3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 9.[1] The Synthesis and Biological Evaluation of Novel Simvastatin Analogs†

George D. Hartman,*,‡ Wasyl Halczenko,‡ Mark E. Duggan,‡ Jill S. Imagire,‡ Robert L. Smith,‡ Steven M. Pitzenberger,‡ Susan L. Fitzpatrick,‡ Alfred W. Alberts,§ Rick Bostedor,§ Yu-sheng Chao,§ John I. Germershausen,§ James L. Gilfillan,§ and Vincent Hunt§

Merck Research Laboratories, West Point, Pennsylvania 19486, and Rahway, New Jersey 07065

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Substitution of hydroxy and hydroxyalkyl functionality at C-7 of the hexahydronaphthalene nucleus of simvastatin has provided novel analogs. The synthetic strategy employed epoxidation or Lewis acid-catalyzed aldol reaction of the 8-keto silyl enol ether as a key reactive intermediate. These analogs were evaluated as potential hypocholesterolemic agents via initial determination of their ability to inhibit HMG-CoA reductase in vitro. Oral activity of these compounds was determined in an acute rat model and a three-week study in cholestyramine-primed dogs. Compounds were identified that possessed in vitro and in vivo activity comparable to that of simvastatin.

Introduction

The efficacy of lovastatin (**1a**) and simvastatin (**1b**) as hypocholesterolemic agents in humans and the novelty of this chemical structural class have fueled an extraordinary outpouring of related chemical,[2] biological,[3] and clinical studies.[4] As part of our ongoing effort to develop structurally diverse, yet biologically potent, alternatives to these agents we initiated a synthetic effort to functionalize the 7-position of the hexahydronaphthalene system. This approach anticipated that modifications at C-7 might be effective in altering the metabolic lability of the C-6 position.[5] In this report we demonstrate methods that provide efficient routes to 7-hydroxy and 7-hydroxyalkyl analogs of simvastatin (**1b**), and we define the synthetic utility of key intermediates. These new methods maintain the integrity of the sensitive lactone function throughout and make efficient use of protecting groups. Finally, we report the in vitro potency of these functionalized analogs for inhibition of HMG-CoA reductase and the oral activity of selected examples in acute rat and chronic dog models.

Chemistry

Our starting point in this effort was the 8α-hydroxy lactone **2** (Scheme I), which was efficiently prepared from lovastatin (**1a**) by sequential deacylation of the 8-acyloxy substituent under basic conditions, relactonization under acidic conditions, and lactone hydroxyl silylation.[6] Oxidation of **2** with pyridinium chlorochromate in the presence of molecular sieves or, alternatively, under Swern[7] conditions provided ketone **3** in >60% yield. Interestingly, treatment of **3** at 0–10 °C with 1 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in methylene chloride provided the corresponding trimethylsilyl ketene acetal **3a** instead of the trimethylsilyl enol ether. However, treatment with a second equivalent of TMSOTf at the same temperature afforded the bis-silylation product **4** in quantitative yield. Regioselective hydrolysis at the ketene acetal function was effected by treatment of **4** with water

† This paper is dedicated to Professor Ralph Hirschmann on the occasion of his 70th birthday.

‡ West Point, Pennsylvania.

§ Rahway, New Jersey.

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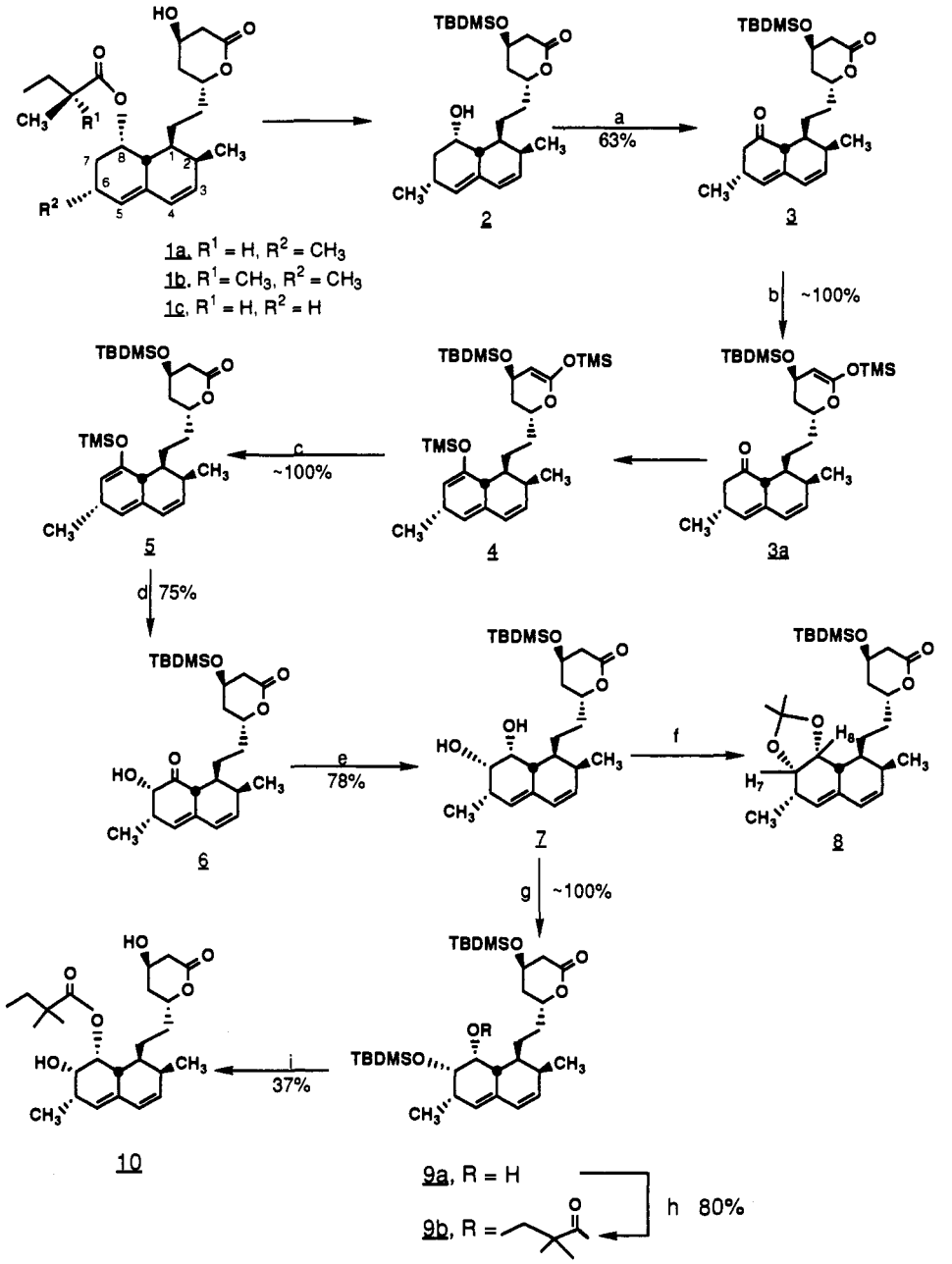
Scheme I [a]



[a] (a) PCC, CH_2Cl_2, 4-Å sieves. (b) TMSOTf, Et_3N, CH_2Cl_2, 0–23 °C, 2.5 h. (c) H_2O, 23 °C, 10 min. (d) MCPBA, EtOAc, 0 °C for 30 min and then 10% aqueous Na_2SO_3 at 0 °C for 5 min. (e) $NaBH_4$ in THF/H_2O, 0 °C, 45 min. (f) 2-Methoxypropene, PPTS. (g) *t*-$BuMe_2SiCl$, DMF, imidazole. (h) $CH_3CH_2C(CH_3)_2COCl$, LiBr, DMAP, pyridine, 80 °C. (i) 48% HF, CH_3CN, 23 °C.

for 10 min at room temperature to give the enol ether **5** in quantitative yield. Treatment of **5** with *m*-chloroperoxybenzoic acid (MCPBA) followed by acidic workup[8] provided the α-hydroxy ketone **6** in 75% isolated yield as a single stereoisomer at C-7 from α-face epoxidation. Reduction of ketone **6** with sodium borohydride ($NaBH_4$) proceeded efficiently with delivery of hydride, as expected, from the β-face to give the cis-diol **7** in 78% yield. To verify the stereochemistry at C-7 and C-8 the acetonide **8** was prepared by treatment of **7** with 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate (PPTS). The proton NMR of **8** revealed a coupling constant of 3.7 Hz between H_8 and H_{8a}, confirming the α-orientation of the C-8 hydroxyl.

