Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Reactivity of Mevinolin-Like Lactone Precursors

G. Bertolini [a], C. Casagrande [a], G. Norcini [a] & F. Santangelo [a]
[a] Medicinal Chemistry Department, Zambon Group S.p.A., Via Lillo del Duca 10, 20091, Bresso, Milan, Italy
Published online: 23 Sep 2006.

To cite this article: G. Bertolini, C. Casagrande, G. Norcini & F. Santangelo (1994) Synthesis and Reactivity of Mevinolin-Like Lactone Precursors, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:13, 1833-1845, DOI: 10.1080/00397919408010191

To link to this article: http://dx.doi.org/10.1080/00397919408010191

SYNTHETIC COMMUNICATIONS, 24(13), 1833-1845 (1994)

SYNTHESIS AND REACTIVITY OF MEVINOLIN-LIKE LACTONE PRECURSORS

G. Bertolini, C. Casagrande, G. Norcini* and F. Santangelo
Medicinal Chemistry Department, Zambon Group S.p.A.
Via Lillo del Duca 10, 20091 Bresso (Milan) Italy

***Abstract**: The synthesis of mevinolin-like lactone precursors and the evaluation of their ability in the N-alkylation of N-potassium-phthalimide are reported.*

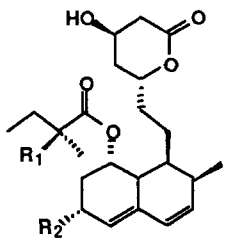
There is convincing evidence that lowering plasma cholesterol levels reduces the risk of myocardial infarction[1,2] and that inhibition of hydroxymethylglutaryl-CoA (HMGCoA) reductase, the rate-limiting enzyme in chloresterol biosynthesis, reduces total cholesterol and low density lipoprotein (LDL) in animal models and man[3,4].

Since the discovery of the first HMG-CoA reductase inhibitor (fig. 1) compactin[5] (**1a**) and mevinolin[6] (**1b**), a lot of papers have been published, describing a large variety of natural[7] and synthetic inhibitors obtained by biotransformation (pravastatin, **1d**)[8] and chemical transformation (simvastatin, **1c**)[9] of natural product or by total synthesis, i.e fluvastatin[10a] (**2**) and HR780[10b] (**3**).

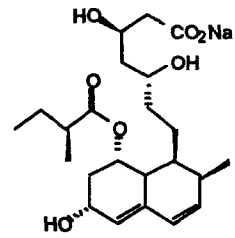
Comparison of the HMG-CoA reductase inhibitor structures reveals that 3,5-dihydroxycarboxylic moiety is present in all compounds and it seems that this group represents a pharmacophore for HMG-CoA reductase inhibitor recognition. Stereospecific synthesis of the 3,5-dihydroxy acid synthons and their utilization have been the subject of several publications[11,12a,12b].

---

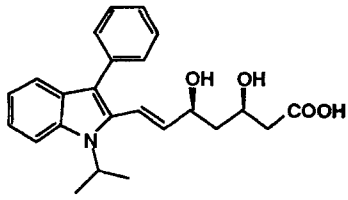
*To whom correspondence should be addressed



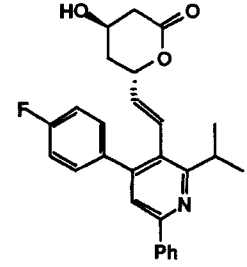
R_1	R_2	
H	H	1a Compactin
H	Me	1b Mevinolin
Me	Me	1c Simvastatin



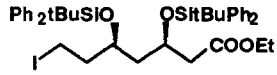
1d Pravastatin



2 Fluvastatin



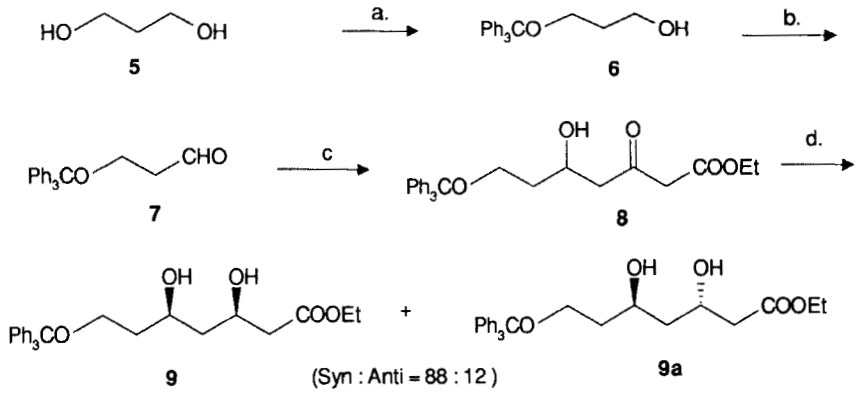
3 HR780



4

Figure 1

Among the numerous mevinolin-like lactone precursors there are no examples of synthons beneficial for the direct introduction of the chain in heterocycles or other systems. Therefore, with the aim of developing a new key intermediate, we synthesized the precursor **4** (Fig. 1) and its potential reactivity was tested using the alkylation of N-potassium phthalimide as a model. Firstly, the diol **5** (Scheme 1) was monoprotected and then oxidated to aldehyde **7**. Condensation with ethyl acetoacetate dianion[13] gave 5-hydroxy-3-ketoesters **8**. In literature, for the diastereoselective reduction of a β-hydroxyketone to 1,3-syn diol, several



