g, 13.0 mmol). After 4 h the reaction mixture was diluted with petroleum ether, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated to give the silyl ether 3a (6.4 g, 100%) as a colorless oil: TLC R_f = 0.70 (50% ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 5.39 (m, 1 H), 5.28 (m, 1 H), 4.57 (m, 1 H), 4.27 (m, 1 H), 2.57 (m, 2 H), 2.20–1.20 (m), 1.15 (s, 3 H), 1.14 (s, 3 H), 1.07 (d, J = 7 Hz, 3 H), 0.86 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-4a(*S*)-bromo-5(*S*)-hydroxy-1,2,3,4,5,6,7,8,8a(*R*)-nonahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (11a). To a stirred solution of olefin 3a (90 g, 0.16 mmol), DMSO (470 mL) THF (230 mL), and H_2O (9.0 mL, 0.5 mol) at 5 °C was added *N*-bromosuccinimide (NBS) (39 g, 0.22 mmol). After 1 h, the yellow reaction mixture was diluted with ether, washed with H_2O, saturated with $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) furnished the bromohydrin 11a (65 g, 61%) as a colorless oil: TLC R_f = 0.38 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 5.08 (m, 1 H), 4.54 (m, 1 H), 4.26 (m, 1 H), 4.13 (d, J = 3 Hz, 1 H), 2.63–2.48 (m, 2 H), 2.35–1.1 (m), 1.31 (d, J = 6 Hz, 3 H), 1.13 (s, 3 H), 1.12

(s, 3 H), 0.87 (s, 9 H), 0.8 (m, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5-oxo-1,2,3,4,5,6,7,8,8a(*R*)-nonahydronaphthyl-1-(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (12a). To a stirred mixture of bromohydrin 11a (2.4 g, 3.8 mmol), 4-Å sieves (2.5 g), and dry CH_2Cl_2 (19 mL) at 0 °C was added pyridinium chlorochromate (PCC) (3.2 g, 15.2 mmol). After the mixture was stirred for 30 min, the ice bath was removed and stirring was continued for 30 min. The reaction mixture was diluted with ether and filtered through a pad of silica gel into a filtration flask that contained acetic acid (0.8 mL, 14.0 mmol). Concentration at 10 °C gave the crude bromo ketone which was reduced immediately. The crude bromo ketone was dissolved in THF/HOAc (30 mL, 5:1) and the resulting solution was treated with zinc (0.74 g, 11.4 mmol) added at ambient temperature. After 1 h of vigorous stirring, the reaction mixture was diluted with ether and the excess zinc removed by filtration. The filtrate was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 15% EtOAc/hexanes) gave ketone **12a** (1.4 g, 69%) as a crystalline solid: mp 147–148 °C (ethyl acetate/hexanes); TLC R_f = 0.38 (30% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 5.31 (m, 1 H), 4.60 (m, 1 H), 4.29 (m, 1 H), 2.58 (m, 2 H), 2.24–1.20 (m), 1.24 (d, J = 7 Hz, 3 H), 1.88 (s, 3 H), 1.17 (s, 3 H), 0.89 (2, 9 H), 0.87 (d, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H), 0.06 (s, 6 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5-oxo-1,2,3,4,4a(*R*),6,7,8,8a(*R*)-nonahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (12). To a stirred solution of the ketone **12a** (21.5 g, 39 mmol) and THF (33 mL) was added a premixed solution of *tert*-butylammonium fluoride (1 M THF, 156 mL, 156 mmol) and acetic acid (10.7 mL, 188 mmol). The resulting solution was heated at 45 °C for 2 h. The cooled reaction mixture was diluted with ether, washed with H_2O (3×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 60% ethyl acetate/hexanes) gave the ketone **12** (13.5 g, 79%) as a white crystalline solid: mp = 158–159 °C (ethyl acetate/hexanes); TLC R_f = 0.37 (80% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 5.36 (m, 1 H), 4.63 (m, 1 H), 4.40 (m, 1 H), 2.78 (dd, J = 18 and 5 Hz, 1 H), 2.60 (m, 2 H), 2.20 (m, 1 H), 2.05–1.15 (m), 1.26 (d, J = 7 Hz, 3 H), 1.21 (s, 3 H), 1.20 (s, 3 H), 0.88 (t, J = 7 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-5-oxo-1,2,3,4,4a(*R*),6,7,8,8a(*R*)-nonahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (13). A stirred solution of ketone **12** (150 mg, 0.34 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (52 mL, 0.34 mmol), and dry CH_3CN was heated at 50 °C for 3 h. The cooled reaction mixture was concentrated and the residue subjected to flash chromatography (silica, 50% ethyl acetate/hexanes) to give the desired ketone **13** (98 mg, 65%) as a crystalline solid: mp = 137–138 °C (ethyl acetate/hexanes); TLC R_f = 0.54 (30% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 5.28 (m, 1 H), 4.60 (m, 1 H), 4.48 (m, 1 H), 2.74 (dd, J = 18 and 5 Hz, 1 H), 2.62 (m, 2 H), 2.47 (ddd, J = 9.9 and 3 Hz, 1 H), 2.33 (m, 1 H), 2.00–1.10 (m), 1.23 (s, 3 H), 1.22 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 0.80 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-5(*R*)-hydroxy-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (14) and 6(*R*)-[2-[8(*S*)-[(2,2-dimethylbutyryl)oxy]-2(*S*),6(*S*)-dimethyl-5(*S*)-hydroxy-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pryan-2-one (15). To a stirred solution of ketone **13** (0.97 g, 2.22 mmol) and THF (22 mL) at −15 °C was added BH_3·THF (3.3 mL, 1 M THF, 3.3 mmol) dropwise. After 30 min the reaction mixture was diluted with ether and the excess BH_3·THF quenched by dropwise addition of H_2O. The etheral portion was washed with H_2O, brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 12% acetone/benzene) gave the faster moving alcohol **14** (675 mg, 69%) as a crystalline solid and the slower moving alcohol **15** (185 mg, 19%) as a colorless foam.

