Chemical Synthesis of 3-Ethylcompactin,† an Inhibitor of 3-Hydroxy-3-methylglutarylcoenzyme A Reductase

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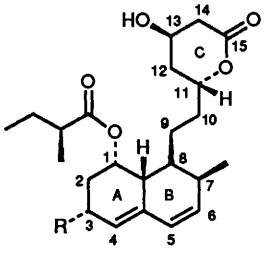
A method is described for stereocontrolled synthesis of (+)-3-ethylcompactin (**1c**), a compound that inhibits rat liver HMG CoA reductase with a similar potency to mevinolin. The synthetic approach is a general one and involves linking a pent-4-enal (**3**) with a substituted cyclohexenone (**2**). Evans asymmetric alkylation was used (Scheme 2) to prepare the oxazolidinone (**6**). Ozonolysis, acetalization, and reduction ($LiAlH_4$) then gave the alcohol (**9**), and this was transformed by Swern oxidation, Wittig methylenation, and acid hydrolysis into (*R*)-3-ethylpent-4-enal (**12**). Aldol condensation (Scheme 3) of the cyclohexenone (**2**) with the aldehyde (**12**), followed by triethylsilylation, and ozonolysis gave the enone aldehyde (**15**). A modified McMurry reaction, requiring an excess of a reagent prepared from C_8K and $TiCl_3$ (2:1 molar ratio) in 1,2-dimethoxyethane, then produced the hexahydronaphthyl ether (**16**), which was converted into (+)-3-ethylcompactin by appropriate modification of the oxygen functionality.

The global incidence[1] of coronary artery disease associated with atherosclerosis[2] has made the search for drugs[3] that lower blood levels of cholesterol [in particular, low-density lipoprotein (LDL) cholesterol][2] an important problem in medicinal chemistry. Many epidemiologic studies[2] of heart disease have shown a positive correlation between high blood levels of cholesterol and the incidence of atherosclerosis, while detailed analysis has specifically implicated elevated levels of low-density lipoprotein cholesterol as a very significant risk factor.

In human beings a considerable portion of total body cholesterol is generated biosynthetically, mainly in the liver,[4] and inhibition of the biosynthesis has appeared as an obvious method for slowing the development of atherosclerosis. In this regard, the discovery of the fungal metabolites compactin (**1a**)[5] and mevinolin (**1b**)[6] represented an important step because



(**1a**) R = H
(**1b**) R = Me
(**1c**) R = Et

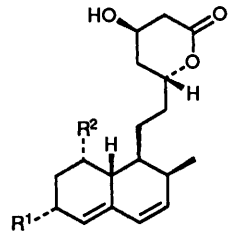
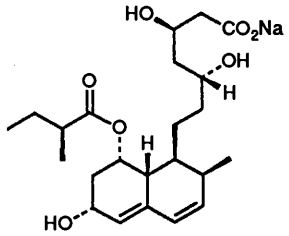
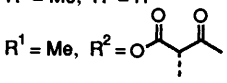
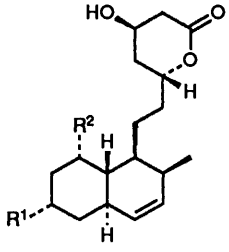
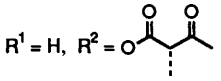
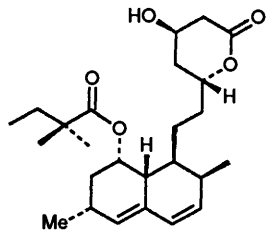
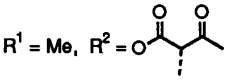
these substances are reversible, competitive inhibitors of HMG CoA reductase,[6a,7] which is the enzyme involved in the rate-limiting step of cholesterol biosynthesis.[8] Administration of compactin or mevinolin causes a substantial decrease in blood levels of LDL cholesterol,[9] but inhibition of the enzyme is not the *direct* cause of this decrease. Cholesterol metabolism is controlled by intricate feedback mechanisms[8d,10] and the mode of action of compactin and mevinolin is not straightforward. When the enzyme is inhibited‡ the cell responds in several ways.[8d,10,11] More of the enzyme is produced so that steroid biosynthesis is maintained, but, in addition, an increased number of LDL receptors are generated on the cell surface and it is this increase in the number of receptors which is directly related to the decrease in plasma levels of LDL cholesterol. The supply of the steroid to the cell is not significantly impaired, it merely occurs at a lower plasma level.[9,10,12]

Against this background, compactin and mevinolin represent significant lead compounds for the design of other cholesterol-lowering drugs, and, obviously, the subject of structure–activity correlations is important in this context. Analogues incorporating major structural changes, such as formal replacement of the AB rings by substituted aromatic units, are readily accessible.[13] Likewise, some chemical modifications to the natural products themselves are easily made, particularly at C-11[14] and C-13,[15] and to the acyl group at C-1.[15–18] There also exist a number of related natural products,[5b,19] some of which have been obtained by deliberate microbial modification§ of others. These natural products are collectively known as mevinic acids, a term that, strictly, refers to the open (hydroxy acid) form resulting from hydrolysis of the lactone subunit.[6a,7a] Compactin and mevinolin are the best known of this small group and a representative selection of the data available on structure–activity relationships among the mevinic acids is collected in Table 1.

It is clear that apparently minor alterations to the basic structure (**1a**) can produce an appreciable alteration in biological activity. Analogues incorporating such modifications are often best available by total synthesis and some would appear to be accessible only in this way. The examples in Table 1 show that modifications to ring A represent a promising starting point and, with these considerations in mind, we developed[20] a flexible synthetic route and have used it to prepare (+)-compactin and (+)-mevinolin. When we began

† Non-systematic numbering is used in this publication, except in the Experimental section.
‡ The biologically active forms of compactin and mevinolin are the hydroxy acids resulting from hydrolysis of the lactone unit (see refs. 6*a*, 7*a*).
§ See, *e.g.* refs. 19*g–s*.

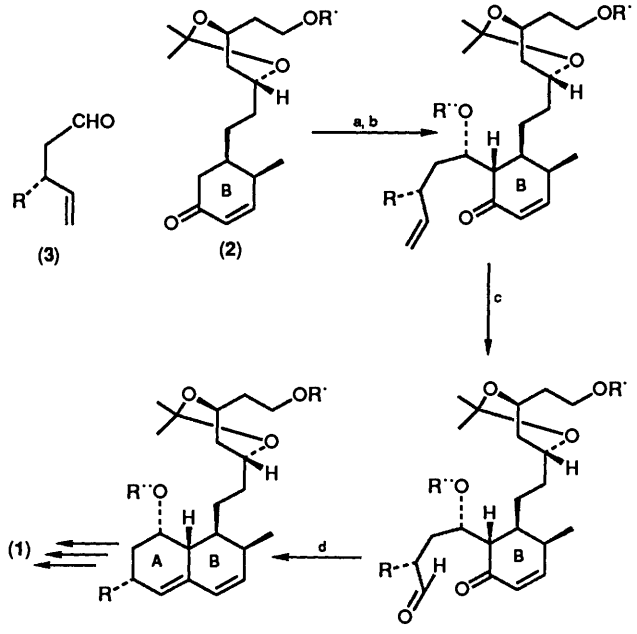
Table 1.

Compound	Rel Potency[a]	Compound	$10^{10}K_i$(M)[b]
(**1a**)	50	(**1a**)	14
(**1b**)	100	(**1b**)	3.0
 R^1 = H, R^2 = OH	2		
R^1 = H, R^2 = H	10		23
R^1 = Me, R^2 = OH	4		
R^1 = Me, R^2 = H	15		
R^1 = Me, R^2 = 	20		
 R^1 = H, R^2 = 	50		1.2
R^1 = Me, R^2 = 	100		
R^1 = Me, R^2 = H	20		

[a] Ref. 7*b*. [b] Ref. 12*c*.

our experiments the data of Table 1 were not available; only the relative potency of compounds (**1a**) and (**1b**) had been reported.[6a]

Our approach to the synthesis of the mevinic acids (Scheme 1) is a general one and it does not require redesign of the sequence for each analogue. Details of the strategy have been given



Scheme 1. R′ = $SiPh_2Bu^t$, R″ = $SiEt_3$. *Reactions:* (a) Aldol condensation, (b) silylation, (c) ozonolysis, (d) dicarbonyl coupling.

elsewhere;[20] here we describe its application to the synthesis of 3-ethylcompactin. This choice of compound was guided by the fact that formal replacement of a hydrogen atom at C-3 by a methyl group (*cf.* compactin and mevinolin) increases the biological activity several fold.[6a] Apart from microbial hydroxylation,[19f,g,h,o,p,s] modifications at C-3 have not been reported.*

Discussion

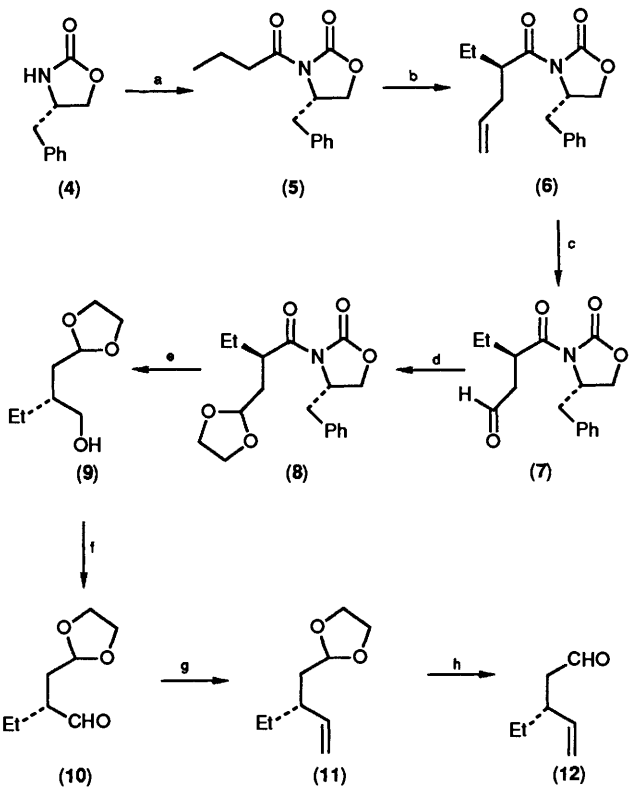
The synthetic route (Scheme 1) involves attachment of the left-hand part of ring A to a complete, but suitably protected, BC ring system (**2**). Compound (**2**) is a known substance[20] available in the indicated homochiral form. For the synthesis of 3-ethylcompactin the appropriate ring A precursor is aldehyde (**3**; R = Et) and its preparation is summarized in Scheme 2.