Selective silylation of the less hindered C-7α (equatorial) hydroxyl group of **7** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in DMF gave the 7-silyloxy derivative **9a**. This was acylated at the C-8 hydroxyl with 2,2-dimethylbutanoyl chloride in pyridine containing 4-(dimethylamino)pyridine (DMAP) and lithium bromide[9] to afford the acylated bis-silyl ether **9b** in 80% yield. Treatment of **9b** with HF in acetonitrile gave the desired diol **10**.

In the course of this work we anticipated that the enol ether **5** would offer access to a variety of 7-substituted analogs.[10] However, we have found that **5** was surprisingly unreactive toward a variety of electrophilic reagents. For example, treatment of **5** with ethyl diazoacetate in the

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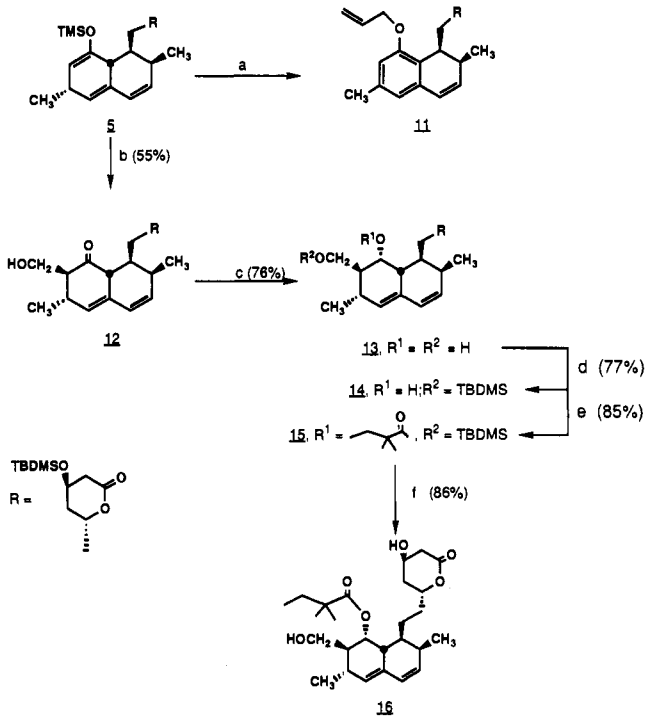
Scheme II [a]



[a] (a) Diallyl carbonate, dppe, $Pd(dba)_3$, 60 °C, THF. (b) CH_2O, $TiCl_4$, CH_2Cl_2, −78 °C. (c) $NaBH_4$, THF/H_2O, 0 °C. (d) *t*-$BuMe_2SiCl$, imidazole, DMF, 0 °C for 2 h. (e) $CH_3CH_2C(CH_3)_2COCl$, LiBr, DMAP, pyridine, 80 °C for 3 h. (f) 48% HF, CH_3CN, 25 °C for 3.5 h.

presence of Cu^{2+} salts, or with acetals and ortho esters in the presence of $TiCl_4$, $ZnBr_2$, $TrSbCl_6$, $SnCl_2$, or TMSOTf resulted either in recovery of intact **5** or, at longer reaction times, the generation of aromatic products. Similarly, treatment of **5** with an alkyl bromide in the presence of $ZnBr_2$, or with acetyl chloride in the presence of $TiCl_4$ or $ZnBr_2$, gave no reaction, while treatment with diallyl carbonate in the presence of dppe and $Pd(dba)_3$ gave the aromatized product **11** (Scheme II) in modest yield.

However, treatment of **5** with formaldehyde in the presence of $TiCl_4$[11] resulted in a facile reaction that afforded the desired hydroxymethyl ketone **12** as a single stereoisomer at C-7 in 55% yield. Unlike the epoxidation reaction of enol ether **5**, reaction with the aldehyde proceeded from the β-face to afford the C-7 axial product. The opposing results of α-face selection for **6** compared to β-face preference for **18a** are probably best explained by an increased steric hindrance on the α-face by the C-6 methyl group in the transition state for the developing secondary alcohol center of **18a**, as compared to the less sterically demanding epoxidation. This effect may be enhanced by the titanium chelation conditions of the aldol reaction. Reduction of **12** with $NaBH_4$ provided in 78% yield the trans diol **13**, which was selectively silylated with TBDMS-Cl to give **14**. Acylation under the conditions previously described, followed by HF-mediated desilylation, gave the desired hydroxymethyl lactone **16** in 73% yield from **14**.

In a similar manner treatment of **5** with acetaldehyde (Scheme III) afforded, by NMR analysis of the crude reaction mixture, a 10/1 mixture of diastereoisomers **18a** and **18b**, respectively. The main product **18a** was derived from axial (β-face) attack on **5** via a transition state, depicted as **17a**, in which the acetaldehyde methyl group was syn to the 6α-methyl function.

Efforts to elaborate **18a** and **18b** into 8-acyloxy derivatives as already described for **12** proved problematic. Attempted reduction of **18a** with $NaBH_4$ resulted in recovery of starting material due to the enhanced β-face hindrance of the hydroxyethyl function. Selective reduction of the hindered ketone function of **18a** required reactivity in excess of that of $Na(OAc)_3BH$ and $(C_2H_5)_3B/NaBH_4$, both of which proved unreactive. After numerous unsuccessful attempts, we found that addition of **18a** to the suspension prepared from the treatment of sodium borohydride with palladium chloride[12-14] in THF at −40 °C resulted in chemo- and stereoselective ketone reduction to give **20** in 62% yield. Treatment of **18a** with $NaBH_4/PdCl_2$ at 10–35 °C afforded product mixtures that contained, in addition to **20**, the compound **28** derived from reduction of the C-3,4 double bond. The olefin reducing capability for this combination of reagents has been noted previously.[15] Clearly, the temperature dependence of the reduction selectivities suggests varied synthetic applications. In addition, the chemoselectivity of the reagent very nicely compliments that of the $NaBH_4$–Cu_2Cl_2/CH_3OH and $NaBH_4$–$CoCl_2/CH_3OH$[16] systems, which effect reduction of α,β-unsaturated esters but not of isolated olefins.

Silylation of the exocyclic hydroxyl function of **20** was effected to give **21** in 85% yield with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in CH_2Cl_2-containing lutidine, since treatment with TBDMS chloride afforded incomplete reaction. In similar fashion to **14**, **21** was acylated in 75% yield with 2,2-dimethylbutanoyl chloride and desilylated in 72% yield to give **25**.

The final analog **27** was prepared by initial treatment of **5** with benzaldehyde in the presence of titanium tetrachloride. This reaction provided adduct **19** in 32% yield as a single stereoisomer possessing the same relative configuration as in **18a**. Reduction of **19** with $NaBH_4/PdCl_2$ proceeded efficiently from the β-face to provide **22** in 57% yield. Silylation to give **23**, followed by acylation and desilylation under conditions described previously for **21** resulted in the desired benzhydrol compound **27**.

