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 B⁶ 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 NaBH4 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_{4e} , H_{8e} of 10 Hz. The selenide 6 was obtained in 64% yield via a two step sequence by first treating triol 4 with Ph₃P/imidazole/iodine in CH₃CN 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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Scheme I. Synthesis of 5-Oxa Analogues



° (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-O₂NPhSeCN 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*-Bu₃SnH/AIBN in toluene at 80 °C produced the 6,6-dimethyl analogue 10 in 84% yield.





16b \xrightarrow{k} 23b, R=Si^BBuPh₂, R¹=CH₂CH₂Ph $\xrightarrow{\theta}$ 24, R=H, R¹=CH₂CH₂Ph

16a

16b

16b

^a (a) 'BuMe₂SiCl, imidazole, DMF; (b) 'BuPh₂SiCl, imidazole DMF; (c) NBS, THF, DMSO, H_2O ; (d) PCC, CH_2Cl_2 , and then Zn, HOAC, THF; (e) Bu₄NF, HOAc, THF; (f) DBU, CH_3CN ; (g) NaBH₄, THF, H_2O ; (h) CuCl, DMF, BnNCO; (i) Ph₂POCl, DMAP, CH₂Cl₂; (j) CH₂Cl₂, COCl₂, NEt₃, and then Bn₂NH; (k) PhCH= CHOCH₃, CSA, CH₂Cl₂ and then Pd/C, EtOAc, H₂.

The olefin 3 also was employed to prepare 5-oxygenated analogues of 2a (Scheme II). Silvlation of the hydroxyl function of 3 with either tert-butyldimethylsilyl chloride or tert-butyldiphenylsilyl chloride under standard conditions gave the silvl 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 silvl ether 12a with n-Bu₄NF/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 BH₃·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 formulaª	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	$C_{25}H_{42}O_{6} = 0.5H_{2}O$	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	C25H42O6	35	70
12	EtOAc/hexane	15 9- 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	C25H42O6	48.6	61
15		oil	$C_{25}H_{42}O_6$	269	11.1
16	EtOAc/hexane	12 9- 131	$C_{25}H_{42}O_6$	40.8	73
18		oil	C33H49O7N-1.5H2O	5	360
20		oil	C ₃₇ H ₅₁ O ₇ P·0.5H ₂ O	6	300
22		oil	C40H55O7N-0.5H2O	16	94
24		oil	C33H50O6	6	300

^aAll new compounds exhibited satisfactory microanalyses: C, H, N $\pm 0.4\%$. ^bFor estimation of relative inhibitory potencies, compactin (1b) was assigned a value of 100 and the IC₅₀ 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, NaBH₄ delivered a hydride axially to ketone 12a to furnish 16a (88%). Desilylation of 16a with n-Bu₄NF/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 NEt₃, 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 (\pm) -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-

Table II. Acute Inhibition of Cholesterol Synthesis in the Rat

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

^aPercent 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	
	1 a	38	
3	16	19	
	1a	25	

^a Percent cholesterol change from the resin-treated dog.

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

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 5 β -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 [¹⁴C]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 [¹⁴C]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⁾ $9\alpha = 6\alpha$ -PhSCH₂- and $9\beta = 6\beta$ -PhSCH₂-.

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HOURS POST DOSE 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-underthe-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 CDCl₃, 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 $\pm 0.4\%$ 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-2H-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 (CDCl₃) 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 1)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-2Hpyran-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 $H_2O(2\times)$ and brine, dried (MgSO₄), 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). NaBH₄ (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 H₂O (2×) and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, EtOAc) gave 4 (6.5 g, 14 mmol) as a colorless oil: ¹H NMR (CDCl₃) 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-2H-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% Na₂SO₃, H₂O ($2\times$), and brine, dried (MgSO₄), 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 (CDCl₃), 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 = 15and 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).