Acylation[21] of the chiral auxiliary (**4**)[22],† with butyryl chloride gave the imide (**5**) and this was allylated in the standard way to produce optically pure compound (**6**).[23] The pendant double bond was cleaved by ozonolysis and the resulting aldehyde (**7**) was protected by conversion into acetal (**8**). At this point the chiral auxiliary had served its purpose and it was removed by the action of lithium aluminium hydride to afford the alcohol (**9**). Swern oxidation produced aldehyde (**10**), and Wittig olefination gave alkene (**11**). Mild acid hydrolysis then yielded the ring A aldehyde (**12**) [corresponding to (**3**; R = Et)]. We knew from work leading to aldehyde (**3**; R = Me) (see Scheme 1)[20] that the reaction sequence of Scheme 2 affords optically pure material and this opinion was confirmed later in the present synthesis.‡

* Recently, chemical modification of the C-3 methyl group of mevinolin was described: T. J. Lee and W. F. Hoffman, European Patent Application 320 052 A2, 1989 (*Chem. Abstr.*, 1990, **111**, 233 285x).

† *rac*-(**4**) was prepared from (±)-phenylalanine. The Mosher imides formed from *rac*-(**4**) with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride were examined by ^{1}H NMR spectroscopy (200 MHz). The two diastereoisomers were readily distinguished, and examination of the Mosher imide from optically active (**4**) showed it to be optically pure.

‡ Coupling with the BC ring system gives a single product (**13**) (see Scheme 3), leading to a single aldehyde (**15**). This aldehyde can be epimerized at C-3 and the epimers are easily distinguished by ^{1}H NMR spectroscopy.



Scheme 2. *Reagents and conditions* (*yields in parentheses*): (a) BuLi, THF, −78 °C; add butyryl chloride, −78 °C, 45 min (86%); (b) LDA, THF, −78 °C; add allyl bromide, −78 °C to room temperature during 2.5 h (74%); (c) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C, 30 min; room temperature, 2 h (92%); (d) $HOCH_2CH_2OH$, PTSA, PhH, reflux, 4Å molecular sieves in Soxhlet, 4.5 h (85%); (e) $LiAlH_4$, THF, room temperature, 30 min (88%); (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add (**9**), −78 °C, 20 min; Et_3N, −78 °C, 20 min; warm to room temperature during 10 min (82%); (g) $Ph_3P{=}CH_2$, THF, 0 °C, 35 min (84%); (h) Et_2O–10% aq. HCl, room temperature, 23 h (65%).

Kinetic deprotonation (Scheme 3) of ketone (**2**) and treatment with aldehyde (**12**) gave the aldol (**13**) in 86% yield. The stereochemistry at C-1, C-8, and C-8a was clear from ^1H NMR measurements.* As expected, the aldehyde approaches the enolate from the less hindered face to establish the indicated stereochemistry at C-8a. The fact that C-1 has the desired *S* chirality was expected on the basis of a standard chair-like transition state for the aldol reaction. Silylation [to compound (**14**)] and ozonolysis led to the keto aldehyde (**15**). This is a sensitive compound and is easily epimerized at C-3 by chromatography over silica gel. Fortunately, it is inert to Florisil. Treatment of compound (**15**) in 1,2-dimethoxyethane (DME) with a special titanium reagent derived from potassium graphite and titanium trichloride served to generate ring A, and compound (**16**) was isolated in 89% yield. In using the titanium reagent close attention must be given to the stoicheiometry and, for optimum results, the following *relative* molar quantities are necessary: keto aldehyde (**15**) (1): C_8K (34): $TiCl_3$ (17). The dicarbonyl coupling [(**15**) ⟶ (**16**)] proceeds without epimerization at C-3 and gives a single product.

Formation of compound (**16**) represents a key step in the synthesis, as all that remains is modification of the oxygen functionality. Both silicon protecting groups were removed by the action of tetrabutylammonium fluoride (TBAF) and the t-butyldiphenylsilyl group was replaced selectively at the C-15 hydroxy function. Although this sequence of operations involves two steps for the net deprotection at C-1 it is still very efficient (93% yield), and it was found through experience in the synthesis of compactin and mevinolin[20] to be the preferred method. Alcohol (**17**) was then acylated (97%) with (*S*)-α-methylbutyric anhydride, bringing the sequence to the ester (**18**). Finally, the lactone unit was elaborated in the following way. Desilylation with TBAF, to give the alcohol (**19**) (89%), and Swern oxidation (91%) afforded aldehyde (**20**). Mild hydrolysis with dil. hydrochloric acid then produced (79%) a mixture of epimeric lactols (**21**) and selective oxidation of the anomeric hydroxy function with Fétizon's reagent gave (+)-3-ethylcompactin in 72% yield.

Table 2. Effect of 3-ethylcompactin and mevinolin on rat liver 3-hydroxy-3-methylglutarylcoenzyme A reductase activity *in vitro*.

Compound [in DMSO (10 μl)]	Concentration in assay	HMG CoA reductase activity (pmol mevalonate formed min^{-1} mg^{-1} microsomal protein) Run #1	Run #2
3-Ethylcompactin (**1c**)	1 nM	730	665
	100 nM	361	367
	1 μM	182	174
	10 μM	20	47
Mevinolin (**1b**)	1 nM	698	665
	100 nM	303	310
	1 μM	113	183
	10 μM	52	37
DMSO	10 μl	652	655
None		1 254	938

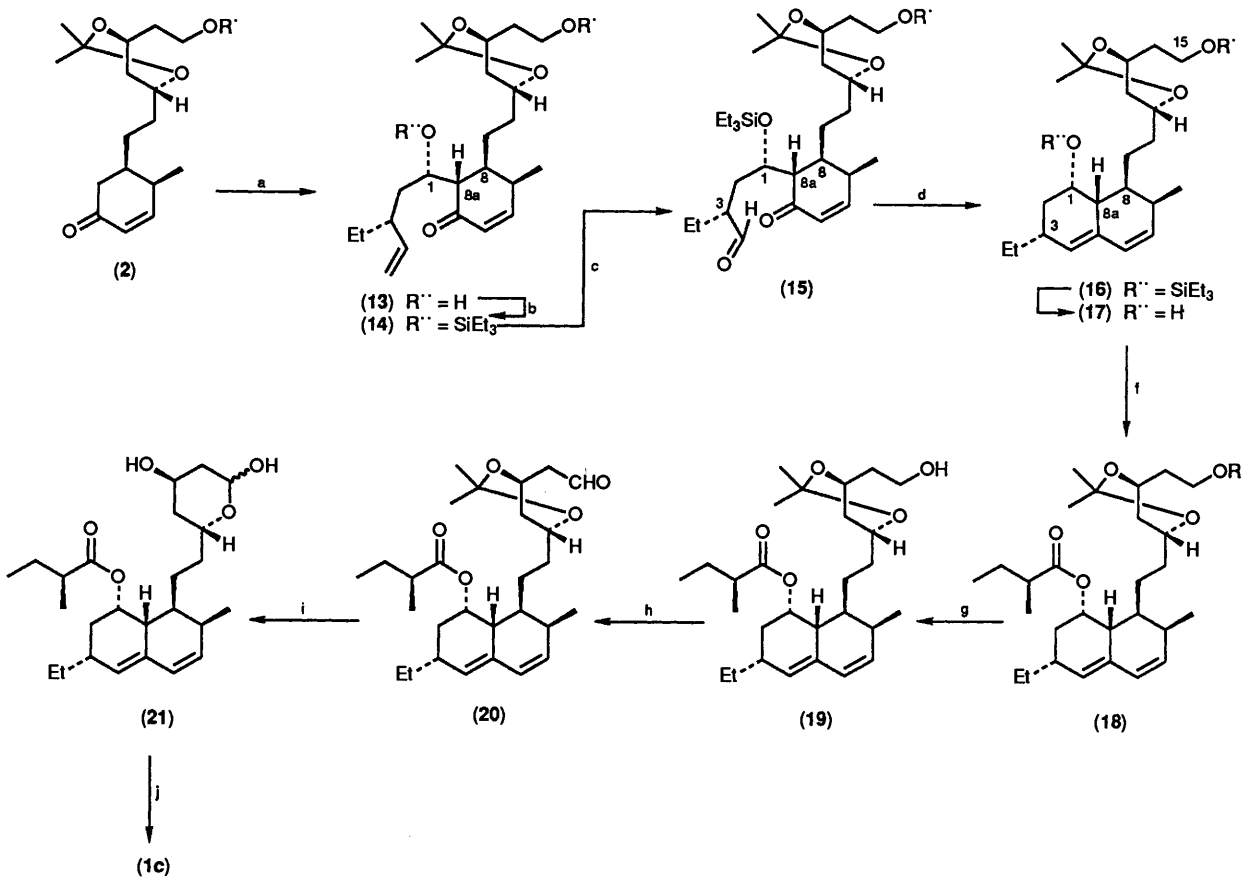
Biological Evaluation.—The ability of 3-ethylcompactin to inhibit rat liver HMG CoA reductase was measured by a standard method[24] described in the Experimental section. For comparison purposes mevinolin was also assayed and the results of two sets of experiments are shown in Table 2. As can be seen, 3-ethylcompactin is of comparable activity to mevinolin. It is clear that, although replacement of the C-3 *pro-R* hydrogen of compactin by a methyl group raises the activity several-fold, when the substituent on C-3 is a little bigger (ethyl *versus* methyl), while the stereochemistry is retained, no appreciable effect on the enzyme inhibition is observed. The mevinic acids probably bind simultaneously[7d] to two sites in the enzyme, and the synthetic method reported here allows the tolerance of the hydrophobic domain to structural changes (including reduction[25] of the C-4–C-4a double bond) in the hexahydronaphthalene substructure of the mevinic acids to be probed.