Results and Discussion

Compounds **10**, **16**, **25**, and **27** were evaluated as the sodium salts of the dihydroxy acid form as in vitro inhibitors of HMG-CoA reductase[3] (Table III). The most potent of the four new compounds prepared in this study was the 7-(*S*)-hydroxyethyl analog **25**, which was approximately 1.6-fold more potent than simvastatin (**1b**). In

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Table I. Proton Chemical Shift Assignments (in $CDCl_3$)

proton(s)	chemical shifts, ppm			
	18a	18b	25	29
1	~2.02	2.00	~1.70	~1.72
2	2.41	~2.40	~2.36	2.37
2-Me	0.93	0.91	0.90	0.88
3	5.81	5.84	5.79	5.78
4	5.98	5.98	5.98	6.00
5	5.43	5.48	5.43	5.50
6	2.80	2.78	2.08	2.55
6-Me	1.15	1.16	~1.11	1.15
7	~2.06	2.20	~1.74	~1.74
8			5.72	5.31
8a	3.09	2.88	2.39	2.25
9	~1.48,~1.65	~1.49,~1.70	~1.38,~1.50	~1.40,~1.45
10	~1.53,~1.77	~1.53,~1.77	~1.30,~1.90	~1.27,1.88
11	4.64	4.62	4.63	4.62
12	~1.70,1.86	~1.66,1.88	~1.70,2.00	~1.72,1.98
13	4.29	4.29	4.37	4.39
14	~2.61,~2.54	2.62,~2.55	2.74,2.62	2.76,2.63
15	4.06	4.05	3.57	3.72
16	1.35	1.26	1.32	1.32
17,18			-1.12	1.13
19			~1.55	~1.56
20			0.83	0.83
TBDMS	0.88,0.07,0.06	0.88,0.08		

Table II. NOE Data for 25 and 29

compd	proton(s) irradiated	NOEs observed
25	15	H-6 (s), CH_3-16 (m), H-8a (m), H-8 (w), H-7 (?*w)
	16,10a	H-6 (m), H-10b (m), H-8a (vw), H-8 (vw)
	6-Me,17,18	H-5 (m), H-6 (m), H-7 (w)
29	15	CH_3-16 (m), H-8a (m), H-6 (w), H-8 (w), H-7 (?*w)
	16,10a	H-15 (m), H-10b (m), H-9 (m), H-7 (w), H-6 (w), H-8 (w), H-8a (w)
	6-Me,17,18	H-6 (m), H-5 (m), H-7 (m), H-20 (m), H-19 (m)
	8a	H-15 (m), H-8 (m), H-9 (w)

* Partially obscured by the water resonance.

addition, 10 and 16 were found to be comparable in potency to 1b, while 27 was somewhat less active. The enhanced potency of 25 compared to 1b in this assay suggests that the normal potency enhancing interactions of both the endo C-6 methyl group and the endo C-8 acyloxy substituent are kept intact and that a new favorable interaction is now additionally made by the C-7 hydroxyethyl function. This new interaction may be polar in nature from differential hydrogen bonding effects of the hydroxyl, or may be the result of favorable hydrophobic interactions of the alkyl chain. The 2.6-fold loss in potency for benzyl alcohol 27, as compared to 25, is taken to mean either that the requisite hydrogen bonding alignments are not energetically achievable, or conversely, that the hydrophobic pocket that was available to the ethyl chain of 25 was not of appropriate dimension to accept the phenyl group of 27. Interestingly, the 1.6-fold increase in potency between 1b and 25, which is due to the presence of the C-7 hydroxyethyl group, is similar to the potency enhancement seen when the endo C-6 methyl group of 1a is introduced into compactin (1c). Overall, the ability of the hexahydronaphthalene nucleus to productively orientate the potency enhancing C-6 methyl, C-8 acyloxy, and C-7 hydroxyalkyl groups affords configurationally defined inhibitors that display excellent in vitro activity.

The initial appraisal of acute oral activity of each new compound was made in the rat[3] following a single 0.45 mg/kg dose of inhibitor (Table III). In this model, as a measure of cholesterol synthesis, the incorporation of [^{14}C]-acetate into cholesterol was monitored 1 h postdosing. The most potent compound in this protocol proved to be the 7β-hydroxymethyl analog 16, which inhibited [^{14}C]-acetate incorporation by 69%, a level which was comparable to that of lovastatin (1a) and simvastatin (1b). Oral activity was also seen in this protocol for 10 (45% inhibition), while 27 and 25, the most potent in vitro inhibitor, showed modest activity. Further appraisal of oral activity was made in the cholestyramine-primed dog model[17] in which dogs were dosed orally once daily at 4 mg/kg with each test compound for 21 consecutive days. Plasma cholesterol was then monitored at set time points. In this protocol the 7β-hydroxy derivative 10, along with 25 and 27, proved to be orally efficacious, causing 30–40% decreases in plasma cholesterol. This depression of plasma cholesterol is somewhat less than that seen for 1a and 1b at a comparable dose. Surprisingly 16, which showed significant activity po in the rat, produced virtually no change in plasma cholesterol in the dog. Unless absorption characteristics of 16 have changed dramatically from other compounds in this class, it seems likely that presystemic metabolism, i.e. a first-pass effect, is responsible for the unexpected lack of oral activity for 16.

In summary, a series of novel 7-substituted simvastatin derivatives was prepared and evaluated in vitro for inhibition of HMG-CoA reductase and in vivo for cholesterol lowering potential in the rat and dog post po dosing. Hydroxyethyl derivative 25 was more potent than simvastatin (1b) when evaluated for in vitro enzyme inhibition. In an acute, po study in the rat, the 7(*S*)-hydroxymethyl derivative 16 was equipotent to 1b, while in a three-week study in cholestyramine-primed dogs, 10 was only some

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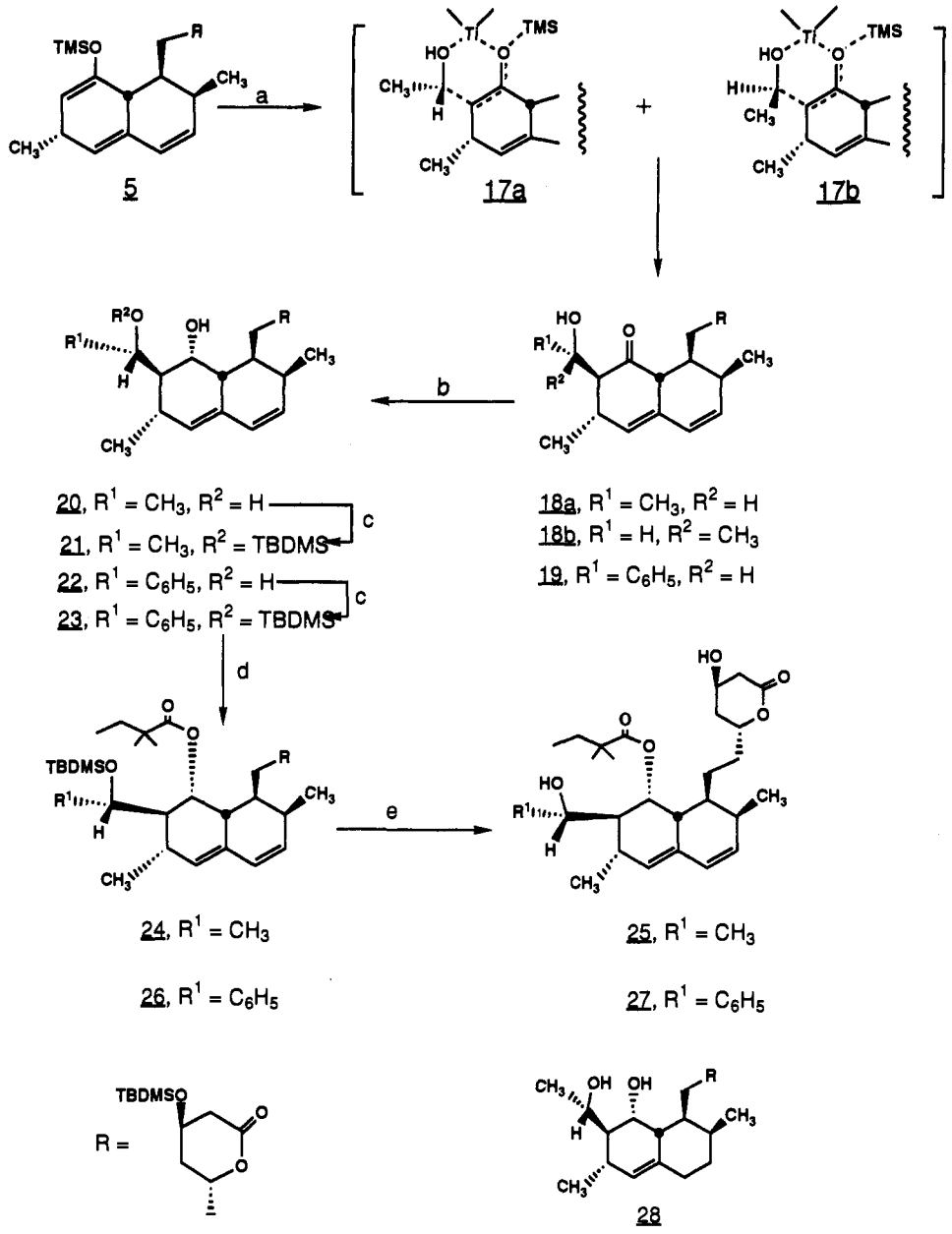
Scheme III [a]