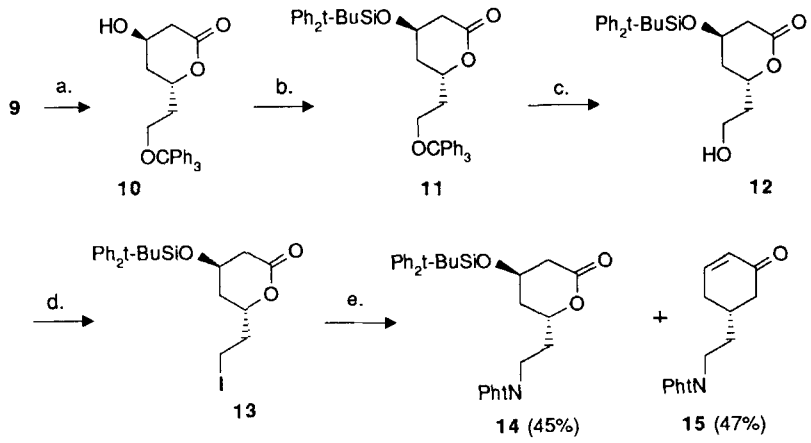
Scheme 1

a. Ph_3COCl, Py, 100°C, 2h, (80%). b. $PySO_3$, DMSO, TEA, 20°C, 10 min., (74%). c. acetoacetate dianion, THF, 0°C, 10 min., (100%). d. $NaBH_4$, EtOH, -70°C, 1.5h, (38%).

methods [14a] are reported but we opted for the simpler one because we needed multigram amount of the intermediate. Synthesis of 1,3-syn diols starting with β diketones using sodium borohydride at low temperature[15] was chosen. Thus, we studied different solvents, temperatures and concentrations and the best result was the reduction with 0,05M $NaBH_4$ at -70°C of in methanol yielding the dihydroxy ester **9**. The opposite diol **9a** was present in a minor amount in the reaction mixture (syn: anti = 88:12) and this rather high selectivity is due to the hydrogen bond between the hydroxy group and the ketone at -70°C which locks the conformation of the molecule.

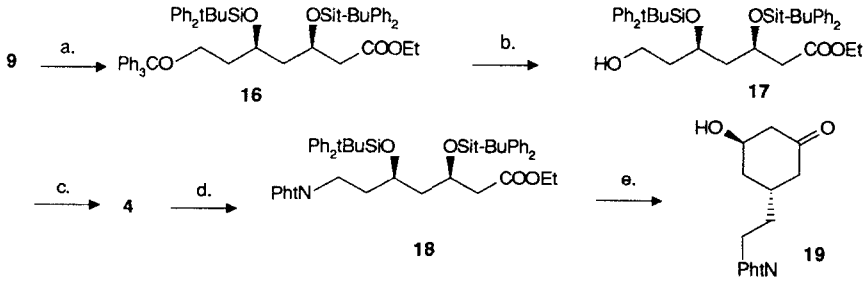
Hydrolylsis of the mixture **9** and **9a** (Scheme 2) with NaOH in a MeOH-H_2O solution and cyclization in refluxing toluene gave the pure lactone **10** in 62% yield after cristallization. The secondary alcohol was protected as silyl ether and after hydrogenation in the presence of Pd/C, the alcohol **12** was converted to the iodide **13**.The reactivity of **13** was tested in the alkylation of N-potassium phthalimide in DMF giving the 1:1 mixture of the desidered compound **14** and the α,β unsaturated lactone **15**.

However, **15** reaction was always present even with other different conditions.



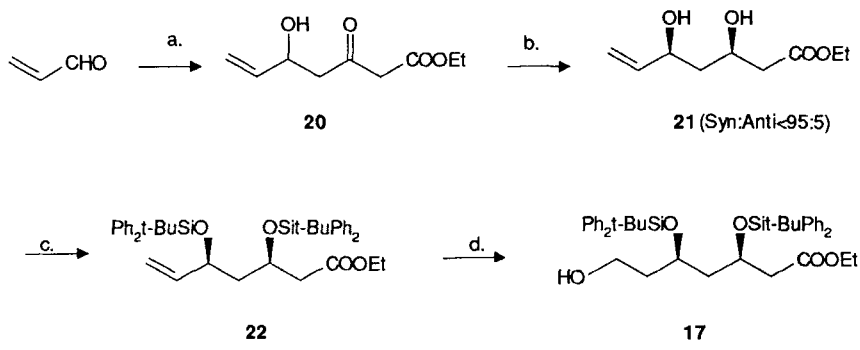
Scheme 2

a. NaOH, MeOH, 20°C, 4h, (62%). b. Ph_2t-BuSiCl, Imidazole, DMF, 80°C, 15h, (100%). c. H_2, Pd/C, EtOH, CH_2Cl_2, (74%). d. I_2, PPh_3, DMF, 20°C, 2h, (60%). e. $PhtN^-K^+$, DMF, 20°C, 3h.



