Pergamon

Bioorganic & Medicinal Chemistry, Vol. 2, No. 8, pp. 799-806, 1994

0968-0896/94 $7.00 + .00

0968-0896(94)00071-9

7-(Disubstituted thiazolyl)-3,5-Dihydroxy-6-Heptenoic/Heptanoic Acid Derivatives as HMG-CoA Reductase Inhibitors[1]

Violetta Cecchetti,[a] Arnaldo Fravolini,[a]* Pier Giuseppe Pagella,[b] Oriana Tabarrini[a] and Andrea Temperini[a]

[a]*Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università di Perugia, 06123 Perugia, Italy*
[b]*Mediolanum Farmaceutici, via S. G. Cottolengo 31, 20143 Milano, Italy*

Abstract—A series of disubstituted thiazoles, functionalized with the essential 3,5-dihydroxy-6-heptenoic or heptanoic chain, were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase *in vitro*. All the synthesized compounds **46–61** showed a moderate inhibitory potency.

Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is responsible for the conversion of HMG-CoA to mevalonic acid and is the rate-limiting enzyme in the biosynthesis of endogenous cholesterol. Two closely related natural products, lovastatin[2] and pravastatin,[3] as well as the semisynthetic compound simvastatin,[4] are potent HMG-CoA reductase inhibitors and are currently being used in the treatment of hypercholesterolaemia.

In design of structurally simplified analogs of these natural products, emphasis has focused on the replacement of the complex decalin with structurally simpler aromatic or heteroaromatic surrogates leading to a variety of synthetic 7-aryl/heteroaryl-3,5-dihydroxyheptanoic acid inhibitors of considerable potency. High activity has been reported for benzene derivatives,[5] quinolines,[6] indoles,[7] pyridines,[8] pyrimidines,[8] pyrroles,[9,10] thiophenes,[10] furans,[10] imidazoles[11] and pyrazoles.[12]

We herein report the synthesis and biological activity of a thiazole series of HMG-CoA reductase inhibitors in which the pharmacophore 3,5-dihydroxyheptenoic and -heptanoic chain is linked at the 2, 4 or 5 position of the disubstituted thiazole nucleus (Figure 1).

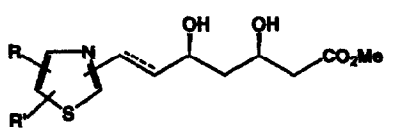


Figure 1.

Chemistry

The target thiazolyl (*E*)-dihydroxyheptenoic and dihydroxyheptanoic acid derivatives **46–61** listed in Table 4 were prepared by the general synthetic route shown in Scheme II.

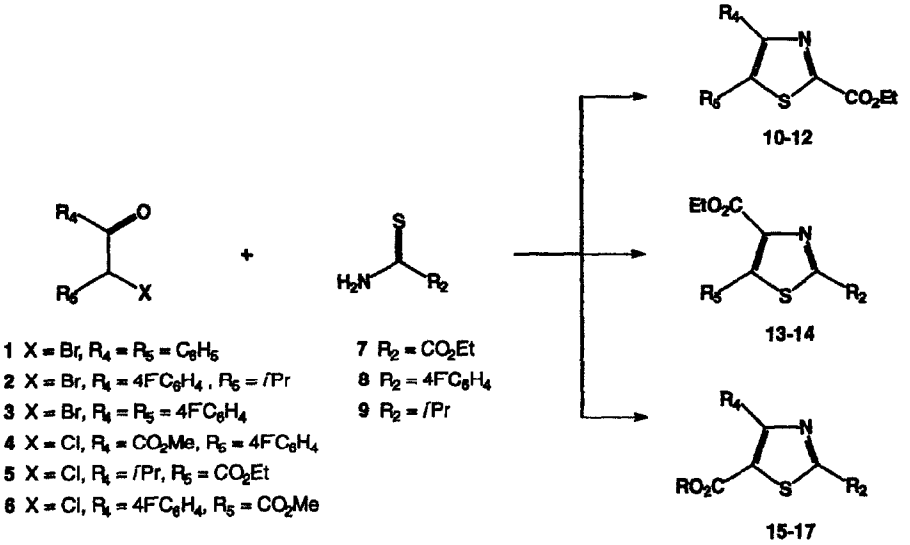
The required thiazole esters **10–17** were synthesized by the Hantzsch procedure via condensation of an appropriate α-halocarbonyl compound (**1–6**) with a suitable thioamide (**7–9**) (Scheme I).

Reduction of thiazole esters **10–13** with DIBAL-*H* directly produced the aldehydes **22–25**, respectively, in good yields; the reduction of thiazole esters **14–17** mainly gave the alcohols **18–21**, which, after oxidation with pyridinium chlorochromate afforded aldehydes **26–29**, respectively. The synthesis of (*E*)-α,β-unsaturated aldehydes **30–37** was accomplished by condensation of the corresponding aldehyde derivatives **22–29** with (triphenylphosphoranylidene)acetaldehyde in toluene. Condensation of **30–37** with the dianion of methyl acetoacetate afforded the racemic β-keto-δ-hydroxy esters **38–45**. Highly stereoselective reduction of the keto group[13] was performed with triethylborane and sodium borohydride to give β,δ-dihydroxy esters **46–53** as a mixture of diastereoisomers with a *syn:anti* ratio > 96:4 (^{13}C NMR). Catalytic hydrogenation of **46–53** over Pd/C led to saturated analogues **54–61**.