[a] (a) CH_3CHO or C_6H_5CHO, $TiCl_4$, CH_2Cl_2, −78 to −50 °C. (b) $NaBH_4$, $PdCl_2$, THF/H_2O, −25 to −10 °C. (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C. (d) $CH_3CHC(CH_3)_2COCl$, LiBr, DMAP, pyridine, 90 °C. (e) 49% HF, CH_3CN, 23 °C.

Table III. Results for in Vitro Inhibition of HMG-CoA Reductase and Oral Efficacy

compd	recrystallization solvent	mp, °C	molecular formula[a]	IC_{50}, nM[b]	relative potency[c]	% change of [^{14}C]cholesterol (±5%)[d]	plasma cholesterol, % change[e]
1a				18.0	1.58	−55	−42
1b				12.1	2.35	−65	−60
10	EtOAc/Et_2O/hexane	138–139	$C_{25}H_{38}O_6$	13.3	2.14	−45	−36
16			$C_{26}H_{40}C_6$	10.8	2.62	−69	0
25		114–117	$C_{27}H_{42}O_6$	7.6	3.73	−28	−32
27			$C_{32}H_{44}O_6$	19.7	1.44	−25	−31

[a] All new compounds exhibited satisfactory elemental analyses: C, H (±0.4%). [b] Values for new compounds represent the average of at least three replicate determinations. [c] Potency is relative to compactin (1c) which is assigned a value of 1.0 (IC_{50} = 28.4 nM). [d] Acute inhibition of cholesterol synthesis in the rat post po administration of test compound at 0.45 mg/kg. [e] Cholestyramine-primed dogs were treated at 4 mg/kg per day for 21 days and were then crossed over to 1a for 21 days.

what less active at lowering plasma cholesterol than was **1b**.

Overall, new analogs have been discovered that express appropriate profiles in vitro as HMG-CoA reductase inhibitors and in vivo activity as hypocholesterolemic agents and whose metabolic patterns and plasma drug activity levels are subjects for future study.

Experimental Section

General Procedures. Reagents and solvents were purchased from commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon or nitrogen. Silica gel (230–400 mesh) was used for column chromatography and silica gel (Analtech) plates for

analytical thin-layer chromatography. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-300 (300 MHz) spectrometer and chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on an LKB-9000S mass spectrometer at 70 eV. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad peak.

6(*R*)-[2-[8-Oxo-2(*S*),6(*R*)-dimethyl-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (3). Method A. To a stirred mixture of alcohol **2** (15.0 g, 34 mmol), crushed 4-Å sieves (~5.0 g), and CH_2Cl_2 (185 mL) at 0 °C was added pyridinium chlorochromate (23.9 g, 0.11 mol). After 5 min the cooling bath was removed and the reaction was stirred for an additional 30 min. The reaction mixture was diluted with ether and filtered through a pad of silica, and the filtrate was concentrated. Flash chromatography (silica, 15–20% ethyl acetate/hexanes) gave **3** (9.4 g, 63%) as a crystalline solid, mp 71–74 °C.

Method B. To a stirred solution of oxalyl chloride (13.1 g, 9.0 mL, 0.10 mol) and CH_2Cl_2 (400 mL) at −78 °C was added dimethyl sulfoxide (10.8 g, 9.8 mL, 0.14 mol) dropwise over a 5-min period. After gas evolution ceased, alcohol **2** (30.0 g, 69 mmol) in CH_2Cl_2 (100 mL) was added in a slow stream over a 2-min period followed by continued stirring at −78 °C for 30 min. Triethylamine (27.6 g, 38.0 mL, 0.28 mol) was next added dropwise over a 5-min period followed by removal of the cooling bath and continued stirring for 20 min. The reaction mixture was diluted with ethyl acetate, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated to furnish ketone **3** (30.0 g, ca. quantitative) as a beige oil: TLC (silica) R_f = 0.50 (30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, J = 9.8 Hz, 1 H), 5.76 (dd, J = 9.8 and 5.9 Hz, 1 H), 5.47 (bs, 1 H), 4.59 (m, 1 H), 4.23 (m, 1 H), 2.80 (m, 2 H), 2.55 (m, 3 H), 2.35 (m, 1 H), 2.03 (dd, J = 14 and 9 Hz, 1 H), 1.95–1.40 (m), 1.07 (d, J = 7 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H), 0.83 (s, 9 H), 0.03 (s, 6 H); MS m/z = 432.

6(*R*)-[2-[8-[(Trimethylsilyl)oxy]-2(*S*),6(S)-dimethyl-1,2,6,-8a(*R*)-tetrahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyranone (5). To a stirred solution of ketone **3** (24.0 g, 56 mmol), triethylamine (29.8 g, 41.1 mL, 0.29 mol), and CH_2Cl_2 (300 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (26.3 g, 22.9 mL, 0.12 mol) portionwise over a 5-min period. After 30 min the cooling bath was removed and H_2O (50 mL) was added to the reaction mixture. After stirring for 5 min the reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 12% ethyl acetate/hexanes) furnished **5** (26.0 g, 92%) as a colorless oil. TLC (silica) R_f = 0.46 (20% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.61 (dd, J = 10 and 5 Hz, 1 H), 5.32 (m, 1 H), 4.84 (dd, J = 4 and 1 Hz, 1 H), 4.62 (m, 1 H), 4.27 (m, 1 H), 0.90 (m, 1 H), 2.63–2.52 (m, 3 H), 2.30 (m, 1 H), 1.95–1.45 (m), 1.01 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.85 (s, 9 H), 0.16 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); MS m/z = 504.

6(*R*)-[2-[8-Oxo-2(*S*),6(*S*)-dimethyl-7(*S*)-hydroxy-1,2,6,7,8,8a-(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6). To stirred solution of silyl enol ether **5** (25.0 g, 49 mmol) and ethyl acetate (500 mL) at 0 °C was added 55% *m*-CPBA (17.1 g, 54 mmol). After 30 min 10% Na_2SO_3 (250 mL) was added to the reaction mixture followed by continued stirring at 0 °C for 5 min. The phases were separated and the organic portion was washed with 1 N HCl, H_2O, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 12% ethyl acetate/hexanes) gave alcohol **5** (16.5 g, 75%) as a foam: TLC (silica) R_f = 0.46 (40% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 1 Hz, 1 H), 5.61 (dd, J = 10 and 5 Hz, 1 H), 5.49 (m, 1 H), 4.69 (dd, J = 6 and 6 Hz, 1 H), 4.62 (m, 1 H), 4.27 (m, 1 H), 3.28 (bd, J = 11 Hz, 1 H), 3.16 (m, 1 H), 2.58 (m, 2 H), 2.38 (m, 1 H), 2.20–1.30 (m), 0.91 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.83 (d, J = 7 Hz, 3 H), 0.04 (s, 6 H); MS m/z = 448.