Scheme 3

a. Ph_2tBuSiCl, Imidazole, DMF, 80°C, 15h (59%). b. aPTS, EtOH/CH_2CH_2, reflux, 10h (81%). c. I_2, PPh_3, DMF, 20°C, 2h (82%). d. $PhtN^-K^+$, DMF, 20°C, 3h (77%). c. HF, CH_3CN, 50°C, 10h (64%).



Scheme 4

a. acetoacetate dianion, THF, 10 min, 0°C, (52.6%). b. Et_3B, MeOH, 20°C, 1h, then 20, -65°C, 30 min, then $NaBH_4$, 3h, -65°C, (68.8%). c. Ph_2t-BuSiCl, Im, DMF, 70°C, 3h, (71%). d. 9BBN, 0°-5°C, 16h, then H_2O_2, 3h, 20°C, (46%).

Thus, we changed strategy and the dihydroxy ester **9** (Scheme 3) was protected as disilyl ether and after removal of the trityl group, the alcohol **17** was converted to the iodide **4** using standard reaction conditions. Finally, the alkylation of N-potassium phthalimide using the iodide **4** gave good results (77% of yield) and **18** was easily converted to the final product **19** in one step by treatment with $HF/H_2O/CH_3CN$ at 50°C. We also tested the reactivity of **4** on different amines and also on imidazole, obtaining moderate to good yield. These results will be published in a Medicinal Chemistry paper.

At last, we studied a simpler synthesis of the alcohol **17** (Scheme 4).

We started from acrolein and the condensation with the ethyl acetoacetate dianion **13** gave the δ-hydroxy-β-keto ester **20** that was stereoselectively reduced to the syn-diol **21**[14b].

After protection as disilyl ether, the olefin **22** was hydroborated to give the alcohol **17** again. The overall yield from acrolein was reasonable for our purpose.

Our studies on the reactivity of mevinolin-like lactone precursors demostrated that the iodide **4** was seen as a very useful and versatile intermediate for the alkylation reaction. In conclusion, this study gave us

some useful indications about the chemistry of new HMG-CoA reductase inhibitors[16] and our experience could prove to be useful for further studies of new synthetic approaches to this class of inhibitors.

EXPERIMENTAL SECTION

^1H and ^{13}C-NMR spectra were recorded with a Varian XL-300 instrument. Chemical shifts (δ) are reported in ppm downfield from internal tetramethyl silane. ^1H-NMR data are reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Mass spectra were obtained with a Finningan 4600 in chemical ionization (CI). Silica gel 60 F_{254} plates (Merck) were used for TLC; 230-400 mesh silica gel (Merck) was used for chromatography. All chemicals and solvents were of analytical grade and were used without further purification. Dry THF was distilled from sodium/benzophenone under nitrogen immediately before use. The reactions were carried out under nitrogen where necessary. Organic extracts were dried over Na_2SO_4.

3-Trityloxypropan-1-ol, 6: A solution of 1,3-propanediol (194 ml, 2.69 mol) and trityl chloride (250 g, 0.89 mol) in pyridine (1500 ml) was maintained at 100°C for 12 hrs. After cooling, the solvent was evaporated under reduced pressure, the residue was diluted with diethyl ether (3000 ml), and washed with water (1000 ml). The organic layer was washed with dil. sulphuric acid and than potassium carbonate (5% water solution). The solvent was evaporated under reduced pressure and the residue was dissolved in methanol. The insoluble was filtered off and the methanol evaporated giving 229.37 g (80%) of product which was used without further purification. ^1H-NMR (300 MHz, $CDCl_3$): δ 1.87 (m, 2H); 3,28 (t, 2H); 3.77 (bq, 2H); 7.32 (m, 15H).

3-Trityloxypropionaldehyde, 7: To a solution of 3-trityloxypropan-1-ol (153 g, 0.48 mol), triethylamine (420 ml, 3.37 mol) in DMSO (800 ml), a solution of pyridinesulphur trioxide complex (230 g, 1.44 mol) in DMSO (650 ml) was added at room temperature. After a 10 minute stirring, the mixture was dropped in ice and dil. hydrochloric acid was added to adjust the pH to about 7.