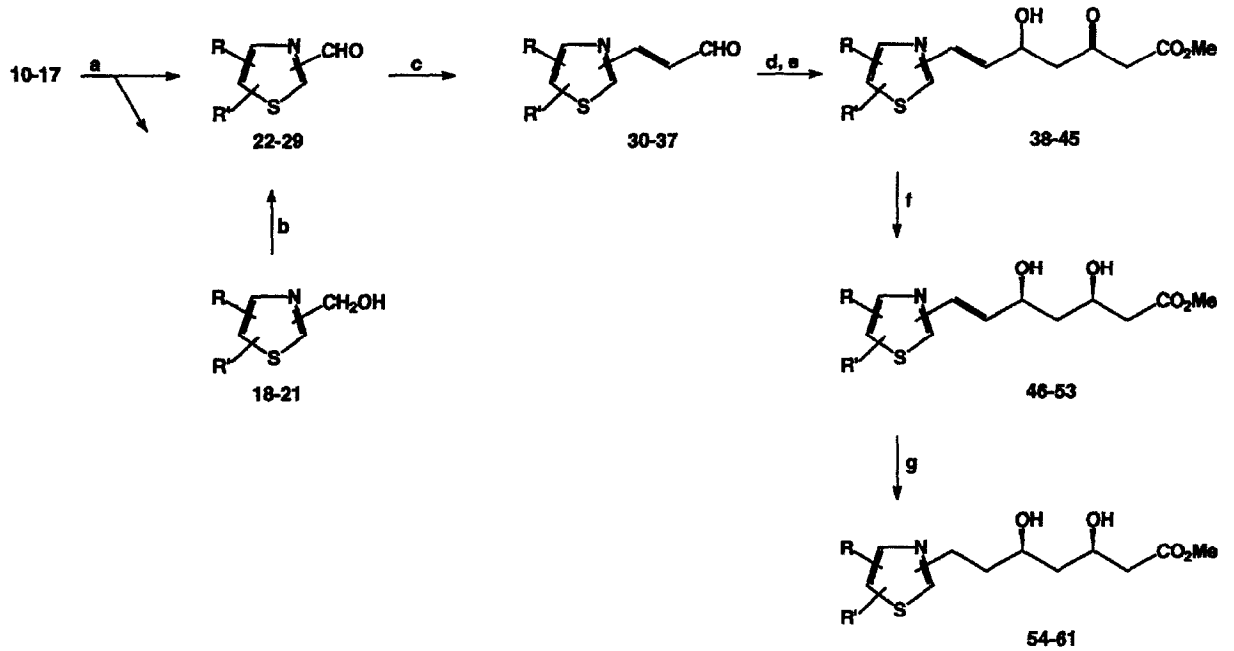
Results and Discussion

The target thiazole methyl esters **46–61** were evaluated, after saponification to the corresponding sodium salts, for their ability to inhibit the *in vitro* conversion of [^{14}C]HMG-CoA to [^{14}C]mevalonic acid by partially purified rat liver HMG-CoA reductase. The biological data are displayed in Table 4 as an IC_{50}. Simvastatin was employed as control drug.

All synthesized compounds showed a moderate activity with IC_{50} values in the order of 10^{-5} M. Positional modifications of heptenoic/heptanoic chain on the thiazole ring as well as size and shape of the two lipophilic groups had little affect on potency. Compounds **54–61**, with a



Scheme I.



Scheme II. Reagents: (a) CH_2Cl_2, DIBAL-*H*, -78 °C; (b) $PyClCrO_3$, CH_2Cl_2/EtOAc 1:1; (c) Ph_3P=CHCHO, toluene, reflux; (d) $CH_3COCH_2CO_2CH_3$, NaH, THF, -30°C; (e) BuLi, -70 °C; (f) BEt_3, O_2, $NaBH_4$, -78 °C, THF; (g) NEt_3, H_2, 10 % Pd/C, MeOH.

saturating ethenyl bridge between the mevalonic portion and thiazole ring, were generally two-to-four times less potent than the unsaturated analogues **46–53**.

The moderate activity shown by the compounds here studied compared to the high activity of the analogues with five-membered heterocyclic systems, such as pyrazole, imidazole, pyrrole, thiophene and furan, seems to indicate that the thiazole nucleus cannot interact fruitfully with the receptor site probably due to unfavorable steric and/or electronic requirements. On the other hand, our results are in agreement with those obtained with isothiazole and isoxazole analogues;[14] this may be an indication that the presence of a third lipophilic substituent, absent in thiazole, isothiazole, and isoxazole nuclei, is necessary for a high inhibitory potency.

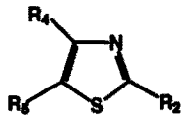
In conclusion, it is clear that a disubstituted thiazole nucleus is not a suitable heteroaromatic anchor system for replacing the hexahydro- naphthalene ring present in the fungal metabolites lovastatin and pravastatin.

Experimental Section

Melting points were determined in capillary tubes (Buchi melting point apparatus) and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H and N are within ± 0.4 % of the theoretical values. NMR spectra were recorded in $CDCl_3$ as solvent with Me_4Si as internal standard using the following spectrometers: Varian EM 390 (90 MHz ^1H), Bruker AC-200 (200 MHz ^1H, 50 MHz

^{13}C). Chemical shifts are given in ppm (δ) and the spectral data are consistent with the assigned structures. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70–230). Reagents and solvents were purchased from common commercial suppliers and were used as received. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Buchi rotary evaporator at low pressure. Yields are of purified product and were not optimized. The physical properties of the synthesized compounds are summarized in Tables 1–4.

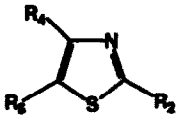
Table 1. Physical properties of thiazole esters



compd	R_2	R_4	R_5	reaction time (h)	% yield	mp, °C	purification method[a]	formula[b]
10	CO_2Et	C_6H_5	C_6H_5	3	80	89-92	A	$C_{18}H_{15}NO_2S$
11	CO_2Et	4F-C_6H_4	*i*-Pr	1	20	<50	A	$C_{15}H_{16}FNO_2S$
12	CO_2Et	4F-C_6H_4	4F-C_6H_4	2	70	119-121	A	$C_{18}H_{13}F_2NO_2S$
13	*i*-Pr	CO_2Et	4F-C_6H_4	5	60	oil	B	$C_{15}H_{16}FNO_2S$
14	4F-C_6H_4	CO_2Et	4F-C_6H_4	12	35	140-142	D	$C_{18}H_{13}F_2NO_2S$
15	*i*-Pr	4F-C_6H_4	CO_2Me	2	88	oil	B	$C_{13}H_{12}FNO_2S$
16	4F-C_6H_4	*i*-Pr	CO_2Et	4	80	<50	B	$C_{15}H_{16}FNO_2S$
17	4F-C_6H_4	4F-C_6H_4	CO_2Me	1	70	198-200	C	$C_{17}H_{11}F_2NO_2S$

[a]Solvent used with silica gel column or for purification as follows: (A) elution with gradient of cycloexane to 10 % EtOAc/cyclohexane, (B) isocratic elution with $CHCl_3$, (C) washed with EtOH, (D) washed with Et_2O.
[b]All compounds had elemental analyses within ± 0.4 % of theoretical value.