Experimental

Except where stated to the contrary, the following particulars apply: all experiments were done under a slight static pressure of argon, purified by passage through a column (3.5 × 42 cm) of R-311 catalyst† and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars. When solutions are added during a specified time and a rinse is used to

* Chemical shifts and coupling patterns were compared with data for the corresponding intermediates in the synthesis of compactin and mevinolin (see ref. 20).

† Supplied by Chemical Dynamics Corp., South Plainfield, NJ.



Scheme 3. R′ = $SiPh_2Bu^t$. *Reagents and conditions (yields in parentheses):* (a) LDA, Et_2O, −78 °C; add (**2**); −78 °C, 45 min; add (**12**), −78 °C, 10 min (86%); (b) Et_3SiCl, Pr^i_2NH, DMAP, Et_2O, 0 °C; room temperature, reaction arbitrarily stopped after 40 h (92%) after correction for recovered (**13**) (2%); (c) O_3, CH_2Cl_2, −78 °C; Ph_3P, − 78 °C, then remove cold-bath, 3 h (81%) after correction for recovered (**14**) (16%); (d) C_8K, $TiCl_3$, DME; addition of (**15**) during 9 h; room temperature, 5 h; reflux, 4 h (89%); (e) TBAF, THF, room temperature, 22 h; Bu^tPh_2SiCl, CH_2Cl_2, Et_3N, DMAP (catalyst), room temperature, 24 h (93% overall); (f) (*S*)-Methylbutyric anhydride, Et_3N, DMAP, CH_2Cl_2, room temperature, reaction arbitrarily stopped after 80 h (97%) after correction for recovered (**17**) (7%); (g) TBAF, THF, room temperature, 3 h (89%); (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; add (**19**), −78 °C, 20 min; Et_3N, −78 °C, 10 min; warm to room temperature during 20 min (91%); (i) Aq. 10% v/v HCl, THF, room temperature, 4 h (79%); (j) Ag_2CO_3–Celite, PhMe, 85–95 °C, 1 h, (72%).

wash all the material into the reaction vessel, then the time stated refers to the main solution; the rinse was usually added at a fast dropwise rate.

Solvents for chromatography or extractions were distilled before use. Where required, solvents for reactions were dried by distillation from a suitable drying agent (see below) under nitrogen or argon, and were transferred by oven-dried syringes.

Products were isolated from solution by evaporation under water-pump vacuum at 25 °C on a rotary evaporator. In those cases where compounds were isolated simply by evaporation of their solutions (and not also by subsequent distillation) the residues were kept under oil-pump vacuum (0.1 mmHg) and checked for constancy of weight. Isolated products were submitted directly for combustion analysis, without need for further purification. M.p.s were determined on a Kofler block melting point apparatus. B.p.s reported for products distilled in a Kugelrohr apparatus refer to the oven temperature.

Commercial TLC plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light, by exposure to iodine, and/or by spraying with phosphomolybdic acid in methanol * followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230–400 mesh).

IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Liquids were usually run as neat films on potassium chloride plates and solids were run as solutions in the specified solvent in 0.5 mm sodium chloride cells. FT-IR measurements were made as casts from the specified solvent and with potassium bromide plates.

^1H NMR spectra were recorded with a Bruker WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometer in the specified deuteriated solvent with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded with a Bruker AM-300 (at 75.469 MHz) or a Bruker AM-400 (at 100.614 MHz) spectrometer with deuteriochloroform as internal standard. Carbon multiplicities, where reported, were determined using the Spin Echo Fourier Transform technique with gated proton decoupling.[26] Tentative assignments to ^{13}C NMR spectra employ the abbreviations s′, d′, t′, and q′, which refer respectively to zero, one, two, and three attached protons.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70 eV.

Optical rotations were measured with a Perkin-Elmer 141 Polarimeter.

* Phosphomolybdic acid (15 g) and cerium(IV) ammonium sulphate (2.5 g) were dissolved in a mixture of water (485 ml) and conc. sulphuric acid (15 ml).

Microanalyses were performed by the microanalytical laboratory of this Department.

Dry solvents were prepared under an inert atmosphere. Dry DME, diethyl ether, and tetrahydrofuran (THF) were distilled shortly before use from sodium and benzophenone ketyl. Dry di-isopropylamine, triethylamine, dichloromethane, chlorotriethylsilane, and toluene were distilled shortly before use from calcium hydride. Light petroleum refers to the fraction boiling between 30–60 °C. Commercial (Aldrich) solutions of butyllithium in hexanes were titrated before use by the diphenylacetic acid method.[27] TBAF was purchased as a 1.1M solution in THF and used at the stated concentration. Commercial (Aldrich) titanium trichloride was stored under argon and transferred to reaction vessels in a glove bag under argon.

(A) Synthesis of the Ring A Aldehyde (12)

(S)-4-*Benzyl*-3-(1-*Oxobutyl*)*oxazolidin*-2-*one* (**5**).[21]—Butyllithium (1.6M in hexanes; 67 ml, 107.2 mmol) was added dropwise from an addition funnel to a magnetically stirred and cooled (−78 °C) solution of the oxazolidinone (**4**) (19.0 g, 107.2 mmol) and a few crystals of 2,2′-dipyridyl in THF (150 ml). When all the butyl-lithium had been added the initially yellow solution turned brick-red. The mixture was stirred for 10 min and freshly distilled butyryl chloride (11.2 ml, 107.8 mmol) was injected during 10 min to the stirred mixture. The mixture was stirred at −78 °C for 45 min and the cold-bath was then removed. After a further 45 min saturated aq. ammonium chloride (25 ml) was added, the mixture was stirred for 10 min, and then most of the THF was evaporated at 30 °C. The residue was extracted with ethyl acetate (3 × 50 ml) and the combined extracts were washed with water (50 ml), dried (Na_2SO_4), and evaporated. Flash chromatography of the residual light-yellow oil over silica gel (4 × 30 cm) with (3:7) diethyl ether–light petroleum gave the title compound (**5**) (23.02 g, 86%) as a homogeneous [TLC, silica gel; (3:7) diethyl ether–light petroleum] oil: FT-IR (CH_2Cl_2 cast) 1 782, 1 701, 1 388, and 1 211 cm^{-1}; δ_H($CDCl_3$; 400 MHz) 1.01 (3 H, t, *J* 7.0 Hz), 1.73 (2 H, doublet of sextets, *J* 2.0, 7.0 Hz), 2.77 (1 H, dd, *J* 13.5, 9.7 Hz), 2.88 (1 H, dt, *J* 17.0, 7.5 Hz), 2.95 (1 H, ddd, *J* 17.0, 8.0, 7.0 Hz), 3.29 (1 H, dd, *J* 13.5, 3.5 Hz), 4.13–4.22 (2 H, m), 4.67 (1 H, ddt, *J* 9.5, 7.5, 3.5 Hz), and 7.19–7.36 (5 H, m); δ_C($CDCl_3$; 100.614 MHz) 13.59 (q), 17.61 (t), 37.28 (t), 37.84 (t), 55.03 (d), 66.07 (t), 127.23 (d), 128.85 (d), 129.33 (d), 135.27 (s), 153.39 (s), and 173.13 (s) (Found: M^+, 247.1209; C, 68.0; H, 6.8; N, 5.6%. Calc. for $C_{14}H_{17}NO_3$: *M*, 247.1209; C, 68.00; H, 6.93; N, 5.66%).