14: Mp = 110–111 °C (diisopropylether); TLC R_f = 0.70 (45% acetone/benzene); ^1H NMR ($CDCl_3$) δ 5.08 (m, 1 H), 4.57 (m, 1 H), 4.36 (m, 1 H), 2.86 (ddd, J = 10, 5, and 5 Hz, 1 H), 2.61 (m, 1 H), 2.05–1.15 (m), 1.17 (s, 6 H), 1.00 (d, J = 7 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H).

15: TLC R_f = 0.63 (45% acetone/benzene); ^1H NMR ($CDCl_3$) δ 5.14 (m, 1 H), 4.59 (m, 1 H), 4.36 (m, 1 H), 3.53 (bs, 1 H), 2.74 (dd, J = 18 and 5 Hz, 1 H), 2.60 (m, 1 H), 2.20 (d, J = 3 Hz, 1 H), 2.00–1.20 (m), 1.17 (s, 3 H), 1.16 (2, 3 H), 0.95 (d, J = 7 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H), 0.84 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-hydroxy-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (16a). To a stirred solution of ketone **12a** (40.0 g, 73 mmol), THF (330 mL) and H_2O (35 mL) at 0 °C was added $NaBH_4$ (8.25 g, 0.21 mmol). After 35 min, the reaction mixture was diluted with ethyl acetate, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 20% ethyl acetate/hexanes) gave alcohol **16a** (35.4 g, 88%) as a colorless oil: TLC R_f = 0.27 (30% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 5.06 (m, 1 H), 4.60 (m, 1 H), 4.14 (m, 1 H), 3.45 (dd, J = 10 and 5 Hz, 1 H), 2.56 (m, 2 H), 2.15–1.15 (m), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.07 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.88 (t, J = 7 Hz, 3 H), 0.86 (d, J = 7 Hz, 3 H), 0.08 (s, 3 H), 0.08 (s, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-hydroxy-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (16). To a stirred solution of silyl ether **16a** (98 mg, 0.18 mmol), THF (530 mL), and HOAc (41 mL, 0.71 mmol) was added tetrabutylammonium fluoride (1 M THF, 530 mL, 0.53 mmol) at ambient temperature. After 20 h, the reaction mixture was diluted with ethyl acetate, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave diol **16** (60 mg, 77%) as a crystalline solid: mp = 142–143 °C (ethyl acetate/hexanes); TLC R_f = 0.15 (60% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$), δ 5.05 (m, 1 H), 4.54 (m, 1 H), 4.31 (m, 1 H), 3.42 (dd, J = 10 and 5 Hz, 1 H), 2.69 (dd, J = 17 and 5 Hz, 1 H), 2.57 (dd, J = 17 and 4 Hz, 1 H), 2.12–1.10 (m), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.06 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H), 0.79 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[(benzylamino)carbonyl]oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,7-tetrahydro-2*H*-pyran-2-one (17a). To a mixture of compound **16a** (227 mg, 0.41 mmol), degassed DMF (2.0 mL), and CuCl (41 mg, 0.41 mmol) at 25 °C was added benzyl isocyanate (82 mg, 0.62 mmol). After 1 h, the dark green mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 20% EtOAc/hexane) furnished compound **17a** (228 mg, 74%) as a colorless oil: TLC R_f = 0.40 (40% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.06 (m, 1 H), 4.93 (m, 1 H), 4.61 (dd, J = 10 and 5 Hz, 1 H), 4.37 (d, J = 6 Hz, 2 H), 4.25 (m, 1 H), 2.55 (m, 2 H), 2.27 (m, 1 H), 2.00–1.10 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 0.86 (s, 9 H), 0.80 (m, 9 H), 0.06 (s, 6 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[[(benzylamino)carbonyl]oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (18). The alcohol **18** was prepared from the silyl ether **17a** (80 mg, 0.11 mmol) by the same procedure used to convert **12a** to **12**: TLC R_f = 0.10 (ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.08 (m, 1 H), 5.02 (t, J = 6 Hz, 1 H), 4.59 (dd, J = 10 and 5 Hz, 1 H), 4.54 (m, 1 H), 4.34 (d, J = 6 Hz, 1 H), 2.58 (dd, J = 18 and 4 Hz, 1 H), 2.26 (m, 1 H), 2.00–1.10 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 0.82 (t, J = 7 Hz, 3 H), 0.78 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[(diphenylphosphinyl)oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (19b). To a stirred solution of **16b** (59 mg, 87 mmol), 4-(dimethylamino)pyridine (DMAP) (43 mg, 0.35 mmol), and CH_2Cl_2 (0.44 mL) at ambient temperature was added diphenylphosphinic chloride (33 mL, 0.17 mmol). After 20 min the reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 45% EtOAc/hexane) gave compound **19b** (34 mg, 321 mmol) as an oil: TLC R_f = 0.18 (50% ethyl acetate/hexanes);