6(*R*)-[2-[8(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-hydroxy-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (7). To a stirred solution of ketone **6** (20.0 g, 45 mmol), THF (400 mL), and H_2O (45 mL) at 0 °C was added $NaBH_4$ (5.1 g, 0.13 mol) in two portions. After 45 min the reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 40% ethyl acetate/hexanes) gave diol **7** (15.6 g, 78%) as a colorless oil: TLC (silica) R_f = 0.69 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.80 (dd, J = 10 and 5 Hz, 1 H), 5.51 (m, 1 H), 4.69 (m, 1 H), 4.30 (m, 1 H), 4.16 (m, 1 H), 3.90 (m, J = 7, 7 and 2 Hz, 1 H), 2.69 (m, 1 H), 2.60 (m, 2 H), 2.39 (m, 1 H), 2.30 (d, 7 Hz, 1 H), 2.27 (m, 1 H), 1.95–1.40 (m), 1.16 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS m/z = 450.

6(*R*)-[2-[7(*S*),8(*R*)-(Isopropylidenedioxy)-2(*S*),6(*S*)-dimethyl-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4-(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (8). To a stirred solution of **7** (20 mg, 0.04 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.22 μmol) in methylene chloride (0.5 mL) was added 2-methoxy-2-propene (5.3 μmol) at 25 °C. After 1.5 h the reaction mixture was diluted with ether, washed with water and brine, and dried ($MgSO_4$), and the organic phase was concentrated. Analysis by TLC showed that **7** was completely consumed, and a single less polar spot **8** was present: R_f of **7** was 0.2 and R_f of **8** was 0.8 on silica gel eluting with hexane(55)/ethyl acetate(45): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (6 H, S), 0.88 (3 H, d, J = 7 Hz), 0.90 (9 H, S), 1.22 (3 H, d, J = 7 Hz), 1.31 (6 H, d), 1.45–1.90 (m), 2.00–2.15 (m), 2.37 (1 H, m), 2.61 (2 H, m), 4.32 (1 H, m), 4.37 (1 H, dd, J = 6 Hz, 6 Hz, H_7), 4.63 (1 H, dd, J = 6.5 Hz, H_8), 4.61 (1 H, m), 5.34 (1 H, bs, H5), 5.90 (1 H, m, Hz), 6.09 (1 H, d, J = 12 Hz); MS m/z = 490.

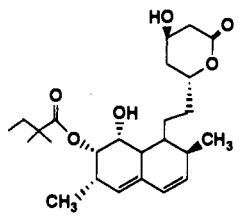
6(*R*)-[2-[8(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[(*tert*-butyldimethylsilyl)oxy]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1-(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9a). To a stirred solution of diol **7** (5.8 g, 13 mmol), imidazole (1.8 g, 2.7 mmol), and DMF (43 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (2.0 g, 14 mmol). After 30 min the cooling bath was removed and stirring was continued overnight. After 20 h the reaction mixture was diluted with hexane, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 15% ethyl acetate/hexanes) gave **9a** (7.3 g, quantitative) as a colorless oil: TLC (silica) R_f = 0.69 (30% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.79 (dd, J = 1 and 5 Hz, 1 H), 5.50 (m, 1 H), 4.65 (m, 1 H), 4.28 (m, 1 H), 4.00 (bs, 1 H), 3.90 (m, 1 H), 2.60 (m, 2 H), 2.50 (m, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 2.00–1.40 (m), 1.16 (dd, J = 7 Hz, 3 H), 0.92 (s, 9 H), 0.9 (d, J = 7 Hz, 3 H), 0.86 (s, 9 H), 0.08 (s, 6 H), 0.04 (s, 6 H); MS m/z = 564.

6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[(*tert*-butyldimethylsilyl)oxy]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9b). To a stirred mixture of alcohol **9a** (0.94 g, 1.7 mmol), anhydrous LiBr (0.72 g, 8.3 mmol; dried at 125 °C for 16 h at 0.05 mmHg), 4-(dimethylamino)pyridine (30 mg, 0.2 mmol), and pyridine (2.0 mL) at 25 °C was added 2,2-dimethylbutanoyl chloride (0.52 g, 0.57 mL, 4.1 mmol) followed by heating at 80 °C for 3.0 h. The cooled reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, 10% ethyl acetate/hexanes) gave ester **9b** (0.88 g, 80%) as a colorless oil: TLC (silica) R_f = 0.42 (20% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.78 (dd, J = 10 and 5 Hz, 1 H), 5.53 (m, 1 H), 4.60 (m, 1 H), 4.29 (m, 1 H), 4.03 (dd, J = 7 and 2 Hz, 3 H), 2.70–2.30 (m), 2.00–1.20 (m), 1.14 (d, J = 7 Hz, 3 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 0.93 (d, J = 7 Hz, 3 H), 0.90 (s, 18 H), 0.89 (t, J = 7 Hz, 3 H), 0.10 (s, 9 H), 0.10 (s, 3 H); MS m/z = 662.

6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-hydroxy-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10). To a vigorously stirred solution of bis-silyl ether **9b** (4.7 g, 7.1 mmol) and acetonitrile (70 mL), in a plastic container, at 25 °C was added 48% HF (30 mL, 71 mmol). After 30 min additional 48% HF (5.0 mL) was added. After 30 min the reaction mixture was carefully poured into a vigorously stirred mixture

of saturated $NaHCO_3$ and ether. When gas evolution subsided the organic portion was washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 70% ethyl acetate/hexanes) gave diol **10** as a foam. This product was crystallized from ethyl acetate/ether/hexanes to give **10** (1.2 g, 37%) as a colorless powder: mp = 138–139 °C; TLC (silica) R_f = 0.15 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 10 Hz, 1 H), 5.82 (dd, J = 10 and 6 Hz, 1 H), 5.68 (m, 1 H), 5.47 (m, 1 H), 4.65 (m, 1 H), 4.42 (m, 1 H), 4.17 (m, 1 H), 3.06 (d, J = 4 Hz, 1 H), 2.77 (dd, J = 17 and 5 Hz, 1 H), 2.70 (m, 1 H), 2.67 (m, 1 H), 2.49 (m, 1 H), 2.40 (m, 1 H), 2.05–1.27 (m), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.12 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 0.89 (s, 3 H). Anal. Calcd for ($C_{25}H_{38}O_6$) C: calcd 69.10; found 69.55. H: calcd 8.81; found, 8.88.

Comments: Approximately 5% of the transacylated product **10a** is formed under these conditions, however, recrystallization easily removes this undesired product. The 7-*tert*-butyldimethylsilyl protecting group is very difficult to remove. When the bis-silyl ether **9b** was heated in THF at 55 °C in the presence of tetrabutylammonium fluoride/acetic acid (1:1) for 20 h only the silyl ether on the lactone was cleaved.



10a

6(*R*)-[2-[8-Oxo-2(*S*),6(*S*)-dimethyl-7(*S*)-(hydroxymethyl)-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (12). Into a stirred solution of silyl enol ether **5** (26.0 g, 51 mmol) in CH_2Cl_2 (550 mL) at −78 °C was bubbled formaldehyde gas generated by heating a flask containing paraformaldehyde (20 g) and phosphorus pentoxide (5 g) gently with a bunsen burner until gas evolution ceased. $TiCl_4$ (6.2 mL, 56 mmol) was then added dropwise, resulting in the formation of an orange heterogeneous mixture. After addition was complete the reaction mixture was stirred for 45 min at −78 °C. The cold solution was poured carefully into a stirred mixture of ether and saturated aqueous $NaHCO_3$ solution. The organic portion was separated and washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 30% ethyl acetate/hexanes) afforded the ketone **12** (12.9 g, 55%) as a colorless oil: TLC R_f = 0.16 (30% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 10 Hz, 1 H), 5.72 (dd, J = 10 and 6 Hz, 1 H), 5.42 (bs, 2 H), 4.57 (m, 1 H), 4.23 (m, 1 H), 3.85 (m, 1 H), 3.77 (m, 1 H), 2.73 (bd, J = 11 Hz, 1 H), 2.53 (m, 3 H), 2.35 (m, 1 H), 2.20 (m, 1 H), 2.00–1.35 (m), 1.13 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H), 0.83 (s, 9 H), 0.02 (s, 6 H); MS m/z = 462.