[S-(R*,S*)]-4-*Benzyl*-3-(2-*Ethyl*-1-*oxopent*-4-*enyl*)*oxazolidin*-2-*one* (**6**).—Butyl-lithium (1.6M in hexanes; 34.4 ml, 55.0 mmol) was added dropwise from an addition funnel to a magnetically stirred and cooled (ice-bath) solution of di-isopropylamine (7.71 ml, 55.0 mmol) in THF (100 ml). The mixture was stirred for 10 min after the end of the addition, cooled to −78 °C and, after an additional 10 min, a solution of the imide (**5**) (13.5 g, 54.6 mmol) in THF (50 ml) was injected during 25 min. The mixture was stirred for 45 min at −78 °C and then freshly distilled allyl bromide (14.3 ml, 165.2 mmol) was injected during 5 min. The cold-bath was removed, the mixture was stirred for 2.5 h, and then saturated aq. ammonium chloride (25 ml) was added. The mixture was stirred for 10 min and then diluted with water (50 ml). Most of the THF was evaporated at 30 °C and the aqueous residue was extracted with diethyl ether (3 × 75 ml). The combined extracts were washed with brine (50 ml), dried (Na_2SO_4), and evaporated. Flash chromatography of the residual light-yellow oil over silica gel (4 × 30 cm) with (1:3) diethyl ether–light petroleum gave the *title compound* (**6**) (11.7 g, 74%) as a homogeneous [TLC, silica gel; (3:7) diethyl ether–light petroleum] oil: FT-IR ($CHCl_3$ cast) 1 780 and 1 692 cm^{-1}; δ_H($CDCl_3$; 300 MHz) 0.92 (3 H, t, *J* 7.5 Hz), 1.50–1.84 (2 H, m), 2.26–2.54 (2 H, m), 2.67 (1 H, dd, *J* 13.0, 10.0 Hz), 3.30 (1 H, dd, *J* 13.0, 3.5 Hz), 3.86 (1 H, tt, *J* 8.0, 6.0 Hz), 4.10–4.21 (2 H, m), 4.64–4.74 (1 H, m), 5.01–5.14 (2 H, m), 5.83 (1 H, ddt, *J* 17.0, 10.0, 7.0 Hz), and 7.18–7.40 (5 H, m); δ_C($CDCl_3$; 75.469 MHz) 11.57 (q′), 24.57 (t′), 36.28 (t′), 38.11 (t′), 43.75 (d′), 55.50 (d′), 65.92 (t′), 117.05 (t′), 127.30 (d′), 128.93 (d′), 129.42 (d′), 135.35 (d′), 135.47 (s′), 153.18 (s′), and 175.93 (s′) (Found: M^+, 287.1522; C, 70.8; H, 7.1: N, 5.0%. $C_{17}H_{21}NO_3$ requires *M*, 287.1522; C, 71.06; H, 7.36; N, 4.87%).

[S-(R*,S*)]-4-*Benzyl*-β-*ethyl*-γ,2-*dioxo*-*oxazolidine*-3-*butanal* (**7**).—Ozonized oxygen, cooled by passage through a glass coil immersed in a cold-bath at −78 °C, was bubbled into a cold (−78 °C) solution of compound (**6**) (11.0 g, 38.28 mmol) in dry dichloromethane (100 ml) for 1.5 h, by which stage the solution had acquired a violet colour. Triphenylphosphine (30.13 g, 114.87 mmol) was added to the stirred mixture. After 30 min the cold-bath was removed, and the mixture was stirred for another 2 h, and then evaporated. The residue was taken up in the minimum amount of dichloromethane, and flash chromatography over silica gel (4 × 25 cm) with, first, (1:4) diethyl ether–light petroleum (to remove unchanged triphenylphosphine), and then (3:2) diethyl ether–light petroleum gave the *title compound* (**7**) (10.2 g, 92%) as a homogeneous [TLC, silica gel; (7:3) diethyl ether–light petroleum; δ_H(400 MHz)] oil: FT-IR ($CDCl_3$ cast) 1 779, 1 722, and 1 695 cm^{-1}; δ_H($CDCl_3$; 400 MHz) 0.97 (3 H, t, *J* 7.5 Hz), 1.49–1.81 (2 H, m), 2.70 (1 H, ddd, *J* 18.5, 4.0, 1.0 Hz), 2.81 (1 H, dd, *J* 13.5, 9.8 Hz), 3.09 (1 H, dd, *J* 18.5, 9.8 Hz), 3.29 (1 H, dd, *J* 13.5, 3.5 Hz), 4.12–4.22 (3 H, m), 4.63–4.71 (1 H, m), 7.23–7.37 (5 H, m), and 9.79 (1 H, s); δ_C($CDCl_3$; 100.614 MHz) 11.24, 24.93, 37.54, 38.44, 45.42, 55.50, 66.03, 127.28, 128.96, 129.52, 135.57, 153.13, 175.27, and 200.22 (Found: M^+ 289.1312; C, 66.3; H, 6.5; N, 4.8%. $C_{16}H_{19}NO_4$ requires *M*, 289.1314; C, 66.42; H, 6.62; N, 4.84%).

[S-(R*,S*)-4-*Benzyl*-3-{β-[(1,3-*dioxolan*-2-*yl*)*methyl*]-α-*oxobutyl*}*oxazolidin*-2-*one* (**8**).—A mixture of compound (**7**) (9.53 g, 32.94 mmol), ethylene glycol (2.39 ml, 42.85 mmol), toluene-*p*-sulphonic acid monohydrate (PTSA) (0.63 g, 3.31 mmol), and benzene (150 ml) was refluxed for 4.5 h with provision for the condensate to pass through a small column (2 × 4 cm) of type 4Å molecular sieves contained in a side-arm addition funnel fitted between the flask and the condenser. The solution was cooled, washed successively with saturated aq. sodium hydrogen carbonate (40 ml) and brine (40 ml), and dried (Na_2SO_4). Evaporation of the solvent, and flash chromatography of the residual light-yellow oil over silica gel (4 × 22 cm) with (3:2) diethyl ether–light petroleum, gave the *title compound* (**8**) (9.41 g, 85%) as a homogenous [TLC, silica gel; (7:3) diethyl ether–light petroleum; δ_H(300 MHz)], viscous oil: FT-IR ($CHCl_3$ cast) 1 779, 1 697, and 1 390 cm^{-1}; δ_H($CDCl_3$; 300 MHz) 0.94 (3 H, t, *J* 7.5 Hz), 1.51–1.63 (1 H, m), 1.67–1.79 (1 H, m), 1.90 (1 H, dt, *J* 14.0, 3.5 Hz), 2.30 (1 H, ddd, *J* 14.0, 10.0, 5.0 Hz), 2.65 (1 H, dd, *J* 13.5, 10.0 Hz), 3.41 (1 H, dd, *J* 13.5, 3.5 Hz), 3.77–3.87 (2 H, m), 3.89–3.99 (2 H, m), 4.00–4.09 (1 H, m), 4.14 (2 H, d, *J* 5.0 Hz), 4.64–4.71 (1 H, m), 5.00 (1 H, dd, *J* 5.0, 3.5 Hz), and 7.20–7.39 (5 H, m); δ_C($CDCl_3$; 100.614 MHz) 11.32, 26.29, 35.69, 37.47, 38.92, 55.72, 64.63, 65.10, 65.78, 103.02, 127.18, 128.90, 129.44, 135.87, 153.18, and 176.35 (Found: M^+, 333.1579; C, 64.9; H, 6.9; N, 4.2%. $C_{18}H_{23}NO_5$ requires *M*, 333.1576; C, 64.85; H, 6.95; N, 4.20%).

(R)-β-[(1,3-*Dioxolan*-2-*yl*)*methyl*]*butan*-1-*ol* (**9**).—A solution of compound (**8**) (7.05 g, 21.14 mmol) in THF (50 ml plus 5 ml as a rinse) was transferred by cannula to a magnetically stirred and cooled (ice-bath) suspension of lithium aluminium hydride (1.60

g, 42.16 mmol) in THF (100 ml). The mixture was stirred for 15 min, the cold-bath was removed and, after a further 30 min, Celite (6 g) was added. The mixture was recooled in ice, and this was followed by successive dropwise addition of water (1.6 ml), 10% w/v aq. sodium hydroxide (1.6 ml), and water (4.8 ml). The ice-bath was removed and the mixture was stirred for 15 min. The mixture was filtered and the solids were washed with ethyl acetate (3 × 50 ml). The combined filtrates were evaporated to obtain an oil. This was distilled [Kugelrohr, 140–150 °C (3 mm)] to isolate the *alcohol* (**9**) (3.015 g, 88%) as a homogeneous [TLC, silica gel; (13:7) diethyl ether–light petroleum] liquid: $\delta_H(CDCl_3$; 200 MHz) 0.93 (3 H, t, *J* 7.0 Hz), 1.10–1.55 (2 H, m), 1.55–1.91 (3 H, m), 2.75 (1 H, br s), 3.51 (1 H, dd, *J* 11.0, 5.5 Hz), 3.63 (1 H, dd, *J* 11.0, 4.0 Hz), 3.77–4.07 (4 H, m), and 4.96 (1 H, t, *J* 4.5 Hz); $\delta_C(CDCl_3$; 100.614 MHz) 11.12, 24.40, 35.54, 38.35, 64.57, 64.67, 65.25, and 103.65; *m/z* 159.1021 [$C_8H_{15}O_3$ $(M - 1)^+$ requires *m/z*, 159.1021] (Found: C, 60.1; H, 10.0. $C_8H_{16}O_3$ requires C, 59.97; H, 10.06%).