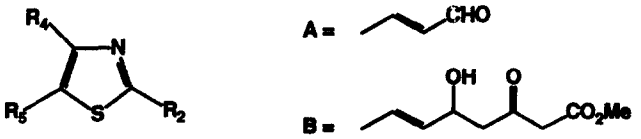
Table 2. Physical properties of alcohols and aldehydes



compd	R_2	R_4	R_5	% yield[a]	mp, °C	formula[b]
18	4F-C_6H_4	CH_2OH	4F-C_6H_4	70	156-160	$C_{16}H_{11}F_2NOS$
19	*i*-Pr	4F-C_6H_4	CH_2OH	95	132-136	$C_{13}H_{14}FNOS$
20	4F-C_6H_4	*i*-Pr	CH_2OH	96	127-130	$C_{13}H_{14}FNOS$
21	4F-C_6H_4	4F-C_6H_4	CH_2OH	85	179-181	$C_{16}H_{11}F_2NOS$
22	CHO	C_6H_5	C_6H_5	45	104-106	$C_{16}H_{11}NOS$
23	CHO	4F-C_6H_4	*i*-Pr	50	oil	$C_{13}H_{12}FNOS$
24	CHO	4F-C_6H_4	4F-C_6H_4	65	96-98	$C_{16}H_9F_2NOS$
25	*i*-Pr	CHO	4F-C_6H_4	58	<50	$C_{13}H_{12}FNOS$
26	4F-C_6H_4	CHO	4F-C_6H_4	50	128-130	$C_{16}H_9F_2NOS$
27	*i*-Pr	4F-C_6H_4	CHO	45	oil	$C_{13}H_{12}FNOS$
28	4F-C_6H_4	*i*-Pr	CHO	60	107-110	$C_{13}H_{12}FNOS$
29	4F-C_6H_4	4F-C_6H_4	CHO	60	184-186	$C_{16}H_9F_2NOS$

[a]All compounds were purified by column chromatography eluting with $CHCl_3$.
[b]All compounds had elemental analyses within ± 0.4 % of theoretical value.

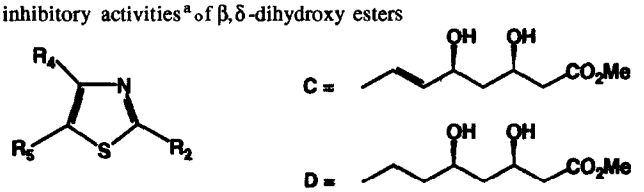
Table 3. Physical properties of (*E*)-α,β-unsatured aldehydes and (*E*)-β-keto-δ-hydroxy esters



compd	R_2	R_4	R_5	% yield[a]	mp, °C	formula[b]
30	A	C_6H_5	C_6H_5	80	111-113	$C_{18}H_{13}NOS$
31	A	4F-C_6H_4	*i*-Pr	80	80-82	$C_{15}H_{14}FNOS$
32	A	4F-C_6H_4	4F-C_6H_4	90	100-102	$C_{18}H_{11}F_2NOS$
33	*i*-Pr	A	4F-C_6H_4	70	78-80	$C_{15}H_{14}FNOS$
34	4F-C_6H_4	A	4F-C_6H_4	90	156-159	$C_{18}H_{11}F_2NOS$
35	*i*-Pr	4F-C_6H_4	A	30	oil	$C_{15}H_{14}FNOS$
36	4F-C_6H_4	*i*-Pr	A	75	142 dec	$C_{15}H_{14}FNOS$
37	4F-C_6H_4	4F-C_6H_4	A	50	176-180	$C_{18}H_{11}F_2NOS$
38	B	C_6H_5	C_6H_5	80	oil	$C_{23}H_{21}NO_4S$
39	B	4F-C_6H_4	*i*-Pr	70	oil	$C_{20}H_{22}FNO_4S$
40	B	4F-C_6H_4	4F-C_6H_4	70	oil	$C_{23}H_{19}F_2NO_4S$
41	*i*-Pr	B	4F-C_6H_4	60	oil	$C_{20}H_{22}FNO_4S$
42	4F-C_6H_4	B	4F-C_6H_4	60	oil	$C_{23}H_{19}F_2NO_4S$
43	*i*-Pr	4F-C_6H_4	B	70	oil	$C_{20}H_{22}FNO_4S$
44	4F-C_6H_4	*i*-Pr	B	60	oil	$C_{20}H_{22}FNO_4S$
45	4F-C_6H_4	4F-C_6H_4	B	75	oil	$C_{23}H_{19}F_2NO_4S$

[a]Compounds **30–37** were purified by column chromatography eluting with CH_2Cl_2, while compounds **38–45** by column chromatography eluting with gradient of CH_2Cl_2 to 60 % EtOAc/CH_2Cl_2.
[b]All compounds had elemental analyses within ± 0.4 % of theoretical value.

Table 4. Physical properties and inhibitory activities[a] of β,δ-dihydroxy esters



compd	R_2	R_4	R_5	% yield[b]	mp, °C	formula[c]	IC_{50} (μM)
46	C	C_6H_5	C_6H_5	70	foam	$C_{23}H_{23}NO_4S$	30
47	C	4F-C_6H_4	*i*-Pr	60	wax	$C_{20}H_{24}FNO_4S$	45
48	C	4F-C_6H_4	4F-C_6H_4	90	oil	$C_{23}H_{21}F_2NO_4S$	37
49	*i*-Pr	C	4F-C6H4	60	oil	$C_{20}H_{24}FNO_4S$	36
50	4F-C_6H_4	C	4F-C_6H_4	70	wax	$C_{23}H_{21}F_2NO_4S$	45
51	*i*-Pr	4F-C_6H_5	C	60	oil	$C_{20}H_{24}FNO_4S$	38
52	4F-C_6H_5	*i*-Pr	C	65	oil	$C_{20}H_{24}FNO_4S$	47
53	4F-C_6H_5	4F-C_6H_5	C	50	oil	$C_{23}H_{21}F_2NO_4S$	55
54	D	C_6H_5	C_6H_5	90	oil	$C_{23}H_{25}NO_4S$	45
55	D	4F-C_6H_4	*i*-Pr	85	oil	$C_{20}H_{26}FNO_4S$	85