methyl-4-[(o-nitrophenyl)seleno]butyl]-2(S)-methyl-5-(R)-hydroxycyclohexyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6tetrahydro-2H-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 NaBH₄ (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 H₂O, and stirred for 5 min. The organic portion was separated in an addition funnel, washed with H_2O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 8% acetone/CH₂Cl₂) gave the selenide 6 (3.8 g, 79%) as a yellow oil: TLC $R_f = 0.50$ (EtOAc); ¹H NMR (CDČl₃) 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]-3methyl-3-butenyl]-2(S)-methyl-5(R)-hydroxycyclohexyl-1-(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-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 NaHCO₃, H₂O, and brine, dried (MgSO₄) 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% CH₃OH/CH₂Cl₂); ¹H NMR (CDCl₃) 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-2H-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-2H-pyran-2-one (8). A stirred heterogeneous mixture of olefin 7 (550 mg, 1.3 mmol), NaHCO₃ (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% Na₂SO₃, H₂O, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% acctone/CH₂Cl₂) 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/CH₂Cl₂); ¹H NMR (CDCl₃) 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-2H-pyran-2-one (9a) and 6(R)-[2-[8(S)-[(2,2-Dimethylbutyryl)oxy]-2(S),6(S)-dimethyl-50xa-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-2H-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 $H_2O(2\times)$ and brine, dried (MgSO₄), 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 (CDCl₃) 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 (CDCl₃) 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-2H-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 $(4\times)$ 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 $R_f = 0.29 (30\% \text{ acetone/hexane}); {}^{1}\text{H NMR} (\text{CDCl}_3) \delta 5.20 (m, 1)$ H), 4.59 (m, 1 H), 4.37 (m, 1 H), 3.63 (m, 1 H), 2.73 (dd, J = 17and 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-2Hpyran-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 H₂O (2×) and brine, dried (MgSO₄), 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 (CDCl₃) 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-2H-pyran-2-one (11a). To a stirred solution of olefin 3a (90 g, 0.16 mmol), DMSO (470 mL) THF (230 mL), and H₂O (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 H₂O, saturated with NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) furnished the bromohydrin 11a (65 g, 61%) as a colorless oil: TLC $R_i = 0.38$ (40% EtOAc/hexanes); ¹H NMR (CDCl₃) 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]-3,4,5,6tetrahydro-2H-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 CH₂Cl₂ (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 H₂O 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 (CDCl₃) & 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-2H-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 $H_2O(3\times)$ and brine, dried (MgSO₄), 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 (CDCl₃) 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-2H-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 CH₃CN 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 (CDCl₃) 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), 2.602 (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-2Hpyran-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-2H-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 BH₃·THF (3.3 mL, 1 M THF, 3.3 mmol) dropwise. After 30 min the reaction mixture was diluted with ether and the excess BH3. 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 (CDCl₃) 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 (CDCl₃) $\delta 5.14$ (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-2H-pyran-2-one (16a). To a stirred solution of ketone 12a (40.0 g, 73 mmol), THF (330 mL) and H₂O (35 mL) at 0 °C was added NaBH₄ (8.25 g, 0.21 mmol). After 35 min, the reaction mixture was diluted with ethyl acetate, washed with H₂O (2×) and brine, dried (MgSO₄), 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 (CDCl₃) 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-2Hpyran-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 H₂O and brine, dried (MgSO₄), 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 (CDCl₃), 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 (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-2Hpyran-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 H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 20% EtOAc/hexane) furnished compound 17a (228 mg, 74%) as a colorless oil: TLC $R_f = 0.40$ (40% Et-OAc/hexanes); ¹H NMR (CDCl₃) & 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)-[[(ben zylamino)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-2H-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 (CDCl₃) 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-2Hpyran-2-one (19b). To a stirred solution of 16b (59 mg, 87 mmol), 4-(dimethylamino)pyridine (DMAP) (43 mg, 0.35 mmol), and CH₂Cl₂ (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 H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 45% EtOAc/hexane) gave compound 19b (34 mg, 321 mmol) as an oil: TLC $R_t = 0.18$ (50% ethyl acetate/hexanes);

3-Hydroxy-3-methylglutaryl-coenzyme A Reductase

¹H NMR (CDCl₃) 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-2H-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); ¹H NMR (CDCl₃) 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 = 7Hz, 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-2Hpyran-2-one (21b). A solution of 16b (25 mg, 37 mmol), triethylamine (21 mL, 0.15 mol), and dry CH₂Cl₂ (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 CH₂Cl₂ (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 (MgSO₄), 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); ¹H NMR (CDCl₃) 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-2H-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); ¹H NMR (CDCl₃) 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-2H-pyran-2-one (23b). To a stirred solution of 16b (270 mg, 0.40 mmol), β -methoxystyrene (165 mL, 1.2 mmol), and dry CH₂Cl₂ (4 mL) at 0 °C was added

 (\pm) -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 NEt₃ (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); ¹H NMR (CDCl₃) 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-2H-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); ¹H NMR (CDCl₃) 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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