(R)-α-[(1,3-*Dioxolan*-2-*yl*)*methyl*]*butanal* (**10**).—Dry dimethyl sulphoxide (DMSO) (2.1 ml, 29.59 mmol) was injected dropwise into a stirred and cooled (−78 °C) solution of freshly distilled oxalyl dichloride (1.24 ml, 14.21 mmol) in dry dichloromethane (40 ml). After 10 min, a solution of the alcohol (**9**) (2.268 g, 14.16 mmol) in dichloromethane (20 ml) was injected during 20 min. The resulting mixture was stirred for a further 20 min and then dry triethylamine (8.5 ml, 60.98 mmol) was injected dropwise. The mixture was stirred at −78 °C for 20 min, the cold-bath was removed and, after 30 min, water (20 ml) was added. The mixture was stirred for 10 min and the aqueous layer was extracted with dichloromethane (2 × 40 ml). The combined organic layers were washed successively with 10% v/v aq. hydrochloric acid (2 × 30 ml), saturated aq. sodium hydrogencarbonate (2 × 30 ml), and brine (30 ml), and dried (Na_2SO_4). The solvent was evaporated at 1 atm through a Vigreaux column, and flash chromatography of the residue over silica gel (4 × 20 cm) with (3:7) diethyl ether–light petroleum gave [after evaporation of appropriate fractions in the same way, followed by Kugelrohr distillation of the residual oil (70–80 °C; 5 mmHg)] the *aldehyde* (**10**) (1.85 g, 82%) as a homogeneous [TLC, silica gel; (3:7) diethyl ether–light petroleum; δ_H(200 MHz)] oil: $\delta_H(CDCl_3$; 200 MHz) 0.93 (3 H, t, *J* 7.0 Hz), 1.41–1.88 (3 H, m), 2.13 (1 H, ddd, *J* 13.5, 9.5, 4.0 Hz), 2.36–2.53 (1 H, m), 3.71–4.03 (4 H, m), 4.97 (1 H, t, *J* 4.0 Hz), and 9.55 (1 H, d, *J* 3.5 Hz); $\delta_C(CDCl_3$; 100.614 MHz) 11.06, 22.21, 32.64, 48.16, 64.64, 64.91, 102.42, and 203.81; *m/z* 157.0871 [$C_8H_{13}O_3$ $(M - 1)^+$ requires *m/z*, 157.0865].

(R)-2-(2-*Ethylbut*-3-*enyl*)-1,3-*dioxolane* (**11**).—Butyl-lithium (1.6M in hexanes; 6.3 ml, 10.1 mmol) was added from a syringe to a magnetically stirred and cooled (−15 °C, ice-methanol bath) suspension of methyltriphenylphosphonium bromide (3.61 g, 10.1 mmol) in THF (50 ml). The resulting clear orange-red solution was stirred at −6 °C to 0 °C for 1 h, and then a solution of aldehyde (**10**) (1.58 g, 9.99 mmol) in THF (15 ml plus 2 ml as a rinse) was injected dropwise during 15 min to the mixture at 0 °C. The mixture was stirred for a further 20 min at this temperature and was then partitioned between water (30 ml) and diethyl ether (3 × 30 ml). The combined organic extracts were washed with brine (30 ml) and dried (Na_2SO_4). The solvent was evaporated at 1 atm through a Vigreaux column, and flash chromatography of the residue over silica gel (4 × 20 cm) with (2:8) diethyl ether–light petroleum gave (after evaporation of appropriate fractions in the same way) a liquid, which was distilled [Kugelrohr (160–165 °C; 760 mmHg)] to obtain the *alkene* (**11**) (1.312 g, 84%) as a homogeneous [TLC, silica gel; (2:8) diethyl ether–light petroleum; δ_H(400 MHz)] oil: $\delta_H(CDCl_3$; 400 MHz) 0.86 (3 H, t, *J* 7.5 Hz), 1.23–1.36 (1 H, m), 1.40–1.53 (1 H, m), 1.67 (2 H, dd, *J* 7.0, 5.5 Hz), 2.09–2.20 (1 H, m), 3.78–3.88 (2 H, m), 3.90–4.01 (2 H, m), 4.86 (1 H, t, *J* 5.2 Hz), 5.01 (1 H, d, *J* 11.5 Hz), 5.02 (1 H, d, *J* 16.0 Hz), and 5.52–5.63 (1 H, m); $\delta_C(CDCl_3$; 100.614 MHz) 11.28, 27.90, 38.74, 41.72, 64.66, 64.49, 103.44, 114.74, and 141.96; *m/z* 155.1070 [$C_9H_{15}O_2$ $(M - 1)^+$ requires *m/z* 155.1072].

(R)-3-*Ethylpent*-4-*enal* (**12**).—A solution of the acetal (**11**) (750 mg, 4.80 mmol) in diethyl ether (75 ml) was stirred vigorously for 26 h with 10% v/v aq. hydrochloric acid (35 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 ml). The combined organic layers were washed successively with saturated aq. sodium hydrogencarbonate (30 ml), water (30 ml), and brine (30 ml), and were then dried (Na_2SO_4). The solvent was evaporated at 1 atm through a Vigreaux column, and Kugelrohr distillation (130–140 °C; 760 mmHg) of the residue gave the *aldehyde* (**12**) (350 mg, 65%): $\delta_H(CDCl_3$; 400 MHz) 0.89 (3 H, t, *J* 7.2 Hz), 1.28–1.53 (2 H, m), 2.40–2.59 (3 H, m), 5.01–5.09 (2 H, m), 5.65 (1 H, ddd, *J* 17.0, 11.0, 8.0 Hz), and 9.72 (1 H, t, *J* 2.2 Hz); $\delta_C(CDCl_3$; 100.614 MHz) 11.31, 27.52, 39.91, 48.15, 115.43, 140.66, and 202.49 (Found: M^+, 112.0087. $C_7H_{12}O$ requires *M*, 112.0888).

(B) Synthesis of 3-Ethylcompactin (1c)

[4S(4α,5α,6β)]-5-(2-{(4S*,6R*)-6-[2-(*t*-*Butyldiphenylsilyloxy*)*ethyl*]-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*}*ethyl*)-6-[(1R*,3S*)-3-*ethyl*-1-*hydroxypent*-4-*enyl*]-4-*methylcyclohex*-2-*enone* (**13**).—Butyl-lithium (1.6M in hexanes; 0.18 ml, 0.288 mmol) was added dropwise to a stirred and cooled (ice-bath) solution of di-isopropylamine (0.04 ml, 0.285 mmol) in diethyl ether (5.0 ml). The mixture was stirred at 0 °C for 10 min and the solution was then cooled to −78 °C. A solution of the enone (**2**) (137.0 mg, 0.256 mmol) in diethyl ether (3.0 ml plus 1.0 ml as a rinse) was added by syringe during *ca.* 15 min. The mixture was stirred at −78 °C for 45 min and then a solution of aldehyde (**12**) (140.0 mg, 1.248 mmol) in diethyl ether (2 ml plus 1 ml as a rinse) was added, also by syringe, during *ca.* 5 min. After a further 10 min, glacial acetic acid (0.07 ml, 1.22 mmol) was injected, the cold-bath was removed and, after 10 min, diethyl ether (20 ml) and water (15 ml) were added to the stirred mixture. The phases were separated and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined organic phases were washed successively with saturated aq. sodium hydrogencarbonate (20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 16 cm) with (3:7) diethyl ether–light petroleum gave the *aldol* (**13**) (142.9 mg, 86%) as a homogeneous [TLC, silica gel; (2:3) diethyl ether–light petroleum] oil: FT-IR (CH_2Cl_2 cast) 3 420 and 1 665 cm^{-1}; $\delta_H(CDCl_3$; 300 MHz) 0.88 (3 H, t, *J* 7.0 Hz), 1.04 (9 H, s), 1.11 (3 H, d, *J* 7.5 Hz), 1.36 (3 H, s), 1.41 (3 H, s), 0.99–1.80 (12 H, series of multiplets), 2.05 (1 H, d, *J* 7.0 Hz), 2.06–2.30 (2 H, m), 2.33 (1 H, t, *J* 6.0 Hz), 2.67–2.81 (1 H, m), 3.61–3.96 (4 H, m), 4.03–4.18 (1 H, m), 4.98–5.10 (2 H, m), 5.41–5.55 (1 H, m), 5.92 (1 H, dd, *J* 10.0, 2.5 Hz), 6.68 (1 H, dd, *J* 10.0, 2.5 Hz), 7.32–7.48 (6 H, m), and 7.60–7.71 (4 H, m); $\delta_C(CDCl_3$; 75.469 MHz) 11.69 (q′, 15.83 (q′), 19.23 (t′), 19.85 (q′), 23.14 (t′), 26.88 (q′), 28.57 (t′), 30.30 (q′), 31.53 (d′), 34.03 (t′), 37.32 (t′), 39.33 (t′), 40.83 (d′), 41.75 (t′), 42.39 (d′), 55.82 (d′), 59.64 (t′), 65.58 (d′), 68.05 (d′), 69.35 (d′), 98.46 (s′), 115.78 (t′), 127.61 (d′), 128.15 (d′), 129.58 (d′), 133.92 (s′), 135.57 (d′), 142.16 (d′), 154.07 (d′), and 201.53 (s′); *m/z* 519.2952 [$C_{32}H_{43}O_4Si$ $(M - CH_3 - C_7H_{12}O)^+$ requires *m/z*, 519.2931] (Found: C, 74.2; H, 9.1. $C_{40}H_{58}O_5Si$ requires C, 74.26; H, 9.04%).