6(*R*)-[2-[8-(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-(hydroxymethyl)-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (13). To a stirred solution of ketone **12** (30 g, 65 mmol), THF (1.2 L), and H_2O (120 mL) at 0 °C was added $NaBH_4$ (12.2 g, 0.32 mol) in 5 portions over a 3.0-h period. The reaction mixture was diluted with ether, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 45% ethyl acetate/hexanes) gave diol **13** (26 g) as a solid. Recrystallization (ethyl acetate/hexanes) gave **13** (23.5 g, 78%) as fine needles: mp = 148–149 °C; TLC R_f = 0.33 (50% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.82 (dd, J = 10 and 6 Hz, 1 H), 5.5 (m, 1 H), 4.70 (m, 1 H), 4.31 (m, 1 H), 3.54 (m, 2 H), 2.60 (m, 2 H), 2.39 (m, 1 H), 2.25–1.45 (m), 1.25 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 0.91 (s, 9 H), 0.02 (s, 3 H), 0.02 (s, 3 H); MS m/z = 464.

6(*R*)-[2-[8-(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[(*tert*-butyldimethylsilyl)oxy]methyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (14). To a stirred solution of diol **13** (2.8 g, 6.0 mmol), imidazole (0.9 g, 13.2 mmol), and dry DMF (5.0 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (1.0 g, 6.3 mmol) in one portion. After 2.0 h the reaction mixture was diluted with hexanes, washed with H_2O (2×) and brine, dried ($MgSO_4$), and concentrated to furnish a crystalline solid. Recrystallization (ethyl acetate/hexanes) gave **14** (2.7 g, 77%) as colorless crystals: mp = 108–109 °C; TLC R_f = 0.26 (20% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 5.99 (d, J = 10 Hz, 1 H), 5.82 (dd, J = 10 and 6 Hz, 1 H), 5.50 (bs, 1 H), 4.69 (m, 1 H), 4.29 (m, 2 H), 3.47 (m, 2 H), 2.60 (m, 2 H), 2.40 (m, 1 H), 2.20–1.40 (m), 1.35 (d, J = 9 Hz, 1 H), 1.21 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 0.90 (s, 18 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 6 H); MS m/z = 578.

6(*R*)-[2-[8-(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[(*tert*-butyldimethylsilyl)oxy]-1,2,6,7,8,8a-(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (15). To a stirred heterogeneous mixture of alcohol **14** (20.0 g, 34 mmol), anhydrous LiBr (14.7 g, 0.17 mol dried at 125 °C for 16 h at 0.05 mmHg), 4-(dimethylamino)pyridine (0.62 g, 5.1 mmol), and dry pyridine (43 mL) at 25 °C was added 2,2-dimethylbutanoyl chloride (9.6 mL, 79 mmol). The resulting mixture was then stirred vigorously at 80 °C for 3.0 h. The cooled reaction mixture was diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 10% ethyl acetate/hexanes) furnished ester **15** (19.6 g, 85%) as a colorless foam: TLC R_f = 0.60 (20% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (d, J = 10 Hz, 1 H), 5.78 (dd, J = 10 and 6 Hz, 1 H), 5.45 (m, 2 H), 4.57 (m, 1 H), 4.30 (m, 1 H), 3.50 (m, 2 H), 2.57 (m, 2 H), 2.38 (m, 1 H), 2.25 (m, 1 H), 2.08 (m, 1 H), 1.95–1.25 (m), 1.14 (s, 3 H), 1.13 (s, 3 H), 1.11 (d, J = 7 Hz, 3 H), 0.90 (s, 18 H), 0.89 (d, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); MS m/z = 676.

6(*R*)-[2-[8-(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-(hydroxymethyl)-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (16). A mixture of bis-silyl ether **15** (19.6 g, 29 mmol), acetonitrile (400 mL), and 48% HF (20 mL) was stirred vigorously in a plastic container for 3.5 h at 25 °C. The reaction mixture was then carefully poured into a stirred mixture of ether and $NaHCO_3$. After gas evolution ceased, the organic portion was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 70% ethyl acetate/hexanes) gave diol **16** (11.2 g, 86%) as a colorless foam: TLC R_f = 0.24 (80% ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 10 Hz, 1 H), 5.81 (dd, J = 10 and 6 Hz, 1 H), 5.48 (m, 2 H), 4.64 (m, 1 H), 4.39 (m, 1 H), 3.58 (m, 2 H), 2.77 (dd, J = 18 and 4 Hz, 1 H), 2.65 (m, 2 H), 2.40 (m, 1 H), 2.29 (m, 1 H), 2.20–1.30 (m), 1.15 (s, 3 H), 1.14 (s, 3 H), 1.14 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.85 (t, J = 7 Hz, 3 H). Anal. ($C_{26}H_{40}O_6$) C: calcd 69.61; found 69.47. H: calcd 8.98; found 8.89.

6(*R*)-[2-[8-Oxo-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxyethyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (18a). To 60 mL of methylene chloride cooled to −78 °C under nitrogen was added 0.1565 mmol (156.5 mL of a 1.0 M solution in CH_2Cl_2) titanium chloride via syringe. To this was added freshly distilled acetaldehyde (0.66 g, 1.5 mmol) dropwise while keeping the temperature <−70 °C. After stirring for 5 min, a solution of 78.85 mg (0.156 mmol) of **5** in 200 mL of methylene chloride was added dropwise while keeping the temperature <−68 °C. After stirring for 1.5 h at −78 °C and at −50 °C for 0.5 h, the reaction mixture was quenched by the addition of 100 mL of water at −60 °C. The organic phase was separated, washed with 4 × 200-mL portions of water and 200 mL of brine, and dried over anhydrous sodium sulfate. The drying agent was filtered, and the solvent was removed on the rotary evaporator. The residue was a viscous amber oil that contained primarily three products. On silica gel eluting with hexane (80)–ethyl acetate (20), these were ketone **2** (R_f 0.65), desired adduct **18a** (R_f 0.4), and diastereomeric alcohol **18b** in an approximate ratio of 3:10:1. This mixture was carefully chromatographed on silica gel eluting with hexane (85)–ethyl acetate (15) to provide 34.5 mg (46%) of pure **18a** as a white solid, mp 75.5–70 °C; see Table I for NMR data for **18a** and **18b**; MS m/z = 476.