^{1}H NMR ($CDCl_3$) δ 7.85–7.25 (m, 20 H), 4.98 (m, 1 H), 4.64 (m, 1 H), 4.28 (m, 2 H), 2.55 (m, 1 H), 2.39 (dd, J = 18 and 4 Hz, 1 H), 2.05–1.10 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 1.12 (d, J = 7 Hz, 3 H), 1.03 (s, 9 H), 0.81 (t, J = 7 Hz, 3 H), 0.73 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[(diphenylphosphinyl)oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (20). The alcohol **20** was prepared from the silyl ether **19b** (63 mg, 73 mmol) by the same procedure used to convert **12a** to **12**: TLC R_f = 0.10 (80% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 4 H), 7.46 (m, 6 H), 5.01 (m, 1 H), 4.54 (m, 1 H), 4.30 (m, 1 H), 4.27 (m, 1 H), 2.62 (m, 3 H), 2.10–1.10 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 1.12 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H), 0.73 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[[(dibenzylamino)carbonyl]oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (21b). A solution of **16b** (25 mg, 37 mmol), triethylamine (21 mL, 0.15 mol), and dry CH_2Cl_2 (200 mL) was added dropwise to a stirred solution of phosgene (20% in toluene, 67 mL, 0.15 mol) and CH_2Cl_2 (600 mL) at 0 °C. After 5 min the cooling bath was removed and the reaction mixture stirred for 20 min. Concentration in situ followed by sequential addition of CH_2Cl_2 (400 mL) and dibenzylamine (8 mL, 41 mmol) at ambient temperature, resulted in a heterogeneous mixture. After 15 min the reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 15–20% ethyl acetate/hexanes) gave compound **21b** (13 mg) as an oil: TLC R_f = 0.68 (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.63–7.26 (m, 20 H), 5.12 (m, 1 H), 4.75 (dd, J = 10 and 5 Hz, 1 H), 4.60 (m, 1 H), 4.40 (m, 2 H), 4.33 (m, 1 H), 2.60 (m, 2 H), 2.20–1.10 (m), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.07 (s, 9 H), 1.00 (d, J = 7 Hz, 3 H), 0.80 (m, 6 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-[[(dibenzylamino)carbonyl]oxy]-1,2,3,4,4a-(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (22). The alcohol **22** was prepared from the silyl ether **21b** (72 mg, 0.08 mmol) by the same procedure used to convert **12a** to **12**: TLC R_f = 0.10 (80% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.37–7.18 (m, 10 H), 5.11 (m, 1 H), 4.75 (dd, J = 10 and 5 Hz, 1 H), 4.59 (m, 1 H), 4.47 (m, 3 H), 4.34 (m, 1 H), 2.72 (dd, J = 18 and 5 Hz, 1 H), 2.61 (dd, J = 18 and 3 Hz, 1 H), 2.32 (m, 1 H), 2.00–1.10 (m), 1.16 (s, 3 H), 1.15 (s, 3 H), 1.00 (d, J = 7 Hz, 3 H), 0.84 (t, J = 7 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-(phenethyloxy)-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(butyldiphenylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (23b). To a stirred solution of **16b** (270 mg, 0.40 mmol), β-methoxystyrene (165 mL, 1.2 mmol), and dry CH_2Cl_2 (4 mL) at 0 °C was added (±)-camphorsulfonic acid (23 mg, 0.10 mmol). After 15 min, the cooling bath was removed and stirring continued for 3 h. The reaction was quenched with NEt_3 (195 mL, 1.2 mmol) and concentrated, and the residue was subjected to flash chromatography (silica, 15% EtOAc/hexane) to afford the intermediate enol ether. The unstable enol ether (150 mg, 0.19 mmol) was treated with 10% Pd/C (30 mg) and ethyl acetate (5.0 mL) and stirred at 25 °C under a hydrogen atmosphere (1 atm) for 8.0 h. The reaction mixture was filtered through a Celite pad and concentrated. Flash chromatography (silica, 15% ethyl acetate/hexane) gave compound **23b** (52 mg, 39%) as a colorless oil: TLC R_f = 0.39 (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.65–7.20 (m, 15 H), 5.00 (m, 1 H), 4.66 (m, 1 H), 4.23 (m, 1 H), 3.78 (m, 1 H), 3.46 (m, 1 H), 3.02 (dd, J = 10 and 4 Hz, 1 H), 2.22 (m, 1 H), 2.05–1.10 (m), 1.14 (s, 3 H), 1.08 (s, 9 H), 0.98 (d, J = 7 Hz, 3 H), 0.82 (t, J = 7 Hz, 3 H), 0.79 (d, J = 7 Hz, 3 H).