The solution was extracted with methylene chloride (5x1000 ml). The organic layer was washed with dil. hydrochloric acid and water, dried with sodium sulphate and the solvent evaporated in vacuum. The resulting oil was crystallized from hexane methylene chloride: 9,1 affording 113.5 g (74%) of pure product. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.65 (m, 2H); 3.47 (t, 2H); 7.30 (m, 10H); 7.44 (m, 5H); 9.78 (t, 1H).

Ethyl 5-hydroxy-7-trityloxy-3-oxoheptanoate 8: Ethyl acetoacetate (18 ml; 143.7 mmols) was added to sodium hydride (50% dispersion in mineral oil, 4.1 g, 172.4 mmols) in dry tetrahydrofuran (210 ml) at 0°C and under a nitrogen atmosphere, by keeping the temperature at about 0°C. After 10 minutes, a solution 1.6M of butyl lithium in hexane (94 ml, 150.8 mmols) was slowly added. After 10 minutes at 0°C a solution of **7** (50 g, 158 mmols) in tetrahydrofuran (70 ml) was rapidly added. Following a 10 minute stirring at the same temperature the mixture was diluted with 50 ml of HCl 6 N and with 300 ml of an ammonium chloride saturated solution. The product was extracted with diethyl ether (3 x 300 ml). The combined organic phases were washed with a sodium chloride saturated solution (2x500 ml), dried and evaporated under vacuum affording 67.6 g of an oily crude which was used directly in the subsequent reduction. An analytical sample was prepared by column chromatography on silica (70-230 mesh); eluant, petroleum ether:ethyl acetate = 8:2. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H); 1.65-1.90 (m, 2H); 2.64 (dd, 1H); 2.68 (dd, 1H); 3.23 (m, 1H); 3.35 (m, 1H); 3.46 (s, 2H); 4.18 (q, 2H); 4.27 (m, 1H); 7.20-7.35 (m, 9H); 7.40-7.45 (m, 6H).

(Syn)-3,5-dihydroxy-7-trityloxyheptanoate, 9 and (anti)-3,5-dihydroxy-7-trityloxy-heptanoate, 9a: A solution of sodium borohydride (9.3 g, 246 mmols) in absolute ethanol (400 ml) pre-cooled at -78°C was added to a solution of **8** (55 g, 123 mmols) in absolute ethanol (1.2 ml) kept at -70°C under nitrogen. The solution was stirred at the same temperature for 1.5 hours then the solvent was evaporated and the residue was collected with methylene chloride (500 ml), a saturated solution of ammonium chloride (100 ml) and subsequently 1 N hydrochloric acid up to pH 4-5 were slowly added to the mixture. The mixture was extracted with methylene chloride (3x100 ml), the organic phase was dried affording a yellow oil (52 g) which was purified by chromatography, eluent: petroleum ether/ethyl acetate by gradual variation of the ethyl acetate percentage from 10% to 30%. A low melting product (21 g, 38%) was obtained. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 3H); 1.50-1.90 (m, 4H); 2.45-2.55 (m, 2H); 3.22 (m, 1H); 3.37 (m, 1H);

3.72 (d, 1H, exchange with D_2O); 3.94 (d, 1H, exchange with D_2O); 4.06 (m, 1H); 4.16 (q, 2H); 4.27 (m, 1H); 7.20-7.35 (m, 9H); 7.40-7.45 (m, 6H). From the ^{13}C-NMR analysis two series of signals were observed: ^{13}C-NMR syn steroisomer **9** (75.5 MHz, $CDCl_3$) δ 14.216 (q); 37.085 (t); 41.795 (t); 42.426 (t); 60.650 (t); 62.961 (t); 68.581 (d); 7.332 (d); 87.260 (s); 127.137 (d); 127.930 (d); 128.545 (d); 143.824 (s); 172.341 (s). ^{13}C-NMR anti steroisomer **9a** (75.4 MHz, $CDCl_3$): 14.216 (q); 36.680 (t); 41.584 (t); 42.673 (t); 65.522 (d); 68.694 (d); 87.409 (s); 127.930 (d); 128.545 (d); 143.739 (s); 172.714 (s).
By the composition of the signals belonging to the same carbon atom, a syn-anti ratio of 88:12 was determined.