[4S(4α,5α,6β)]-5-(2-{(4S*,6R*)-6-[2-(*t*-*Butyldiphenylsilyloxy*)*ethyl*]-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*}*ethyl*-6-[(1R*,3S*)-3-*ethyl*-1-(*triethylsilyloxy*)*pent*-4-*enyl*]-4-*methyl*-

cyclohex-2-enone (**14**).—Dry di-isopropylamine (0.151 ml, 1.08 mmol), 4-(dimethylamino)pyridine (DMAP) (10.5 mg, 0.086 mmol), and chlorotriethylsilane (0.18 ml, 1.07 mmol) were added to a stirred and cooled (ice-bath) solution of the alcohol (**13**) (140.0 mg, 0.216 mmol) in dry diethyl ether (10 ml). After 30 min the ice-bath was removed and the mixture was stirred for 40 h at room temperature [TLC control, silica; (1:4) diethyl ether–light petroleum]. Water (5 ml) and diethyl ether (25 ml) were then added. The aqueous layer was separated and the ethereal layer was washed with water (15 ml). The combined aqueous phases were extracted with diethyl ether (3 × 20 ml) and the combined extracts were washed with saturated aq. sodium hydrogencarbonate (15 ml) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm) with, first, (1:4) diethyl ether–light petroleum, and then (1:1) diethyl ether–light petroleum gave the *protected diol* (**14**) [149.1 mg, 92% after correction for recovered starting material (3.0 mg)] as a homogeneous [TLC, silica; (1:4) diethyl ether–light petroleum], thick oil: FT-IR (CH_2Cl_2 cast) 1 670 cm^{-1}; δ_H($CDCl_3$; 400 MHz) 0.59 (6 H, q, *J* 8.0 Hz), 0.85 (3 H, t, *J* 7.3 Hz), 0.95 (9 H, t, *J* 8.0 Hz), 1.05 (9 H, s), 1.06 (3 H, d, *J* 7.0 Hz), 1.36 (3 H, s), 1.41 (3 H, s), 1.06–1.81 (12 H, series of multiplets), 2.01–2.18 (2 H, m), 2.44 (1 H, dd, *J* 8.5, 4.0 Hz), 2.64–2.74 (1 H, m), 3.64–3.79 (2 H, m), 3.80–3.88 (1 H, m), 4.07–4.15 (1 H, m), 4.42–4.49 (1 H, m), 5.01 (1 H, dd, *J* 17.5, 2.0 Hz), 5.07 (1 H, dd, *J* 10.5, 2.0 Hz), 5.53 (1 H, ddd, *J* 17.5, 10.5, 9.0 Hz), 5.88 (1 H, dd, *J* 10.0, 1.5 Hz), 6.78 (1 H, dd, *J* 10.0, 5.0 Hz), 7.35–7.45 (6 H, m), and 7.64–67.69 (4 H, m); δ_C($CDCl_3$; 75.46 MHz) 5.37, 7.00, 11.53, 14.09, 19.20, 19.78, 24.36, 26.64, 28.63, 30.26, 31.25, 33.83, 37.39, 39.22, 39.40, 39.80, 42.10, 54.55, 59.65, 65.52, 69.21, 70.55, 98.39, 114.98, 127.60, 128.47, 129.55, 133.94, 133.98, 135.54, 142.56, 154.00, and 199.63 (Found: M^+, 760.4918; C, 72.3; H, 9.2. $C_{46}H_{72}O_5Si_2$ requires *M*, 760.4918; C, 72.58; H, 9.53%).

[1S,αS*.γR*-(1α,5β,6β)]-6-(2-{(4S*,6R*)-6-[2-(*t-Butyldiphenylsilyloxy)ethyl*]-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*}*ethyl*)-α-*ethyl*-5-*methyl*-2-*oxo*-γ-(*triethylsilyloxy*)*cyclohex*-3-*enebutanal* (**15**).—This experiment was done using the apparatus described by Rubin,[28] but with a pear-shaped reagent bulb. Ozonized oxygen, cooled by passage through a glass coil immersed in a solid CO_2–acetone bath, was bubbled for 4 min into dry dichloromethane (6 ml) at −78 °C. The resulting solution was transferred into the other bulb of the apparatus, which contained a cold (−78 °C) solution of the alkene (**14**) (51.5 mg, 0.0677 mmol) in dichloromethane (3 ml). The resulting mixture was stirred for 1 min, the solution was purged with argon, and triphenylphosphine (53.2 mg, 0.203 mmol) was then added. The cold-bath was removed and the mixture was stirred for 3 h. Evaporation of the solvent, and flash chromatography of the residue over Florisil (1 × 16 cm) with (successively) (1:9), (1:3), and (1:0) diethyl ether–light petroleum, gave the *title aldehyde* (**15**) [35.1 mg, 81% after correction for recovered (**14**) (8.2 mg)] as an apparently homogeneous [TLC, silica gel; (4:6) diethyl ether–light petroleum] oil: δ_H($CDCl_3$; 400 MHz) 0.57 (6 H, q, *J* 8.0 Hz), 0.92 (3 H, t, *J* 6.5 Hz), 0.93 (9 H, t, *J* 8.0 Hz), 1.04 (9 H, s), 1.08 (3 H, d, *J* 7.5 Hz), 1.09–1.76 (11 H, series of multiplets), 1.35 (3 H, s), 1.40 (3 H, s), 1.85 (1 H, ddd, *J* 12.5, 9.5, 3.0 Hz), 2.09–2.18 (1 H, m), 2.31–2.41 (1 H, m), 2.46 (1 H, dd, *J* 9.0, 5.0 Hz), 2.69–2.79 (1 H, m), 3.68 (1 H, dt, *J* 10.0, 5.0 Hz), 3.71–3.80 (1 H, m), 3.80–3.89 (1 H, m), 4.07–4.16 (1 H, m), 4.44–4.51 (1 H, m), 5.89 (1 H, dd, *J* 10.5, 1.8 Hz), 6.79 (1 H, dd, *J* 10.5, 4.5 Hz), 7.32–7.60 (6 H, m), 7.65–7.75 (4 H, m), and 9.63 (1 H, d, *J* 2.5 Hz); δ_C($CDCl_3$; 100.614 MHz) 5.16, 6.93, 11.48, 14.14, 19.21, 19.80, 22.52, 24.07, 26.85, 30.27, 31.24, 33.64, 33.72, 37.39, 39.41, 39.47, 49.90, 54.12, 59.65, 65.52, 69.10, 69.99, 98.42, 127.61, 128.27, 129.56, 133.83, 133.95, 135.55, 153.97, 199.41, and 204.67 (Found: M^+, 762.4711. $C_{45}H_{70}O_6Si_2$ requires *M*, 762.4710).

(4S*-*cis*)-4-[2-(*t-Butyldiphenylsilyloxy)ethyl*]-6-{2-[1S(1α,2α,-6β,8β,8aα)-6-*ethyl*-1,2,6,7,8,8a-*hexahydro*-2-*methyl*-8-(*triethylsilyloxy)naphthalen*-1-*yl*]*ethyl*}-2,2-*dimethyl*-1,3-*dioxolane* (**16**).—Freshly prepared potassium graphite (C_8K) (211.0 mg, 1.56 mmol) and titanium trichloride (122.0 mg, 0.791 mmol) were weighed under argon in a glove bag and transferred successively to a 50-ml three-necked flask containing dry DME (10 ml). The mixture was stirred and refluxed for 2 h under argon and then cooled to room temperature. A solution of the enone aldehyde (**15**) (35.0 mg, 0.0459 mmol) in dry DME (5 ml) † was added by syringe pump during 9 h to the stirred slurry of titanium reagent. The mixture was stirred for an additional 5 h, and was then refluxed for 5 h, cooled to room temperature, and filtered under a blanket of argon through a pad of Florisil (3.5 × 6 cm) contained in a sintered funnel equipped with an argon inlet near the top. The column was washed with diethyl ether (3 × 50 ml). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (1 × 14 cm) with (1:9) diethyl ether–light petroleum gave the *title compound* (**16**) (30.0 mg, 89%) as an apparently homogeneous [TLC, silica; (1:9) diethyl ether–light petroleum] oil: δ_H($CDCl_3$; 400 MHz) 0.55–0.70 (6 H, m), 0.87 (3 H, d, *J* 7.0 Hz), 0.96 (9 H, t, *J* 8.0 Hz), 0.97 (3 H, t, *J* 7.5 Hz), 1.07 (9 H, s), 1.11–1.29 (3 H, m), 1.40 (3 H, s), 1.46 (3 H, s), 1.48–1.89 (10 H, m), 2.00–2.12 (2 H, m), 2.34–2.44 (1 H, m), 3.71 (1 H, dt, *J* 10.0, 5.5 Hz), 3.78–3.91 (2 H, m), 4.11–4.20 (1 H, m), 4.28 (1 H, br q, *J* 3.0 Hz), 5.56 (1 H, br s), 5.76 (1 H, dd, *J* 9.5, 6.5 Hz), 5.99 (1 H, d, *J* 9.5 Hz), 7.3–7.46 (6 H, m), and 7.64–7.71 (4 H, m); δ_C($CDCl_3$; 100.614 MHz) 5.43, 7.20, 12.80, 14.22, 19.21, 19.77, 24.15, 26.84, 30.21, 30.30, 30.41, 33.44, 34.76, 35.26, 35.86, 37.33, 39.44, 40.23, 59.68, 65.58, 65.76, 69.74, 98.39, 127.60, 128.05, 128.96, 129.55, 132.02, 132.83, 133.90, 133.98, and 135.55 (Found: M^+, 730.4795. $C_{45}H_{70}O_4Si_2$ requires *M*, 740.4812).