Table 4. *Continued*

compd	R_2	R_4	R_5	% yield[b]	mp, °C	formula[c]	IC_{50} (μM)
56	D	4F-C_6H_4	4F-C_6H_4	70	oil	$C_{23}H_{23}F_2NO_4S$	75
57	*i*-Pr	D	4F-C_6H_4	70	oil	$C_{20}H_{26}FNO_4S$	180
58	4F-C_6H_4	D	4F-C_6H_4	70	oil	$C_{23}H_{23}F_2NO_4S$	125
59	*i*-Pr	4F-C_6H_4	D	85	oil	$C_{20}H_{26}FNO_4S$	100
60	4F-C_6H_4	*i*-Pr	D	100	oil	$C_{20}H_{26}FNO_4S$	38
61	4F-C_6H_4	4F-C_6H_4	D	65	oil	$C_{23}H_{23}F_2NO_4S$	90
simvastatin							0.07

[a]All compounds in this table were tested after being converted to the sodium salts of the corresponding dihydroxy carboxylic acids; for assay protocol see the Experimental Section.
[b]Compounds **46–53** were purified by column chromatography eluting witht gradient of CH_2Cl_2/EtOAc 3:7 to CH_2Cl_2/EtOAc 1:1, while compounds **54–61** by column chromatography eluting with gradient of CH_2Cl_2/EtOAc 8:2 to EtOAc/CH_2Cl_2 6:4.
[c]All compounds had elemental analyses within ± 0.4 % of theoretical value.

Desyl bromide (**1**) was obtained from Aldrich Chimica, while 2-bromo-1-(4-fluorophenyl)-3-methyl-1-butanone (**2**),[15] 2-bromo-1,2-bis-(4-fluorophenyl)ethanone (**3**),[15] ethyl thioxamate (**7**)[16] and iso-propylthioamide (**9**)[17] were prepared according to the literature.

Methyl 3-chloro-3-(4-fluorophenyl)-2-oxopropanoate (4)

Sulfuryl chloride (5.8 mL, 71 mmol) was added dropwise to a solution of methyl 4-fluorophenylpyruvate (14 g, 71 mmol) in CH_2Cl_2 (20 mL), cooled at 0 °C. The resulting mixture was warmed to 65–70 °C for 15 min, then cooled and extracted with Et_2O. The combined organic phases were washed with brine and evaporated to dryness to give **4** (14.5 g, 88 %) as an oil which was used in the next step without further purification. ^1H NMR δ 3.70 (s, 1H), 3.90 (s, 3H), 6.90–7.50 (m, 4H).

According to this procedure, compounds **5** and **6** were prepared starting from ethyl 4-methyl-3-oxopentanoate and methyl 3-(4-fluorophenyl)-3-oxopropanoate, respectively: **5**, oil (90 %); **6**, oil (93 %).

4-Fluorothiobenzamide (8)

P_2S_5 (4 g, 15 mmol) was carefully added portionwise to a refluxing solution of 4-fluorobenzenamide (10 g, 72 mmol) in xylene (50 mL). After 10 min the hot mixture was filtered and then allowed to cool to room temperature. The resulting precipitate was collected to give **8** (6 g, 54 %) as a crystalline yellow solid: mp 152–153 °C (lit.[18] 149–151 °C).

General procedure for the synthesis of thiazole esters 10–17

This procedure is illustrated by the synthesis of ethyl 4,5-diphenylthiazole-2-carboxylate (**10**).

A mixture of ethyl thioxamate (**7**) (13.3 g, 0.1 mol) and desyl bromide (**1**) (27.5 g, 0.1 mol) dissolved in a minimum amount of dry EtOH, was refluxed for 3 h. The mixture was then poured into alkaline water (200 mL) and extracted with EtOAc. The combined organic phases were washed with brine, dried and evaporated to dryness. The residue was purified by column chromatography eluting with a gradient of cyclohexane to 10 % EtOAc/cyclohexane to give **10** (24.7 g, 80 %): mp 89–92 °C; ^1H NMR δ 1.45 (t, J = 7 Hz, 3H), 4.50 (q, J = 7 Hz, 2H), 7.15–7.60 (m, 10H). Anal. ($C_{18}H_{15}NO_2S$) C, H, N.

General procedure for the synthesis of thiazole-substituted aldehydes 22–25

This procedure is illustrated by the synthesis of 4,5-diphenylthiazole-2-carboxaldehyde (**22**).

DIBAL-*H* (14 mL, 1 M solution in CH_2Cl_2) was added dropwise to a solution of thiazole ester **10** (2 g, 6.5 mmol) in dry CH_2Cl_2 (50 mL) cooled to –78 °C, under nitrogen atmosphere. After stirring for 3 h at –78 °C the reaction was quenched by adding saturated aqueous solution of Na_2SO_4 (10 mL) and the mixture was allowed to warm to room temperature. Then it was acidified with dilute HCl, filtered and washed with EtOAc. The filtrate was washed with brine, dried and evaporated to dryness. The solid residue was chromatographed on a silica gel column eluting with $CHCl_3$ to give **22** (0.78 g, 45 %): mp 104–106 °C; ^1H NMR δ 7.20–7.60 (m, 10H), 9.90 (s, 1H); ^{13}C NMR δ 183.95, 163.02, 153.27, 133.83, 130.87, 129.55, 129.35, 129.04, 128.98, 128.56, 128.50. Anal. ($C_{16}H_{11}NOS$) C, H, N.

General procedure for the synthesis of thiazole-substituted aldehydes 26–29

This procedure is illustrated by the synthesis of 2,5-di-(4-fluorophenyl)thiazole-4-carboxaldehyde (**26**).

Following the above reduction with DIBAL-*H*, thiazole ester **14** afforded the intermediate alcohol **18** (70 %) which was pure enough to be submitted to the next step: mp 156–160 °C; ^1H NMR δ 4.76 (s, 2H), 7.00–7.25 (m, 4H), 7.35–7.60 (m, 2H), 7.75–8.00 (m, 2H).