(Trans)-6-(2-trityloxyethyl)-4-hydroxy-tetrahydropyran-2-one, 10: The mixture of esters **9** and **9a** (44.5 g, 99.3 mmols) was dissolved in MeOH (940 ml) and a 3 M solution of NaOH (50 ml) was added. The reaction mixture was stirred at room temperature for 4 hrs and the solvent was removed under reduced pressure. CH_2Cl_2 (500 ml) and H_2O (300 ml) were added and the aqueous phase was acidified to pH 2 with HCl 1N and the two phases separated and the aqueous phase extracted with CH_2Cl_2 (3x100 ml). The combined organic phases were washed with a 0.1 M solution of HCl, dried and the solvent was removed giving 36.2 g of crude product. The crude acid was dissolved in toluene (860 ml) and heated to 100°C for 13 hrs. The solvent was then removed under reduced pressure and the crude product was purified by column chromatograph, eluent n-hexane-ethylacete 6:4. The product was washed with hot isopropyl ether (300 ml) affording 24.8 g of pure **10** (trans: cis ≤ 97:3) (62%). ^1H-NMR (300 MHz, $CDCl_3$): δ 1.65-2.10 (m, 4H); 2.58 (ddd, 1H); 2.69 (dd, 1H); 3.28 (m, 2H); 4.32 (m, 1H); 4.89 (m, 1H); 7.20-7.35 (m, 9H); 7.44 (d, 6H). M.S. (CI, ammonia): m/e 402 $[M]^+$, 243.

(Trans)-6-(2-trityloxyethyl)-4-diphenyltertbutylsilyloxytetrahydropyran-2-one, 11: **10** (5.5 g, 13.64 mmol) was dissolved in DMF (13.6 ml) then imidazole (1.86 g, 27.28 mmol) and diphenyltertbutylsilyl chloride (4.2 ml, 16.37 mmol) were added. The reaction mixture was heated to 80°C for 15 hrs., then cooled to room temperature and poured into water (130 ml) and extracted with Et_2O (3x130 ml). The combined organic phases were washed with a 0.1 M solution of HCl (100 ml), a saturated solution of $NaHCO_3$ (100 ml) and water (100 ml), then dried. The solvent was removed under reduced pressure affording 8.56 g of crude **11**. ^1H-NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.52 (m, 1H); 1.70-2.00 (m, 3H); 2.39 (dd, 1H); 2.55 (ddd, 1H); 3.19 (m, 1H); 3.38 (m, 1H); 4.27 (m, 1H); 5.12 (m, 1H); 7.20-7.50 (m, 21H); 7.62 (d, 4H); M.S. (CI, isobutane): 257, 243.

(Trans)-6-(2-hydroxyethyl)-4-diphenyltertbutylsilyloxytetrahydropyran-2-one, 12: Crude **12** (8.56 g, 13.35 mmol) was dissolved in a mixture of EtOH-CH_2Cl_2 (1:1) (133 ml) and Pd/C 10% (850 mg) was added. The reaction mixture was hydrogenated in a Parr apparatus (40 p.s.i.). The catalyst was filtered off and the solvents were removed under reduced pressure. The crude product was purified by column chromatography, eluant n-hexane-ethyl acetate 6:4 affording 4 g (74%) of pure **12**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H); 1.50-1.95 (m, 4H); 2.46 (dd, 1H); 2.61 (ddd, 1H); 3.83 (m, 2H); 4.29 (m, 1H); 5.01 (m, 1H); 7.35-7.50 (m, 6H); 7.63 (m, 4H). M.S. (CI, isobutane): 399 $[M+1]^+$, 257, 143.

(Trans)-6-(2-iodoethyl)-4-diphenylterbutylsilyloxytetrahydropyran-2-one, 13: Triphenylphosphine (3.5 g, 13.19 mmol) and **12** (4.8 g, 11.99 mmol) were dissolved in DMF (8 ml). A solution of iodine (3.4 g, 13.19 mmol) in DMF (4 ml) was added slowly in order to keep the temperature below 55°C. The reaction mixture was stirred at room temperature for 2 hrs, then poured into water (120 ml) and extracted with ethyl ether (3 x 100 ml). The combined organic phases were washed with a 5% solution of sodium metabisulfite (50 ml), then with a saturated solution of $NaHCO_3$ (50 ml) and finally with brine (50 ml). The organic phase was dried and the solvent was removed under reduced pressure. The crude product was purified by column chromatography, eluat n-hexane-ethyl acetate 8:2 affording 3.7 g of pure **13** (60%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H); 1.51 (m, 1H); 1.76 (m, 1H); 2.00 (m, 1H); 2.17 (m, 1H); 2.46 (dd, $J_{3a,3b}$=17.3 Hz, $J_{3a,4}$=4.5 Hz 1H); 2.62 (ddd, $J_{3a,3b}$=17.3 Hz, $J_{3b,4}$=3.7 Hz, $J_{3b,5a}$=1.5 Hz, 1H); 3.31 (m, 2H); 4.30 (m, 1H); 4.97 (m, 1H); 7.35-7.50 (m, 6H); 7.60-7.70 (m, 4H); M.S. (CI, isobutane): 509 $[M+1]^+$, 253.