[1S(1α,3α,7β,8β,8aβ)]-8-(2-{(4S*,6R*)-6-[2-(*t-Butyldiphenylsilyloxy)ethyl*]-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*}*ethyl*)-3-*ethyl*-1,2,3,7,8,8a-*hexahydro*-7-*methylnaphthalen*-1-*ol* (**17**).—TBAF (1.1M in THF; 0.4 ml, 0.44 mmol) was added to a solution of compound (**16**) (30.0 mg, 0.041 mmol) in THF (1.0 ml) and the mixture was stirred for 22 h at room temperature [TLC control, silica; (3:2) diethyl ether–light petroleum]. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 16 cm) with, first, (1:1) diethyl ether–light petroleum, and then diethyl ether gave the *diol* (**17**; R′ = R″ = H) (15.0 mg, 96%) as a homogeneous (TLC, silica; diethyl ether) oil: δ_H($CDCl_3$; 400 MHz) 0.89 (3 H, d, *J* 7.0 Hz), 0.99 (3 H, t, *J* 7.5 Hz), 1.39 (3 H, s), 1.44 (3 H, s), 1.20–1.87 (13 H, series of multiplets), 1.97 (1 H, dd, *J* 14.5, 3.5 Hz), 2.07–2.19 (2 H, m), 2.34–2.65 (2 H, m), 3.71–3.89 (2 H, m), 4.06–4.15 (1 H, m), 4.18–4.24 (1 H, m), 5.61 (1 H, br s), 5.79 (1 H, dd, *J* 10.0, 6.0 Hz), and 5.99 (1 H, d, *J* 10.0, Hz); δ_C($CDCl_3$; 100.614 MHz) 12.69, 13.97, 19.86, 23.44, 30.24, 30.70, 30.75, 33.14, 33.46, 34.69, 36.05, 37.01, 38.09, 39.26, 60.94, 65.19, 68.72, 69.46, 98.85, 128.44, 128.53, 131.87, and 133.85 (Found: M^+, 378.2765. $C_{23}H_{38}O_4$ requires *M*, 378.2770).

t-Butyl(chloro)diphenylsilane (0.01 ml, 0.038 mmol), triethylamine (0.006 ml, 0.04 mmol), and DMAP (3 mg, 0.024 mmol) were added successively to a stirred and cooled (ice-bath) solution of the above diol (14.5 mg, 0.0383 mmol) in dry dichloromethane (2 ml). The cold-bath was removed and the mixture was stirred for 24 h and was then evaporated. Flash

† The starting material was dissolved in DME (4 ml) and the solution was drawn up into the syringe. A further portion of DME (1 ml) was injected into the flask. This rinse was also drawn into the syringe followed by a bubble of argon (to expel all the solution by the end of the addition). The addition was performed using a syringe pump.

chromatography of the residue over silica gel (1 × 16 cm) with (3:17) diethyl ether–light petroleum gave the *title compound* (**17**) (23.0 mg, 97%) as a homogenous [TLC, silica gel; (1:4) diethyl ether–light petroleum] oil: δ_H($CDCl_3$; 400 MHz) 0.89 (3 H, d, *J* 7.0 Hz), 0.99 (3 H, t, *J* 7.0 Hz), 1.05 (9 H, s), 1.06–1.86 (13 H, series of multiplets), 1.35 (3 H, s), 1.42 (3 H, s), 1.96 (1 H, dd, *J* 14.5, 3.5 Hz), 2.08–2.20 (2 H, m), 2.34–2.44 (1 H, m), 3.69 (1 H, dt, *J* 10.0, 5.0 Hz), 3.77–3.88 (2 H, m), 4.06–4.15 (1 H, m), 4.19–4.25 (1 H, m), 5.63 (1 H, br s), 5.79 (1 H, dd, *J* 9.5, 6.0 Hz), 5.99 (1 H, d, *J* 9.5 Hz), 7.32–7.45 (6 H, m), and 7.65–7.75 (4 H, m); δ_C($CDCl_3$; 100.614 MHz) 12.71, 14.01, 19.21, 19.85, 23.40, 26.55, 26.84, 30.27, 30.66, 30.78, 33.16, 33.44, 34.74, 35.97, 37.48, 39.26, 39.34, 59.66, 65.17, 65.62, 68.73, 98.49, 127.60, 128.44, 128.56, 129.54, 131.93, 133.86, 134.79, and 135.56 (Found: M^+, 616.3960. $C_{39}H_{56}O_4Si$ requires *M*, 616.3948).

[1S(1α,3α,7β,8β,8aβ)]-8-(2-{(4S*,6R*)-6-[2-(*t-Butyldiphenylsilyloxy)ethyl*]-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*}*ethyl*)-3-*ethyl*-1,2,3,7,8,8a-*hexahydro*-7-*methylnaphthalen*-1-*yl* (R*)-2-*Methylbutyrate* (**18**).—DMAP (30 mg, 0.245 mmol), dry triethylamine (0.085 ml, 0.610 mmol) and (*S*)-2-methylbutyric anhydride (0.110 g, 0.590 mmol) were added in that order to a stirred solution of compound (**17**) (21.5 mg, 0.034 85 mmol) in dry dichloromethane (4 ml). The mixture was stirred for 80 h and was then evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm) with (2:23) diethyl ether–light petroleum gave the *ester* (**18**) [22.2 mg, 97% after correction for recovered (**17**) (1.5 mg)] as a homogeneous [TLC, silica; (1:4) diethyl ether–light petroleum] oil: FT-IR (CH_2Cl_2 cast), 1 726 cm^{-1}; δ_H($CDCl_3$; 400 MHz) 0.88 (3 H, t, *J* 7.5 Hz), 0.89 (3 H, d, *J* 7.0 Hz), 0.94 (3 H, t, *J* 7.5 Hz), 1.05 (9 H, s), 1.11 (3 H, d, *J* 7.0 Hz), 1.07–1.75 (13 H, series of multiplets), 1.36 (3 H, s), 1.43 (3 H, s), 1.83 (1 H, ddd, *J* 15.0, 8.0, 2.0 Hz), 2.07–2.19 (2 H, m), 2.24–2.45 (3 H, m), 3.65–3.77 (2 H, m), 3.80–3.88 (1 H, m), 4.07–4.16 (1 H, m), 5.34 (1 H, q, *J* 3.0 Hz), 5.62 (1 H, br s), 5.80 (1 H, dd, *J* 10.0, 6.0 Hz), 6.01 (1 H, d, *J* 10.0 Hz), 7.35–7.46 (6 H, m), and 7.65–7.71 (4 H, m); δ_C($CDCl_3$; 100.614 MHz) 11.73, 12.54, 13.82, 16.18, 19.21, 19.89, 23.90, 26.83, 29.72, 30.01, 30.25, 30.70, 33.85, 34.76, 36.77, 37.43, 37.74, 39.36, 41.40, 59.62, 65.39, 67.87, 69.56, 98.38, 127.57, 127.60, 127.97, 128.28, 129.52, 132.30, 133.58, 133.94, 133.99, 135.55, and 176.32 (Found: M^+, 700.4518. $C_{44}H_{64}O_5Si$ requires *M*, 700.4523).

[1S(1α,3α,7β,8β,8aβ)]-3-*Ethyl*-1,2,3,7,8,8a-*Hexahydro*-8-{2-[(4S*,6R*)-6-(2-*hydroxyethyl*)-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*]*ethyl*}-7-*methylnaphthalen*-1-*yl* (R*)-2-*Methylbutyrate* (**19**).—TBAF (1.1M in THF; 0.04 ml, 0.044 mmol) was added to a solution of compound (**18**) (21.5 mg, 0.030 66 mmol) in dry THF (1 ml) and the mixture was stirred at room temperature for 3 h (TLC control). Evaporation of the solvent, and flash chromatography of the residue over silica gel (1 × 16 cm) with, first, (2:3) diethyl ether–light petroleum, and then (3:2) diethyl ether–light petroleum gave the *title compound* (**19**) (12.7 g, 89%) as a homogeneous [TLC, silica; (7:3) diethyl ether–light petroleum] oil: δ_H($CDCl_3$; 400 MHz) 0.88 (3 H, d, *J* 7.0 Hz), 0.89 (3 H, t, *J* 7.5 Hz), 0.93 (3 H, t, *J* 7.5 Hz), 1.10 (3 H, d, *J* 7.0 Hz), 1.12–1.75 (13 H, series of multiplets), 1.37 (3 H, s), 1.45 (3 H, s), 1.83 (1 H, ddd, *J* 15.0, 8.5, 2.0 Hz), 2.06–2.16 (2 H, m), 2.23–2.44 (4 H, m), 3.69–3.82 (3 H, m), 4.04–4.13 (1 H, m), 5.34 (1 H, q, *J* 2.5 Hz), 5.61 (1 H, br s), 5.79 (1 H, dd, *J* 10.0, 6.5 Hz), and 6.00 (1 H, d, *J* 10.0, Hz); δ_C($CDCl_3$; 100.614 MHz) 11.74, 12.54, 13.80, 16.19, 19.91, 23.81, 26.87, 29.71, 30.02, 30.21, 30.66, 33.77, 34.73, 36.77, 36.83, 37.68, 38.03, 41.41, 61.04, 67.62, 69.45, 69.53, 98.57, 128.01, 128.28, 132.20, 133.49, and 177.10 (Found: M^+, 462.3341. $C_{28}H_{46}O_5$ requires *M*, 462.3345).