Pyridinium chlorochromate (2.6 g, 12 mmol) was added portionwise to a solution of alcohol **18** (3.65 g, 12 mmol)

in CH_2Cl_2:EtOAc 1:1 (80 mL). After stirring at room temperature for 1 h the reaction mixture was poured into water, alkalinized with 2 N NaOH and filtered. The filtrate was extracted with CH_2Cl_2. The combined organic phases were dried and evaporated to dryness. The resulting residue was chromatographed on silica gel column eluting with CH_2Cl_2 to give **26** (1.8 g, 50 %): mp 128–130 °C; ^{1}H NMR δ 7.10–7.30 (m, 4H), 7.50–7.70 (m, 2H), 7.90–8.10 (m, 2H), 10.00 (s, 1H). ^{13}C NMR δ 184.12, 180.77, 167.00, 166.35, 161.98, 132.20, 132.03, 129.07, 128.87, 116.54, 116.40, 116.09, 115.98. Anal. ($C_{16}H_9F_2NOS$) C, H, N.

General procedure for the synthesis of (E)-α,β-unsaturated aldehydes 30–37

This procedure is illustrated by the synthesis of (*E*)-3-(4,5-diphenylthiazol-2-yl)-2-propenal (**30**).

A mixture of aldehyde **22** (5 g, 18.8 mmol) and (triphenylphosphoranylidene)acetaldehyde (6.3 g, 20.7 mmol) in dry toluene (100 mL) was refluxed for 1 h and then evaporated to dryness. The residue was purified by column chromatography eluting with CH_2Cl_2 to give **30** (4.3 g, 79 %): mp 111–113 °C; ^{1}H NMR δ 6.85 (dd, *J* = 15 and 8.5 Hz, 1H), 7.20–7.70 (m, 11H), 9.78 (d, *J* = 8.5 Hz, 1H). Anal. ($C_{18}H_{13}NOS$) C, H, N.

General procedure for the synthesis of β-keto-δ-hydroxy esters 38–45

This procedure is illustrated by the synthesis of methyl (*E*)-7-(4,5-diphenylthiazol-2-yl)-5-hydroxy-3-oxo-6-heptenoate (**38**).

A solution of methyl acetoacetate (3.03 g, 26 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred suspension of NaH (60 % oil suspension, 1.12 g, 28 mmol) in anhydrous THF (100 mL) at –30 °C and under a nitrogen atmosphere. When gas evolution was complete, the reaction mixture was cooled to –70 °C and then *n*-butyllithium (17.8 mL, 1.6 M solution in hexane) was added. The resulting yellow solution was stirred for 15 min at –70 °C and then treated with a solution of α,β-unsaturated aldehyde **30** (4.47 g, 15.4 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred for 1 h maintaining a temperature below –30 °C and then quenched by the addition of saturated aqueous solution of NH_4Cl (15 mL). After neutralization with 1 N HCl, the solution was extracted with EtOAc. The combined organic layers were dried and evaporated to dryness to give a residue which was purified by column chromatography eluting with a gradient of CH_2Cl_2 to 60 % EtOAc/CH_2Cl_2 to give **38** (5.1 g, 82 %) as an oil. ^{1}H NMR δ 2.85 (d, *J* = 7 Hz , 2H), 3.55 (s, 2H), 3.75 (s, 3H), 4.80 (bs, 1H), 6.53 (dd, *J* = 15 and 5 Hz, 1H), 6.88 (d, *J* = 15 Hz, 1H), 7.15–7.60 (m, 10H). Anal. ($C_{23}H_{21}NO_4S$) C, H, N.

General procedure for the synthesis of β,δ-dihydroxy esters 46–53

This procedure is illustrated by the synthesis of methyl (±)-*syn*-(*E*)-7-(4,5-diphenylthiazol-2-yl)-3,5-dihydroxy-6-heptenoate (**46**).

A solution of triethylborane (15.5 mL, 1 M solution in THF) was added to a solution of β-keto-δ-hydroxy ester **38** (5.1 g, 12.5 mmol) in dry THF (100 mL) under nitrogen atmosphere. Dry air was bubbled through the solution with a syringe. After 6 h at 0–5 °C, the reaction mixture was cooled to –78 °C and then treated at once with $NaBH_4$ (0.57 g, 15 mmol). After 12 h at –20 °C under nitrogen, the mixture was quenched by addition of MeOH (5 mL), then acidified with 1 N HCl and extracted with EtOAc. The combined organic layers were washed with water, dried and evaporated to dryness. The residue was stirred for 24 h with MeOH. The solvent was removed and the residue was purified by column chromatography eluting with a gradient of CH_2Cl_2:EtOAc 3:7 to CH_2Cl_2:EtOAc 1:1 to give **46** (3.3 g, 64 %) as a foam which was a 98:2 mixture of *syn:anti* diastereoisomers determined by ^{13}C NMR; ^{1}H NMR δ 1.70–1.85 (m, 2H), 2.45–2.55 (m, 2H), 3.70 (s, 3H), 3.90–4.10 (bs, 1H), 4.25–4.40 (m, 1H), 4.50–4.65 (m, 1H), 6.55 (dd, *J* = 15.8 and 5.3 Hz, 1H), 6.89 (dd, *J* = 15.8 and 1.3 Hz, 1H), 7.20–7.35 (m, 6H), 7.40–7.55 (m, 7H). ^{13}C NMR δ 172.79, 163.81, 150.56, 138.06, 134.85, 132.00, 129.57, 129.09, 128.70, 128.28, 128.16, 127.87, 123.14, 71.56, 68.31, 51.81, 41.43, 41.36. Anal. ($C_{23}H_{23}NO_4S$) C, H, N.

The physical properties of target β,δ-dihydroxy esters **47–53** are reported in Table 4 while their spectral data are enumerated below:

Compound 47. ^{1}H NMR δ 1.30 (d, *J* = 6.5 Hz, 6H), 1.65–1.80 (m, 2H), 2.45–2.60 (m, 2H), 3.35 (sept, *J* = 6.5 Hz, 1H), 3.70 (s, 3H), 4.05–4.60 (m, 4H), 6.45 (dd, *J* = 15.4 and 5.8 Hz, 1H), 6.82 (d, *J* = 15.4 Hz, 1H), 7.10 (t, *J* = 8.6 Hz, 2H), 7.40–7.60 (m, 2H). ^{13}C NMR 172.62, 162.43, 159.95, 149.00, 142.60, 137.81, 130.59, 130.42, 123.20, 115.53, 115.10, 71.30, 68.09, 51.70, 42.31, 41.54, 27.61, 27.75.