(Trans)-6-(2-N-phthalimmidoylethyl)-4-diphenyltertbutylsilyloxytetrahydropiran-2-one, 14: To a solution of **13** (200 mg, 0.39 mmol) in dry DMF (3.9 ml), N-potassium phtalimmide (80 mg, 0.43 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 hrs, then it was poured into water (40 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with water (30 ml), dried and the solvent was removed under reduced pressure. The crude product was purified by column chromatography, eluant n-hexane-ethyl acetate 7:3 affording 94 mg of **14** (45%), 52 mg of **15** (47%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 9H); 1.62 (m, 1H); 1.80-2.10 (m, 3H); 2.42 (dd, 1H); 2.56 (ddd, 1H); 3.88 (m, 2H); 4.30 (m, 1H); 4.90 (m, 1H); 7.35-7.50 (m, 6H); 7.61 (d, 4H); 7.72 (dd, 2H); 7.85 (dd, 2H).

Ethyl (syn)-3,5-di-(diphenylterbutylsilyloxy)-7-trityloxyheptanoate, 16: A mixture of **9** and **9a** (51 g, 113.8 mmol), terbutyldiphenylsilyl chloride (70 ml, 273 mmols) and imidazole (31 g, 455 mmols) in dimethyl- formamide (115 ml) was continously stirred for 6 hours at 50°C. The solution was poured into water (1:1) and extracted with diethyl ether (4 x 500 ml). The collected ether phases were washed with water (500 ml), 0.1 M hydrochloric acid (500 ml), a saturated sodium bicarbonate solution (500 ml) and a saturated sodium chloride solution (500 ml). The organic phase was dried and the solvent was evaporated thereby obtaining an oily product (113.8 g) which solidified when treated with diethyl ether. After filtration, 62 g (59%) of product (m.p. 141-142°C) was obtained.
From ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.4 MHz) it resulted to be the syn stereoisomers with a purity higher than 97%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.83 (S, 9H); 0.92 (s, 9H); 1.15 (t, 3H); 1.40-1.75 (m, 4H); 2.17 (dd, 1H); 2.27 (dd, 1H); 2.70-2.95 (m, 2H); 3.87 (m, 1H); 3.96 (m, 2H); 4.35 (m, 1H); 7.20-7.65 (m, 35H).
^{13}C-NMR (75.4 MHz, $CDCl_3$) meaningful signals: δ 14.092 (q); 19.134 (s); 19.174 (s); 26.858 (q); 26.946 (q); 36.818 (t); 42.005 (t); 43.905 (t); 60.084 (t); 60.386 (t); 68.174 (d); 68.641 (d); 86.253 (s); 135.911 (d); 144.251 (s); 171.237 (s).

Ethyl (syn)-3,5-di-(diphenylter.butylsilyloxy)-7-hydroxyheptanoate, 17: p-Toluene sulphonic acid (470 mg, 2.4 mmols) was added to a solution of **16** (23 g, 24.8 mmol) in ethanol/methylene chloride 1:1 (250 ml). The mixture was refluxed for about 10 hours. Triethylamine (350 µl, 2.48 mmols) was added and the mixture was evaporated to dryness thereby obtaining a crude (colorless oil) which was purified by column chromatography, eluant: petroleum ether:ethyl acetate=9:1 obtaining 13.7 g of product (81%) (m. p. 75-77°C). ^{1}H-NMR (300 MHz, CDCl3): δ 0.93 (s, 9H); 1.16 (t, 3H); 1.35-1.60 (m, 2H); 1.75-1.90 (m, 2H); 2.17 (dd, 1H); 2.23 (dd, 1H) 3.35-3.55 (m, 2H); 3.98 (q, 2H); 4.06 (m, 1H); 4.15 (m, 1H); 7.30-7.45 (m, 12H); 7.55-7.65 (m, 8H).

Ethyl (syn)-3,5-di-(diphenylter.butylsilyl-oxy)-7-iodoheptanoate, 4: A solution of iodine (2 g, 8.05 mmols) in dimethylformamide (5 ml) was slowly added to a solution of **17** (5 g, 7.32 mmols) and triphenyl phosphine (2.1 g, 8.05 mmols) in dimethylformamide (10 ml) under nitrogen in order to keep the temperature below 55°C. The mixture was stirred for 1 hour at room temperature. It was poured in 150 ml water and 150 ml diethyl ether. The phases were separated and the aqueous phase was extracted with diethyl ether (3x100 ml). The reunited ether phases were washed with a 5% solution of sodium sulphate with a saturated sodium bicarbonate solution and with water. The organic phase

was dried and the solvent was evaporated obtaining a crude (7.7 g) which was purified by column chromatography eluant: petroleum ether/ethyl acetate 98:2, thus affording an oily product (4.78 g, 82%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H); 0.97 (s, 9H); 1.18 (t, 3H); 1.55-1.80 (m, 4H); 2.27 (dd, 1H); 2.30 (dd, 1H); 2.78 (m, 2H); 3.78 (m, 1H); 4.00 (m, 2H); 4.20 (m, 1H); 7.30-7.45 (m, 12H); 7.55-7.65 (m, 8H).