6(*R*)-[2-[8(*S*)-[(2,2-Dimethylbutyryl)oxy]-2(*S*),6(*R*)-dimethyl-5(*R*)-(phenethyloxy)-1,2,3,4,4a(*R*),5,6,7,8,8a(*R*)-decahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (24). The alcohol **24** was prepared from the silyl ether **23b** (39 mg, 50 mmol) by the same procedure used to convert **12a** to **12**: TLC R_f = 0.19 (40% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.05 (m, 1 H), 4.55 (m, 1 H), 4.32 (m, 1 H), 3.73 (m, 1 H), 3.47 (m, 1 H), 3.01 (dd, J = 10 and 5 Hz, 1 H), 2.88 (m, 2 H), 2.71 (dd, J = 18 and 5 Hz, 1 H), 2.59 (dd, J = 18 and 4 Hz, 1 H), 2.22 (m, 2 H), 2.00–1.10 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 0.99 (d, J = 7 Hz, 3 H), 0.82 (t, J = Hz, 3 H), 0.78 (d, J = 7 Hz, 3 H).

Determination of Hypocholesterolemic Activity In Cholestyramine-Primed Dogs. Male beagle dogs were fed a low cholesterol, semisynthetic diet once a day in the morning in sufficient quantity to maintain a constant body weight. The animals were trained to consume their entire ration each day. Cholestyramine (12 g) was administered daily in the diet. This amount routinely resulted in an average reduction in plasma total cholesterol of approximately 35%. Dogs were bled twice a week from the jugular vein and plasma cholesterol was determined after extraction and saponification by a colorimetric procedure (Liebermann Burchard). After the establishment of pretreatment plasma cholesterol levels, one dog each was dosed with 4 mg/kg of the test compound mixed directly into the diet for 21 days. After cessation of treatment, the dogs were immediately crossed over to 1a at the corresponding dose for an additional 2–3 weeks.

Determination of Plasma Drug Activity Levels in Dogs. A single, oral 50 mg/kg capsule dose of each compound was administered to three male dogs under fasting conditions. Plasma samples were obtained from the jugular vein at 0, 0.5, 1, 2, 4, 6, 8, 10, and 24 h post dose. Plasma samples were assayed for total inhibitors by using the HMG-CoA reductase inhibition assay.[13]

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