Compound 48. ^{1}H NMR δ 1.70–1.85 (m, 2H), 2.52 (d, *J* = 6 Hz, 2H), 3.70 (s, 3H), 3.90–4.00 (bs, 1H), 4.10–4.20 (bs, 1H), 4.15–4.40 (m, 1H), 4.55–4.65 (m, 1H), 6.58 (dd, *J* = 15 and 4.9 Hz, 1H), 6.80 (dd, *J* = 15 Hz, 1H), 6.90–7.10 (m, 4H), 7.20–7.50 (m, 4H). ^{13}C NMR δ 172.75, 169.00, 164.98, 164.00, 160.20, 149.63, 138.47, 131.43, 131.27, 130.87, 130.72, 122.83, 116.15, 115.73, 115.56, 115.13, 71.44, 68.28, 51.81, 42.33, 41.46.

Compound 49. ^{1}H NMR δ 1.45 (d, *J* = 7 Hz, 6H), 1.65–1.85 (m, 2H), 2.55 (d, *J* = 7 Hz, 2H), 3.20–3.45 (m, 2H), 3.70–3.80 (m, 4H), 4.20–4.70 (m, 2H), 6.50–6.75 (m, 2H), 7.10 (t, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 8.5 and 5.1 Hz, 2H). ^{13}C NMR 176.10, 172.86, 146.87, 135.77, 135.41, 131.52, 131.36, 121.25, 116.00, 115.58, 72.34, 68.42, 51.81, 42.70, 41.45, 35.55, 23.13.

Compound 50. ^{1}H NMR δ 1.70–1.90 (m, 2H), 2.50 (d, *J* = 6.4 Hz, 2H), 3.70 (s, 3H), 3.90–4.00 (bs, 1H), 4.20–4.40 (m, 1H), 4.50–4.70 (m, 1H), 6.62 (d, *J* = 15 Hz, 1H), 6.80 (dd, *J* = 15 and 6.4 Hz, 1H), 7.00–7.20 (m, 4H), 7.35–7.50 (m, 2H), 7.85–8.00 (m, 2H). ^{13}C NMR δ 172.68, 166.36, 165.10, 164.37, 161.38, 160.15, 148.44, 136.32, 132.65, 131.44, 131.27, 129.64, 128.42, 128.25, 127.12, 120.64, 116.09, 115.66, 72.03, 68.27, 51.69, 42.57, 41.46.

Compound 51. ^{1}H NMR δ 1.42 (d, *J* = 7 Hz, 6H), 1.65–1.85 (m, 2H), 2.50 (d, *J* = 6.5 Hz, 2H), 3.30 (sept, *J* = 7 Hz, 1H), 3.50–3.60 (bs, 1H), 3.70 (s, 3H), 3.75–3.85 (bs, 1H), 4.20–4.60 (m, 2H), 6.59 (dd, *J* = 15.4 and 6.2, 1H), 6.75(dd, *J* = 15.4 and 1.5, 1H), 7.10 (t, *J* = 8.7 Hz, 2H), 7.55 (dd, *J* = 8.7 and 5.2 Hz, 2H). ^{13}C NMR 172.81, 165.00, 160.06, 150.50, 134.74, 130.95, 130.79, 129.82, 120.75, 115.58, 115.16, 72.18, 68.25, 51.81, 42.54, 41.32, 33.50, 23.18, 23.05.

Compound 52. ^{1}H NMR δ 1.32 (d, *J* = 7 Hz, 6H), 1.70–1.80 (m, 2H), 2.55 (d, *J* = 7.4 Hz, 2H), 3.20 (sept, *J* = 7 Hz, 1H), 3.70 (s, 3H), 3.80–4.00 (m, 2H), 4.25–4.40 (m, 1H), 4.50–4.60 (m, 1H), 5.95 (dd, *J* = 14.8 and 6.6 Hz, 1H), 6.80 (d, *J* = 14.8 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 2H), 7.88 (dd, *J* = 8.8 and 5.5 Hz, 2H). ^{13}C NMR δ 172.73, 166.19, 163.04, 161.22, 160.72, 133.41, 130.30, 128.36, 128.20, 119.66, 115.98, 115.53, 72.18, 68.26, 51.73, 42.73, 41.46, 28.54, 22.44.

Compound 53. ^{1}H NMR δ 1.60–1.80 (m, 2H), 2.40–2.60 (m, 2H), 3.70 (s, 3H), 3.85–4.00 (m, 2H), 4.20–4.35 (m, 1H), 4.40–4.60 (m, 1H), 6.05 (dd, *J* = 15.7 and 6.3 Hz, 1H), 6.78 (dd, *J* = 15.7 Hz, 1H), 7.05–7.25 (m, 4H), 7.55–7.70 (m, 2H), 7.85–8.00 (m, 2H). ^{13}C NMR δ 172.70, 165.17, 163.28, 161.47, 160.24, 152.04, 135.73, 131.27, 130.98,130.82, 129.72, 128.50, 128.33, 120.38, 116.16, 115.72, 115.64, 115.22, 71.95, 68.20, 51.73, 42.57, 41.40.

General procedure for the synthesis of hydrogenated β,δ-dihydroxy esters 54–61

This procedure is illustrated by the synthesis of methyl (±)-*syn*-7-(4,5-diphenylthiazol-2-yl)-3,5-dihydroxyheptanoate (**54**).