Ethyl (syn)-3,5-di-(diphenylterbutylsilyloxy)-7-(N-phthalimmidoyl)heptanoate, 18: To a solution of **4** (73 mg, 0.09 mmol) in dry DMF (1 ml), N-potassium phthalimmide (18.5 mg, 0.1 mmol) was added. The reaction mixture was stirred at room temperature for 24 hrs, then it was poured in water (20 ml) and extracted with ethyl ether (3x20 ml). The combined organic phases was washed with water, dried and evaporated under reduced pressure.

The crude product was purified by column chromatography eluant n-hexane ethyl acetate 9:1 affording 56 mg pure **18** (77%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 18H); 1.18 (t, 3H); 1.53 (m, 2H); 1.91 (m, 2H); 2.35 (d, 2H); 3.42 (m, 2H); 3.82 (m, 1H); 4.01 (m, 2H); 4.37 (m, 1H); 7.15-7.45 (m, 12H); 7.55-7-70 (m, 8H); 7.69 (dd, 2H); 7.79 (dd, 2H).

Trans-6-[2-(N-phthalimmidoyl)ethyl]-4-hydroxytetrahydropiran-2-one, 19: To a solution of **18** (53 mg, 0.06 mmol) in acetonitrile (1.2 ml), a 40% aqueous solution of hydrofluoric acid (0.2 ml) was added. The reaction mixture was maintained at 50°C for 10 hrs. Hydrofluoric acid was neutralized with $NaHCO_3$, and the mixture was diluted with a small amount of water and with ethyl acetate (20 ml); the precipitated salts were filtered and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with brine, dried and evaporated under reduced pressure. The crude product was purified by column chromatography, eluant n-hexane-ethyl acetate 1:1 affording 12 mg of pure **19** (64%).

Ethyl 5-hydroxy-3-keto-hept-6-enoate, 20: To a suspension of sodium hydride (18.2 g, 0.76 mol) in dry THF (1700 ml), ethyl acetoacetate (88.6 ml, 0.695 mol) was added drop by drop under nitrogen at 0°C. After a 10 minute stirring, a solution of n-butyl lithium 1.6 M in hexane (456 ml, 0.73 mol) was dropped at the same temperature. After 10 minutes acrolein (50.8 ml, 0.76 mmol) was added, then after another 10 minutes water (36 ml) was slowly added at 0°C, pH was adjusted at 5-6 with conc. hydrochloric acid. The solution was evaporated at reduced pressure and the residue diluted with water (1000 ml) and extracted with diethyl ether (3 x 250 ml). The organic phase was dried with sodium

sulphate and the solvent evaporated at reduced pressure. The residue was purified by chromatography eluant n-hexane/ethyl acetate 7:3 affording 66.8 g of pure product 52.6%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H); 2.73 (d, 2H); 3.45 (s, 2H); 4.14 (q, 2H); 4.55 (bq, 1H); 5.10 (d, 1H); 5.25 (d, 1H); 5.82 (m, 1H).

Ethyl (syn)-3,5-dihydroxy-hept-6-enoate, 21: To a solution of methanol (10.8 ml) in an. THF (40 ml) triethylborane (1M in THF, 5.9 ml, 5.9 mmol) was added at 20°C in a nitrogen atmosphere. After 1 hr under stirring the solution was cooled to -65°C and ethyl-5-hydroxy-3-ketohept-6-enoate **20** (1 g, 5.4 mmol) was added. After 30 minutes at the same temperature $NaBH_4$ (0.22 g, 5.9 mmol) was added in portions. The reaction was complete in 3 hrs, then ethyl acetate (200 ml) and ammonium chloride 5% in water (50 ml) were added at room temperature. The organic layer was dried over sodium sulphate and the solvent evaporated in vacuo. Methanol (3 x 100 ml) was added and evaporated under reduced pressure. The crude was purified by chromatography, eluant: n-hexane/ethylacetate 6:4 affording 0.7 g of oil (68.8%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H); 1.63 (m, 2H); 2.46 (m, 2H); 3.60 (bs, 1H); 3.95 (d, 1H); 4.13 (q, 2H); 4.25 (m, 1H); 4.35 (m, 1H); 5.06 (d, 1H); 5.23 (d, 1H); 5.82 (m, 1H).

Ethyl (syn)-3,5-di-(diphenyltertbutylsilyloxy)-hept-6-enoate, 22: A solution of **21** (0.4 g, 2.1 mmol), imidazole (0.57 g, 8.4 mmol) and tert-butyldiphenylsilyl chloride (1.3 ml, 5.1 mmol) in DMF (5 ml) was heated at 70°C under nitrogen for 3 hrs. After cooling the solution was dropped in water (50 ml) and extracted with ethylether (3 x 20 ml). The organic layer was washed with water and dried over sodium sulphate. After evaporation of the solvent in vacuo the product was purified by chromatography, eluant: n-hexane/toluene 1:1 affording 1 g (71%) of pure product.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H); 0.99 (s, 9H); 1.26 (t, 3H); 1.68 (m, 1H); 1.87 (m, 1H); 2.32 (m, 1H); 2.44 (m, 1H); 4.00 (m, 2H); 4.22 (m, 2H); 4.64 (d, 1H); 4.73 (d, 1H); 5.44 (m, 1H); 7.24-7.70 (m, 20H).