[1S(1α,3α,7β,8β,8aβ)]-3-*Ethyl*-8-{2-[(4S*,6R*)-6-*formylmethyl*-2,2-*dimethyl*-1,3-*dioxan*-4-*yl*]*ethyl*}-1,2,3,7,8,8a-*hexahydro*-7-*methylnaphthalen*-1-*yl* (R*)-2-*Methylbutyrate* (**20**).—Dry DMSO (0.010 ml, 0.141 mmol) was added to a stirred solution of oxalyl dichloride (0.008 ml, 0.092 mmol) in dry dichloromethane (2 ml) at −78 °C (argon atmosphere). After 10 min a solution of alcohol (**19**) (11.8 mg, 0.0255 mmol) in dry dichloromethane (1 ml plus 0.5 ml as a rinse) was added by syringe. After 20 min, dry triethylamine (0.50 ml, 0.359 mmol) was added and, after a further 10 min, the cold-bath was removed and the solution was stirred for 20 min more. A few drops of water were then added and the mixture was concentrated at room temperature. Flash chromatography of the residue over silica gel (1 × 16 cm) with (2:3) diethyl ether–light petroleum gave *aldehyde* (**20**) (10.8 mg, 91%) as a homogeneous [TLC, silica; (2:3) diethyl ether–light petroleum] oil: δ_H($CDCl_3$; 400 MHz) 0.87 (3 H, d, *J* 7.5 Hz), 0.88 (3 H, t, *J* 7.0 Hz), 0.93 (3 H, t, *J* 7.5 Hz), 1.09 (3 H, d, *J* 7.0 Hz), 1.11–1.71 (11 H, series of multiplets), 1.36 (3 H, s), 1.45 (3 H, s), 1.82 (1 H, ddd, *J* 15.0, 8.5, 2.0 Hz), 2.06–2.17 (2 H, m), 2.23–2.42 (3 H, m), 2.47 (1 H, ddd, *J* 16.5, 5.0, 1.8 Hz), 2.58 (1 H, ddd, *J* 16.5, 7.5, 2.5 Hz), 3.72–3.81 (1 H, m), 4.34–4.42 (1 H, m), 5.33 (1 H, q, *J* 3.0 Hz), 5.61 (1 H, br s), 5.78 (1 H, dd, *J* 10.0, 6.5 Hz), 5.99 (1 H, d, *J* 10.0 Hz), and 9.78 (1 H, t, *J* 2.0 Hz); δ_C($CDCl_3$; 100.614 MHz) 11.72, 12.52, 13.81, 16.18, 19.77, 23.83, 26.86, 29.73, 30.04, 30.69, 33.72, 34.75, 36.79, 37.73, 41.42, 49.83, 64.66, 67.82, 69.29, 98.76, 128.05, 128.32, 132.22, 133.44, 176.61, and 200.97 (Found: M^+, 460.3201. $C_{28}H_{44}O_5$ requires *M*, 460.3189).

[1S(1α,3α,7β,8β,8aβ)]-3-*Ethyl*-1,2,3,7,8,8a-*hexahydro*-7-*methyl*-8-{2-[(2S*,4S*,6R*)- *and* (2S*,4S*,6S*)-*tetrahydro*-4,6-*dihydroxy*-2H-*pyran*-2-*yl*]*ethyl*}*naphthalen*-1-*yl* (R*)-2-*Methylbutyrate* (**21**).—Aq. hydrochloric acid (10% v/v; 0.38 ml) was added to a solution of aldehyde (**20**) (10.0 mg, 0.0217 mmol) in THF (1 ml) and the mixture was stirred at room temperature for 4 h under argon. By this stage all of the starting material had been hydrolysed (TLC, silica; diethyl ether). Solid sodium hydrogencarbonate (200 mg) was added cautiously to the stirred mixture, followed by ethyl acetate (10 ml) and water (2 ml). The organic phase was separated and washed with water (2 ml), and the combined aqueous phases were extracted with ethyl acetate (4 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford, after being dried for 12 h under oil-pump vacuum, a mixture of anomeric lactols (**21**) (7.3 mg, 79%). These were oxidized immediately without characterization.

[1S(1α,3α,7β,8β,8aβ)]-3-*Ethyl*-1,2,3,7,8,8a-*hexahydro*-7-*methyl*-8-{2-[(2S*,4S*)-*tetrahydro*-4-*hydroxy*-6-*oxo*-2H-*pyran*-2-*yl*]*ethyl*}*naphthalen*-1-*yl* (R*)-2-*Methylbutyrate* (**1c**).—Silver carbonate on Celite (170.0 mg, 0.292 mmol) was added to a stirred solution of the dry lactols (**21**) (5.0 mg, 0.0119 mmol) in dry toluene (2 ml) and the mixture was stirred at 85–95 °C (oil-bath temperature) for 1 h under argon. At this stage, TLC [silica; (9:1) diethyl ether–ethyl acetate] showed that all the starting material had reacted. The mixture was cooled to room temperature and filtered through a column of Celite (1 × 4 cm), the solids being washed with ethyl acetate (5 × 20 ml). Evaporation of the combined filtrates, and chromatography of the residue over Florisil (0.6 × 5 cm) with (9:1) diethyl ether–ethyl acetate gave 3-ethylcompactin (**1c**) (3.6 mg, 72%) as a homogeneous [TLC, silica; (9:1) diethyl ether–ethyl acetate; δ_H(400 MHz)] solid, m.p. 116–118 °C; $[\alpha]_D^{28}$ +286.8° (*c* 0.2545 in MeCN); δ_H($CDCl_3$; 400 MHz) 0.88 (3 H, t, *J* 7.5 Hz), 0.90 (3 H, d, *J* 7.0 Hz), 0.93 (3 H, t, *J* 7.5 Hz), 1.10 (3 H, d, *J* 6.5 Hz), 1.21–1.56 (6 H, m), 1.60–1.74 (3 H, m), 1.80–1.92 (2 H, m), 1.92–2.01 (2 H, m), 2.04–2.19 (2 H, m), 2.25–2.42 (3 H, m), 2.62 (1 H, ddd, *J* 18.0, 4.0, 1.5 Hz), 2.74 (1 H, dd, *J* 18.0, 5.0 Hz), 4.34–4.41 (1 H, m), 4.56–4.65 (1 H, m), 5.37 (1 H, q, *J* 3.0 Hz), 5.62 (1 H, br s), 5.79 (1 H, dd, *J* 9.5, 6.0 Hz), and 6.00 (1 H, d, *J* 9.5 Hz);

δ_C($CDCl_3$; 100.614 MHz) 11.72, 12.51, 13.89, 16.22, 24.26, 26.84, 29.74, 30.15, 30.71, 32.97, 34.71, 36.25, 36.61, 37.75, 38.62, 41.48, 62.75, 67.80, 76.23, 128.27, 128.43, 131.94, 133.06, 170.09, and 176.74 (Found: M^+, 418.2706. $C_{25}H_{38}O_5$ requires M, 418.2719).

Biological Evaluation.—3-Ethylcompactin (**1c**) and mevinolin (**1b**) were dissolved in DMSO. Aliquots (10 μl) of each were incubated for 30 min at 37 °C with aq. buffer (pH 7.4) to delactonize the compounds. The buffer was 50mM in potassium phosphate, 70mM in potassium chloride, 30mM in ethylenediaminetetra-acetic acid, and 10mM in dithiothreitol. Control incubations were done with DMSO (10 μl).

The assay of HMG CoA reductase was carried out as described by George and Ramasarma.[24] At the end of a 30-min incubation period (to allow for delactonization), rat liver microsomes (75 μg protein) were added to each tube along with glucuse 6-phosphate (577 μM), glucose 6-phosphate dehydrogenase (0.05 unit/assay), and NADPH (53 μM), and the mixture was incubated for an additional 10 min at 37 °C.

The HMG CoA reductase reaction was initiated by addition of [3-^{14}C]HMG CoA (240 μM, final) and allowed to proceed for 20 min at 37 °C in a total volume of 100 μl. The reaction was terminated by addition of 5M HCl (25 μl) containing known amounts of [^{3}H]mevalonolactone as internal standard and non-radioactive mevalonolactone (0.6 mg/assay) as carrier. The mevalonic acid formed in the assay was allowed to lactonize by incubation of the mixture for 30 min at 37 °C. The precipitated protein was removed by centrifugation in a microfuge. An aliquot of the supernatant (40 μl) was applied to a silica gel G (0.25 mm thickness) plate and the chromatogram was developed with (3:2) acetone–benzene. The spot corresponding to mevalonolactone (R_F 0.5) was scraped off and the radioactivity was estimated by liquid scintillation counting. The amount of mevalonic acid formed was calculated from the recovery of internal standard. Microsomal protein was estimated using standard[29,30] procedures. The specific activity of HMG CoA reductase is expressed (Table 2) as picomoles of mevalonic acid formed per mg of microsomal protein.

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