A stirred solution of the olefinic β,δ-dihydroxy ester **46** (0.41 g, 1 mmol) in MeOH (40 mL) and Et_3N (0.2 mL) was hydrogenated over 10 % Pd/C (40 mg) at atmospheric pressure and room temperature for 30 min. The mixture was filtered off and the filtrate was evaporated to dryness and purified by column chromatography eluting with a gradient of CH_2Cl_2:EtOAc 8:2 to CH_2Cl_2:EtOAc 6:4 to afford **54** (0.32 g, 78 %) as an oil; ^{1}H NMR δ 1.60–1.72 (m, 2H), 1.90–2.10 (m, 2H), 2.50 (dd, *J* = 8 and 4 Hz, 2H), 3.15 (t, *J* = 7.6 Hz, 2H), 3.70 (s, 3H), 3.95–4.10 (m, 1H), 4.25–4.40 (m, 1H), 4.45–4.50 (bs, 1H), 5.00–5.10 (bs, 1H), 7.20–7.35 (m, 6H), 7.40–7.50 (m, 4H). ^{13}C NMR δ 172.37, 168.58, 149.00,134.52, 132.17, 131.84, 129.40, 128.81, 128.52, 128.13, 127.90, 127.62, 70.79, 28.41, 51.47, 42.42, 41.72, 36.75, 29.36. Anal. ($C_{23}H_{25}NO_4S$) C, H, N.

The physical properties of target hydrogenated β,δ-dihydroxy esters **55–61** are reported in Table 4 while their spectral data are enumerated below:

Compound 55. ^{1}H NMR δ 1.30 (d, *J* = 6.9 Hz, 6H), 1.60–1.70(m, 2H), 1.85–2.00 (m, 2H), 2.40–2.55 (m, 2H), 3.05–3.20 (m, 2H), 3.35 (sept, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 3.90–4.10 (m, 1H), 4.20–4.45 (m, 2H), 5.05–5.20 (bs, 1H), 7.10 (t, *J* = 8.6 Hz, 2H), 7.48 (dd, *J* = 8.6 and 5.2 Hz, 2H). ^{13}C NMR δ 172.50, 166.84, 159.84, 147.63, 142.10, 130.45, 130.28, 115.51, 115.08, 71.08, 68.57, 51.56, 42.51, 41.77, 36.67, 29.62, 27.47, 25.78.

Compound 56. ^{1}H NMR δ 1.60–1.75 (m, 2H), 1.90–2.10 (m, 2H), 2.45–2.55 (m, 2H), 3.17 (t, *J* = 7.7 Hz, 2H), 3.70 (s, 3H), 3.75–4.10 (m, 1H), 4.25–4.40 (m, 1H), 4.40–4.50 (bs, 1H), 4.80–4.90 (bs, 1H), 6.88–7.05 (m, 4H), 7.20–7.32 (m, 2H), 7.35–7.50 (m, 2H). ^{13}C NMR δ 162.36, 168.80, 164.86, 164.68, 159.85, 148.19, 131.24, 131.07, 130.73, 130.61, 127.74, 115.92, 115.48, 115.35, 114.91, 70.65, 68.36, 51.43, 42.39, 41.66, 36.80, 29.28.

Compound 57. ^{1}H NMR δ 1.40 (d, *J* = 7 Hz, 6H), 1.55–1.90 (m, 4H), 2.40–2.60 (m, 2H), 2.70–3.05 (m, 2H), 3.25 (sept, *J* = 7 Hz, 1H), 3.70 (s, 3H), 3.90–4.10 (m, 1H), 4.20–4.40 (m, 1H), 4.45–4.60 (bs, 1H), 5.60–5.90 (bs, 1H), 7.10 (t, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.4 and 5.3 Hz, 2H). ^{13}C NMR δ 180.74, 172.51, 164.95, 150.05, 131.21, 131.04, 130.05, 115.98, 115.55, 71.86, 68.87, 51.61, 42.58, 41.94, 36.69, 33.08, 25.75, 22.91.

Compound 58. ^{1}H NMR δ 1.59–1.74 (m, 2H), 1.84–2.10 (m, 2H), 2.44–2.60 (m, 2H), 2.80–3.09 (m, 2H), 3.70 (s, 3H), 3.90–4.10 (m, 1H), 4.00–4.20 (m, 2H), 7.00–7.15 (m, 4H), 7.30–7.50 (m, 2H), 7.75–7.95 (m, 2H). ^{13}C NMR δ 172.53, 166.38, 164.50, 161.39, 160.11, 152.07, 131.20, 131.04, 129.43, 128.22, 128.05, 127.43, 116.34, 116.10, 115.90, 115.67, 71.63, 68.72, 51.61, 42.50, 41.78, 36.75, 25.68.

Compound 59. ^{1}H NMR δ 1.40 (d, *J* = 7 Hz, 6H), 1.45–1.60 (m, 2H), 1.70–1.80 (m, 2H), 2.45 (d, *J* = 6.8 Hz, 2H), 2.85–3.10 (m, 2H), 3.30 (sept, *J* = 7 Hz, 1H), 3.70 (s, 3H), 3.75–4.00 (m, 2H), 4.10–4.30 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 2H), 7.55 (dd, *J* = 8.6 and 5.2 Hz, 2H). ^{13}C NMR δ 174.28, 172.81, 164.60, 132.28, 130.48, 130.32, 115.44, 115.00, 70.85, 68.88, 51.76, 42.06, 41.40, 39.74, 33.28, 23.16, 22.92.

Compound 60. ^{1}H NMR δ 1.32 (dd, *J* = 7.2 and 1.5 Hz, 6H), 1.55–1.90 (m, 4H), 2.50 (d, *J* = 7 Hz, 2H), 3.85–3.00 (m, 2H), 3.10 (sept, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 3.85–4.00 (m, 1H), 4.20–4.40 (m, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 7.88 (dd, *J* = 8.6 and 5.3 Hz, 2H). ^{13}C NMR δ 172.90, 165.96, 163.80, 158.88, 130.61, 128.10, 127.93, 115.89, 115.47, 70.80, 69.01, 51.79, 42.44, 41.45, 39.92, 29.67, 28.23, 22.72.

Compound 61. ^{1}H NMR δ 1.45–1.70 (m, 2H), 1.75–2.00 (m, 2H), 2.45 (d, *J* = 5.5 Hz, 2H), 2.90–3.15 (m, 2H), 3.70 (s, 3H), 3.75–4.00 (m, 2H), 4.15–4.30 (m, 1H), 7.05–7.20 (m, 4H), 7.60–7.70 (m, 2H), 7.90–8.00 (m, 2H). ^{13}C NMR δ 172.80, 164.86, 162.94, 161.24, 159.95, 150.92, 134.19, 130.56, 130.39, 128.22, 128.06, 116.06, 115.61, 115.55, 115.11, 70.71, 68.88, 51.75, 42.22, 41.38, 39.66, 23.15.