6(*R*)-[2-[8-(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxyethyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-

pyran-2-one (20). To a solution of 40.0 g (0.084 mol) of **18a** in 880 mL of a 10:1 mixture of tetrahydrofuran–water cooled to −40 °C was added 14.88 g (0.084 mol) of palladium chloride followed by 19.0 g (0.5 mol) of sodium borohydride in one portion. The internal reaction temperature was gradually allowed to rise to −25 °C at which point gas evolution became more vigorous. This mixture was stirred for 1.5 h as the internal temperature gradually rose to −10 °C. The reaction mixture was then diluted with 1 L of ether and 0.5 L of water while the temperature was kept at 0–10 °C. Excess borohydride was decomposed with the careful addition of 10 mL of 1 N HCl followed by stirring for 10 min. The organic phase was separated, and the aqueous phase was reextracted with 250 mL of ether. The combined organic phase was washed with 4 × 500-mL portions of water and 500 mL of brine, and then dried over anhydrous sodium sulfate. The drying agent was filtered and the solvent removed on the rotary evaporator to give a viscous residue. This was chromatographed on silica gel eluting with hexane (60)–ethyl acetate (40) to provide 2.1 g of starting ketone **18a**, R_f 0.60, and 28 g of a residue that was triturated with hexane to give 25.1 g (62%) of **20** as a white solid: mp 124–126 °C; R_f 0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (6 H, s), 0.88 (9 H, S), 0.90 (3 H, d), 1.30 (3 H, d), 1.35–2.0 (10 H, m), 2.0–2.12 (1 H, m), 2.22–2.31 (1 H, m), 2.31–2.45 (1 H, m), 2.50–2.69 (2 H, m), 3.50–3.62 (1 H, m), 4.25–4.34 (1 H, m), 4.50 (1 H, m), 4.62–4.73 (1 H, m), 5.48 (1 H, m), 5.82 (1 H, dd), 5.99 (1 H, d); MS m/z = 478.

6(*R*)-[2-[8(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-[(*tert*-butyldimethylsilyl)oxy]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (21). To a solution of 21.45 g (0.0448 mol) **20** in 300 mL of methylene chloride cooled to −10 °C under nitrogen was added 11.08 g (0.1034 mol) of 2,6-lutidine followed by 12.44 g (0.047 mol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate added dropwise. After stirring for 45 min at −10 °C the reaction was quenched by adding 100 mL of H_2O followed by 500 mL of methylene chloride. The organic phase was separated, washed with 2 × 200-mL portions of water, 4 × 200-mL portions of 1 N HCl, and 200 mL of brine, and dried over anhydrous sodium sulfate. The organic phase was filtered, and after the solvent was removed on the rotary evaporator, the residue was chromatographed on silica gel eluting with hexane (80)–ethyl acetate (20) to provide **21** as a clear, viscous oil: R_f 0.35; yield was 22.5 g (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8 (12 H, m), 0.82–0.92 (21 H, m), 1.18 (3 H, d), 1.22 (3 H, d), 1.31–1.96 (9 H, m), 2.02–2.1 (1 H, m), 2.23–2.45 (2 H, m), 2.50–2.65 (2 H, m), 3.65–3.75 (1 H, m), 4.26–4.34 (1 H, m), 4.36–4.42 (1 H, m), 4.60–4.72 (1 H, m), 5.45–5.49 (1 H, m), 5.81 (1 H, dd), 5.99 (1 H, d); MS m/z = 592.

6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (24). A flask was charged with 31.14 g (0.358 mol) of lithium bromide and heated at 120 °C under full vacuum overnight. To this solid under nitrogen was added a solution of 42.5 g (0.0717 mol) of **21** and 1.50 g (0.0123 mol) of 2,6-(dimethylamino)pyridine (DMAP) in 120 mL of pyridine at room temperature. After the mixture was stirred for 5 min, 23.99 g (0.18 mol) of 2,2-dimethylbutanoyl chloride was added and the resulting mixture was stirred at 90 °C for 2 h. The cooled reaction mixture was diluted with 1 L of ether and 750 mL of water. The separated organic phase was washed with 2 × 250-mL portions of water, 4 × 250-mL portions of 1 N HCl, and 300 mL brine and dried over anhydrous sodium sulfate. The drying agent was filtered and the solvent removed on the rotary evaporator to give an amber residue. This was chromatographed on silica gel eluting with hexane (90)–ethyl acetate (10) to provide 37.0 g (75%) of **24** as a viscous, yellow oil: R_f 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01–0.11 (12 H, m), 0.78–0.95 (24 H, m), 1.10 (9 H, m), 1.28 (3 H, d), 1.30–1.80 (8 H, m), 1.80–1.95 (2 H, m), 2.08–2.20 (1 H, m), 2.27–2.50 (2 H, m), 2.50–2.65 (2 H, m), 3.72–3.85 (1 H, m), 4.24–4.33 (1 H, m), 4.50–4.65 (1 H, m), 5.42 (1 H, m), 5.63 (1 H, m), 5.74 (1 H, dd), 5.96 (1 H, d); MS m/z = 690.

6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxyethyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (25). To a solution of 37.0 g (0.0525 mol) of **24** in 300 mL of acetonitrile at room temperature was added 30 mL of an aqueous solution of HF (49%). After stirring at room temperature for 2 h, the reaction mixture was diluted with 1 L of saturated sodium bicarbonate solution and 2 L of ether. The organic phase was separated and the aqueous phase was reextracted with ether. The combined organic phase was washed with 3 × 500-mL portions of saturated sodium bicarbonate solution, 500 mL of water, and 500 mL brine and dried over sodium sulfate. Filtration and solvent removal on the rotary evaporator gave a yellow residue that was purified by flash chromatography on silica gel eluting with hexane (70)–acetone (30) to give a clear oil. This was stirred with a small amount of ether to give 17.7 g (72%) pure **25** as a white solid: mp 114–117 °C; R_f 0.3 (30% acetone in hexane); please see Table I for NMR data on **25**. Anal. ($C_{27}H_{42}O_6$) C: calcd 70.10; found 70.48. H: calcd 9.10; found 8.70.

6(*R*)-[2-[8-Oxo-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxybenzyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (19). $TiCl_4$ (5.69 g, 0.03 mol, 3.30 mL) was added dropwise at <−70 °C to 275 mL of CH_2Cl_2 cooled to −75 °C, followed by 5.64 g (0.06 mol) of benzaldehyde. The resulting yellow mixture was stirred at −70 °C for 5 min, and then a solution of **5** (15.15 g, 0.03 mol) in CH_2Cl_2 (25 mL) was added at <−70 °C. This mixture was stirred at −70 °C for 2 h and then allowed to warm to −30 °C over 45 min. This solution was quenched through the addition of 50 mL of H_2O, diluted with 700 mL of CH_2Cl_2 and 150 mL of H_2O and brine, and dried (Na_2SO_4), and the solvent was removed to give a yellow residue. This was chromatographed on silica gel eluting with hexane (80)–ethyl acetate (20) and then with hexane (70)–acetone (30) to give after solvent removal a solid residue, R_f 0.25 with hexane (80)–ethyl acetate (20). This residue was triturated with hexane (75 mL) to give **19** as a white solid: 5.2 g (32%); mp 170–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (12 H, m), 1.30–2.05 (8 H, m), 2.39–2.51 (1 H, m), 2.56–2.67 (3 H, m), 3.30 (1 H, d, J = 11 Hz), 4.29 (1 H, m), 4.98 (1 H, m), 5.41 (1 H, m), 5.84 (1 H, m), 5.98 (1 H, d, J = 12 Hz), 7.28–7.42 (5 H, m).

6(*R*)-[2-[8-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxybenzyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]-ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (22). To a stirred solution of **19** (0.539 g, 1.0 mmol) in 10 mL of THF (10)–H_2O (1) was added $PdCl_2$ (0.177 g, 1.0 mmol), and the resulting mixture was cooled to −30 °C. To this was added $NaBH_4$ (0.38 g, 10.0 mmol) in one portion resulting in foaming and only a very mild exotherm. With vigorous stirring the reaction was allowed to warm to −20 °C, at which point gas evolution became more vigorous, and over the next 45 min the temperature was allowed to rise gradually to −5 °C. The reaction mixture was carefully diluted with 200 mL of ether and 50 mL of water while cooling at 0 °C. The organic phase was separated and the aqueous phase was reextracted with 200 mL of Et_2O. The combined organic phase was washed with 4 × 50 mL of H_2O and 50 mL of brine and dried $NaSO_4$. The solvent was removed on the rotary evaporator to give a residue which was purified by flash chromatography on silica gel eluting with hexane (70)–ethyl acetate (30). This provided 2.57 g (57%) of **22** as a foam: R_f (silica gel) 0.45 with hexane (50)–ethyl acetate (50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (6 H, s), 0.89 (8 H, s), 0.95 (5 H, m), 1.70–2.0 (10 H, m), 2.05 (2 H, m), 2.32 (1 H, dd), 2.42 (2 H, m), 2.60 (2 H, m), 4.32 (2 H, m), 4.70 (2 H, m), 5.43 (1 H, m), 5.84 (1 H, m), 6.0 (1 H, d), 7.30–7.41 (5 H, m); MS m/z = 540.