Ethyl (syn)-3,5-di(diphenyltertbutylsilyloxy)-7-hydroxy heptanoate, 17: A 0.5 M solution of 9-borabicyclononane in tetrahydrofuran (3.6 ml, 1.8 mmols) was added in 30 minutes at 0°C under an inert atmosphere to a solution of **22** (0.5 g, 0.75 mmols) in anhydrous tetrahydrofuran (4 ml). After the addition, it was stirred at 0-5°C for 16 hours, the excess of 9-boracicyclononane was decomposed with a few drops of water and a solution of 35% hydrogen peroxide (0.89 ml, 9.15 mmols) was added in 20 minutes at

0°C, keeping the pH between 7 and 8 by adding a 3 N aqueous solution of potassium hydroxide (0.37 ml). After 3 hours at room temperature, the reaction mixture was poured into a sodium chloride saturated solution (30 ml) and extracted with ethyl acetate (4 x 15 ml). The reunited organic phases were washed with a 1 M sodium thiosulphate solution, dried and the solvent evaporated thereby obtaining a crude (0.76 g) (colourless oil) which was purified by column chromatography eluant, toluene/ethyl acetate=95:5 affording the product (0.38 g, 46%) (m.p. 75-77°C).

REFERENCES

1. Lipid Research Clinics Program, J. Am. Med. Assoc. 1984, 251, 351-364.
2. Frick M.H. et al., Engl. J. Med. 1987, 317, 1237.
3. Roth B.D., Sliskovic D.R., Trivedi B.K. Ann. Rep. Med. Chem. 1989, 24, 147-156.
4. Grundy S.M., N. Engl. J. Med. 1988, 319, 24-32.
5. a. Endo A., Kuroda M., Tsujita Y., J. Antibiotics, 1976, 29, 1346-1348; b. Endo A., Kuroda Y., Tanzawa K. Febs Lett. 1976, 72, 323-326; c. Brown A.G., Smale T.C., King T.J., Hasen Kamp. R., Thompson R.H. , J. Chem. Soc. Perkin Trans. 1, 1976, 1165-1169.
6. a. Endo., J. Antibiotics, 1979, 32, 852-854; b. Alberts A., Chen J., Kuron G., Hunt V., Huff J. Hoffman C., Rothrock J., Lopez M., Joshua H., Harris E., Patchett A., Monaghan R., Currie S., Staphy E., Alberts-Schonberg G., Hensens O., Hirshfield J., Hoogsteen R., Liesch J., Springer J., Proc. Natl. Acad. Sci. U.S.A., 1980, 77, 3957-3961.
7. Tsujita Y., Kuroda M., Shimada Y., Tanzawa K., Arai M., Kaneko I., Yanaka M., Masuka H., Tarumi C., Watanabe Y., Fujii S., Biochim. Biophys. Acta, 1986, 877, 50-60.
8. a. Serizawa N., Nakagawa K., Hamano K., Tsujita Y., Terahara A., Kuwano H., J. Antibiotics, 1983, 36, 604-607; b. Serizawa N., Serizawa S., Nakagawa K., Furuya K., Okazaki J., J. Antibiotics, 1983, 36, 887-891.
9. Hoffman W.F., Albert A.W. Anderson P.S., Chen J.S., Smith R.L., Williard A.K., J. Med. Chem., 1986, 29, 849-852.
10. a. Kathawala F.G., Exciting developments in the area of HMG-CoA reductase, inhibitors. In Trends in Medicinal Chemistry '88; der Goot H., Domany G., Pallos L., Timmerman H., Eds; Elsevier Science Publishers B.V.: Amsterdam, 1989, pp 709-728. b. Booder E., Bartmann W., Beck G., Bergmann A., Granzer E., Jendralla H., v.Kerekjarta K., Kesseler K., Krause R., Paulus E., Schubert W., Wess G., Rational approaches to enzyme inhibitors: new HMG-CoA reductase inhibitors. In Trends in drug research; Claassen V. Ed.; Elsevier Science Publishers B.V.; Amsterdam, 1990, pp 49-71.
11. For a review see: Rosen T., Heathcok C.H. ; Tetrahedron 1986, 42, 4909-4951.
12. a. Hoefle M.L., EP179, 559, b. Roth B.D. U.S. Pat. 4,735,958
13. Huckin St. N., Weiler L., Can J. Chem., 1974, 52, 2157-2164.

(Received in the UK 01 December 1993)