HMG-CoA reductase inhibition assay

The inhibitory activity of compounds **46–61** on rat liver HMG-CoA reductase was evaluated with soluble-enzyme

preparations obtained from the microsomal fraction as described by Philipp *et al.*[19] The test was performed according to the method reported by Avigan *et al.*[20] The complete assay medium contained the following in a total volume of 0.2 mL: Tris, 6 mM; EDTA, 2.5 mM; DTT, 2.5 mM; NADP, 50 mM; glucose-6-phosphate, 50 mM; glucose-6-phosphate dehydrogenase, 2.8 units; HMG-CoA, 0.91 mM containing 100 nCi of [^{14}C]HMG-CoA (New England Nuclear); partially purified enzyme stock solution, 50 μL. Test compounds or simvastatin (after conversion to their corresponding sodium carboxylate through reaction with 1 equiv. of 1 N NaOH in MeOH) were added to the assay system in 10 μL volumes at multiconcentration levels. After a 30 min incubation at 37 °C, the reaction was stopped by the addition of 75 μL of 2 N $HClO_4$. After an additional 25 min incubation period at 37 °C and 10 min in an ice bath 75 μL of 3 N potassium acetate and 150 μL of water were added and the mixture was centrifuged. The supernatant (400 μL) was added to a 0.6 × 8 cm column containing 100–200 mesh AG1 × 8, Cl form (Bio-Rad). The [^{14}C]mevalonolactone was eluted with distilled water (3.8 mL) into scintillation vials. Ten mL of scintillation liquid was added to each vial and the radioactivity was measured in a Canberra–Packard Model 4000 Tricarb scintillation counter. The assay was carried out in triplicate; IC_{50} values were determined by plotting percentage inhibition against test compound concentration (four or five levels).

Acknowledgement

This research was assisted in part by a grant from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

References and Notes

1. This work was previously presented in part: Temperini, A.; Fravolini, A.; Cecchetti, V; Tabarrini, O.; Pagella, P. G. *XIIth International Symposium on Medicinal Chemistry*, p. 250B, Basel, Switzerland, September 1992.

2. Alberts, A. W. *Am. J. Cardiol.* **1988**, *62*, 10J.

3. Yoshino, G.; Kazumi, T.; Uenoyama, R.; Inui, A.; Kasama, T.; Iwatani, I.; Iwai, M.; Yokono, K.; Otsuki, M.; Baba, S. *Lancet* **1986**, *2*, 740.

4. Mol, M, J. T. M.; Erkelens, D. W.; Gevers Leuven, J. A.; Schouten, J. A.; Stalenhoef, A. F. H. *Lancet* **1986**, *2*, 936.

5. (a) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, Jr E. J.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffmann, W. F; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170; (b) Jendralla, H.; Wess, G.; Kesseler, K.; Beck, G. Eur. Pat Appl. EP 418 648; *Chem. Abstr.* **1991**, *115*, 158965w; (c) Jendralla, H.; Granzer, E.; v. Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L. J.; Granata, S.; Herchen, J.; Kleine, H.; Schüssler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962.

6. (a) Coppola, G. M.; Scallen, T. J.; DelPrete, A.; Montano, R. *Heterocycles* **1989**, *29*, 1497; (b) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson E.; Krause, B. R.; Newton, R. S.; Sekerke, C.; Shaw, M. K. *J. Med. Chem.* **1991**, *34*, 367.

7. Kathawalla, F. G. PCT Int. Appl. WO 84 02 131; *Chem. Abstr.* **1985**, *102*, 24475j.

8. Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 52.

9. (a) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 21; (b) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; v. Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61; (c) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357; (d) Procopiou, P. A.; Draper, C. D.; Huston, J. L.; Inglis, G. G. A.; Ross, B. C.; Watson, N. S. *J. Med. Chem.* **1993**, *36*, 3658.

10. Hübsch, W.; Angerbauer, R.; Fey, P.; Schmidt, D. XIth *International Symposium on Medicinal Chemistry*, p. 38, Jerusalem, Israel, September 1990.

11. (a) Wareing, J. R. PCT Int. Appl. WO 86 07 054; *Chem. Abstr.* **1987**, *107*, 59029x; (b) Bertolini, G.; Casagrande, C.; Santangelo, F. Eur. Pat. Appl. EP 436 851; *Chem. Abstr.* **1991**, *115*, 183301j; (c) Chan, C.; Bailey, E. J.; Hartley, C. D.; Hayman, D. F.; Huston, J. L.; Inglis, G. G. A.; Jones, P. S.; Keeling, S. E.; Kirk, B. E.; Lamont, R. B.; Lester, M. G.; Pritchard, J. M.; Ross, B. C.; Scicinski, J. J.; Spooner, S. J.; Smith, G.; Steeples, I. P.; Watson, N. S. *J. Med. Chem.* **1993**, *36*, 3646.

12. (a) Wareing, J. R. PCT Int. Appl. WO 86 00 307; *Chem. Abstr.* **1987**, *106*, 5023b; (b) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31; (c) Sliskovic, D. R.; Blankley, C. J.; Krause, B. R.; Newton, R. S.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Sekerke, C.; Shaw, M. K.; Stanfield, R. L. *J. Med. Chem.* **1992**, *35*, 2095.

13. Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

14. Maier, R.; Woitun, E.; Mueller, P.; Bomhard, A.; Eisele, B.; Grube; H. Ger. Offen. DE 3 621 372; *Chem. Abstr.* **1988**, *108*, 167456p.

15. Baader, E.; Jendralla, H.; Kerekjarto, B.; Beck, G. Eur. Pat. Appl. EP 324 347; *Chem. Abstr.* **1990**, *112*, 21003z.

16. Reissert, A. *Ber.* **1904**, *37*, 3721.

17. Cottet, R.; Gallo, R.; Metzger, J. *Bull. Soc. Chim. France* **1967**, *12*, 4499.

18. Stephenson, L.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc. (C)* **1969**, 861.

19. Philipp, B. W.; Shapiro, D. J. *J. Lipid. Res.* **1979**, *20*, 588.

20. Avigan, J.; Bhathena, S. J.; Schreiner, M. E. *J. Lipid. Res.* **1975**, *16*, 151.

(*Received* 17 *February* 1994; *accepted* 17 *May* 1994)