6(*R*)-[2-[8(*R*)-Hydroxy-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-[(*tert*-butyldimethylsilyl)oxy]benzyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)-oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (23). To a solution of **22** (2.72 g, 0.005 mol) in methylene chloride (60 mL) cooled to −10 °C was added 2,6-lutidine (1.25 g, 0.017 mol, 1.36 mL) followed by TBDMSOTf (1.40 g, 0.0053 mol, 1.22 mL) dropwise, and the resulting mixture was stirred at 10 °C for 1 h. The reaction was quenched with the addition of 20 mL of H_2O, and this was diluted with 300 mL ether. The organic phase was separated, washed with H_2O (100 mL), 3 × 75-mL portions of 1 H HCl, and brine, and dried (Na_2SO_4). Solvent removal gave a viscous residue which was chromatographed on silica gel eluting with hexane

(80)–ethyl acetate (20) to give the desired product **22**: R_f 0.6 with hexane (70)–ethyl acetate (30) as a white solid; mp 130–135 °C; 2.43 g (78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (3 H, d), 0.56 (6 H, s), 1.30–1.47 (25 H, m), 2.0–2.45 (6 H, m), 2.68 (1 H, m), 2.88 (2 H, m), 3.07 (2 H, m), 4.78 (2 H, m), 5.02 (1 H, m), 5.14 (1 H, m), 5.90 (1 H, m), 6.30 (1 H, m), 6.49 (1 H, d), 7.73–7.81 (5 H, m); MS m/z = 654.

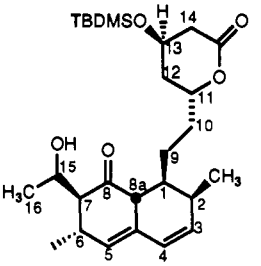
6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-[(*tert*-butyldimethylsilyl)oxy]benzyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (26). To a solution of **23** (2.43 g, 4.0 mmol) in 10 mL of pyridine was added 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), and this solution was added via syringe to lithium bromide (2.18 g, 25.2 mmol) which had been dried overnight at 130 °C under high vacuum. This mixture was stirred for 5 min at 23 °C, the 2,2-dimethylbutanoyl chloride (1.68 g, 12.6 mmol) was added via syringe, and the resulting mixture was heated at 90 °C for 30 h. The reaction mixture was then cooled and diluted with 350 mL of ether and 100 mL of water. The organic phase was separated and the aqueous phase was reextracted with 200 mL of Et_2O. The combined organic phase was washed with 2 × 100-mL portions of water, 3 × 100-mL portions of 1 N HCl, and brine and dried over Na_2SO_4. Solvent removal provided a foam which had R_f 0.4 (silica gel) with hexane (80)–ethyl acetate (20), and the analysis showed that this crude material 3.04 g (102%) had only a minor impurity at R_f 0.25. This material was used directly in the next step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (6 H, m), 0.58 (3 H, s), 1.37 (20 H, m), 1.67 (13 H, m), 2.0–2.5 (11 H, m), 2.72 (1 H, m), 2.90 (2 H, m), 3.07 (2 H, m), 3.96 (2 H, m), 4.82 (2 H, m), 5.09 (1 H, m), 5.90 (1 H, bs), 6.25–6.40 (2 H, m), 6.50 (1 H, m), 7.71–7.90 (5 H, m); MS m/z = 752.

6(*R*)-[2-[8(*R*)-[(2,2-Dimethylbutanoyl)oxy]-2(*S*),6(*S*)-dimethyl-7(*S*)-[1(*S*)-hydroxybenzyl]-1,2,6,7,8,8a(*R*)-hexahydronaphthyl-1(*S*)]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (27). To a solution of **26** (3.04 g, 4.0 mmol) in acetonitrile (30 mL) at 23 °C was added 49% aqueous HF (5 mL), and this solution was stirred for 1.5 h. The reaction mixture was then carefully poured into a stirred mixture of 600 mL of ether and 100 mL of saturated $NaHCO_3$ at 0–10 °C. The organic phase was separated, washed with 3 × 100-mL portions of saturated $NaHCO_3$, 2 × 100-mL portions of water, 150 mL of brine, and dried Na_2SO_4. Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with hexane (70)–ethyl acetate (30) to give 1.3 g (61%) **27** as a foam: R_f 0.3 (silica gel) eluting with hexane (70)–acetone (30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3 H, m), 0.95 (3 H, d), 1.13 (6 H, m), 2.55–2.70 (2 H, m), 4.46 (2 H, m), 4.65 (1 H, m), 5.40 (1 H, bs), 5.85 (2 H, m), 6.00 (1 H, d), 7.30–7.40 (5 H, m). Anal. ($C_{32}H_{44}O_6$) C: calcd 73.25; found 73.58. H: calcd 8.4; found 8.53.

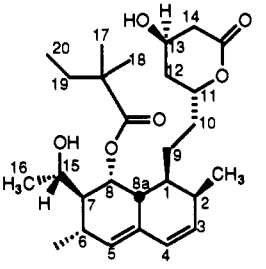
The chemical shift assignments in Table I were obtained from the 1D and 2D COSY spectra of each compound. Connectivity information

Discussion of Stereochemical Assignments for 18a and 18b Based on NMR Studies.

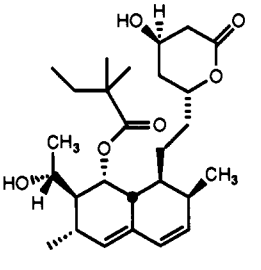
The proton spectra of **18a** compare well with the spectra of **18b** with the exception of (1) slightly different chemical shifts for H-7, H-5, H-8a, and CH_3-16 and (2) different line shapes for H-7 and H-15. The similar line shapes of the H-5, H-6, and H-8a resonances and dissimilar line shapes for the H-7 and H-15 resonances suggest that C-15 is the epimeric center and that the stereochemistry at C-7 is the same for both molecules.



18a and 18b



25



29

Reduction and acylation of **18a** and **18b** at C-8 provided compounds with well-defined ring conformations which enabled us to unambiguously determine the configurations at C-7 and C-15. **25** is the reduced and acylated product of **18a**, and **29** is the reduced and acylated product of **18b**. Table II contains the NOE data for **25** and **29**. In both compounds, the NOE observed in H-8a upon irradiation of H-15 places the hydroxyethyl side chain on the β-face of the molecule.

A large coupling (~8.4 Hz) between H-7 and H-15 in the proton spectrum of **25** suggests a preferred conformation for the hydroxyethyl side chain where H-15 is anti to H-7. Irradiation of H-15 produced enhancements in the H-6 and H-8a resonances while irradiation of CH_3-16 enhanced the H-6 resonance. Examination of models show that only the *S* configuration at C-15 is consistent with these observations. The preferred conformation of the molecule contrasts with the motionally averaged nature of the hydroxyethyl group of its isomer, **29**. Irradiation of CH_3-16 of **29** produced NOEs in H-8, H-7, H-8a, and H-6, consistent with the *R* configuration at C-15 *and* an average of at least two C7–C15 rotamers (see below). This is further supported by an H7–H15 coupling of ~4 Hz, an averaged value. Despite the rotational mobility of the hydroxyethyl group, the intensity pattern of NOEs suggests that the methyl group spends most of its time in the neighborhood of H-8. This too is consistent with the *R*-configuration assignment.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **3**, **5–8**, **9a,b**, **12–16**, **18a**, and **20–27** (22 pages). Ordering information is given on any current masthead page.