A New Method for the Synthesis of Antihypercholesterolemic Agent Simvastatin

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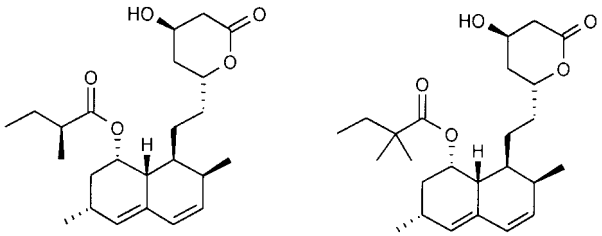
A new synthetic method for the preparation of the cholesterol-lowering drug simvastatin from the naturally occurring lovastatin is reported. The synthesis employs first the protection of the OH group of lovastatin (**1**) and then the protection of the lactone C=O group to prevent enolization *via* conversion to the orthoesters **4a** and **4b**. Alkylation of the 2-methylbutyrate side chain is then successfully achieved. Removal of the protecting groups affords antihypercholesterolemic agent simvastatin (**2**).

Introduction. – Simvastatin (**2**), like other statins (lovastatin (**1**), pravastatin, mevastatin, atorvastatin, fluvastatin, cervastatin, *etc.*, derivatives and analogs thereof) is a (hydroxymethyl)glutaryl coenzyme A reductase (HMG-CoA reductase) inhibitor and is used as an antihypercholesterolemic agent [1–5].



Lovastatin (**1**) Simvastatin (**2**)

Simvastatin (**2**) is prepared from a fermentation product, lovastatin (**1**). It has been reported [6] that **1** cannot be converted directly to simvastatin (**2**) by an alkylation reaction. Because of higher acidity of the lactone α-H atoms compared with the α-H atoms of the ester side chain, alkylation occurs preferentially in the α-position of the lactone. In general, there are two known routes to introduce the additional α-Me group to the 8-acyl side chain of **1**. One involves a deacylation/reacylation procedure, comprised of de-esterification of 2-methylbutanoyloxy side chain of **1** and re-esterification with 2,2-dialkylbutyric acid [7][8]. The other one involves protection reactions and an alkylation of the methylbutanoyloxy side chain with methylhalide/metal alkylamide, and deprotection reactions. In many of the synthetic procedures described in the literature, the latter methodology is used to prepare **2** from **1** [9–15].

All synthetic approaches to prepare simvastatin (**2**) suffer from severe disadvantages, such as an excessive number steps, including those involving the ring opening of

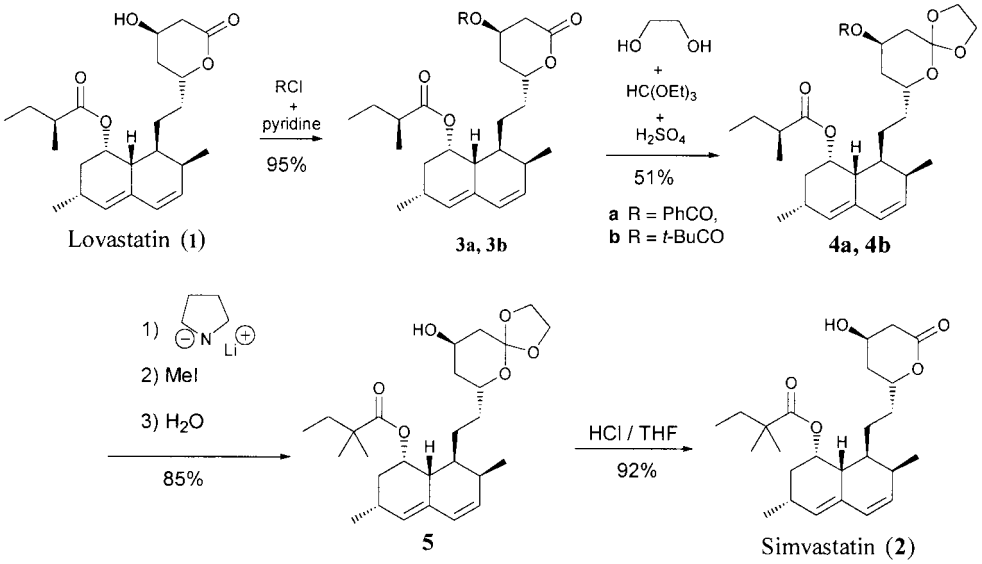
the lactone group of **1**, the insertion and removal of protecting groups and necessity for lactonization, and/or use of expensive reagents.

We report here a less-expensive, safe, and reliable method to synthesize simvastatin (**2**) from lovastatin (**1**). Both the protection and the removal of the protecting groups and methylation reactions are easy to handle, and **2** is obtained in only four steps with inexpensive reagents.

Results and Discussion. – In this study, we decided to methylate the (*S*)-2-methylbutanoyloxy side chain of **1** in order to avoid the problematic deacylation/reacylation reactions. To achieve our goal, we needed to protect the lactone C=O group to prevent an alkylation at the α-position of the lactone ring. Although the protection of the C=O group of a lactone [16][17] as an orthoformate derivative with ethyleneglycol has been reported, no such method has been used in the preparation of **2**.

Our synthesis started with the conversion of **1** to its benzoate derivative **3a** with PhCOCl and pyridine in CH_2Cl_2 in 95% yield. Then, **3a** treated with ethane-1,2-diol, $(EtO)_3CH$, and a catalytic amount of H_2SO_4 in THF gave the desired orthoformate **4a** in 51% yield (*Scheme*). The methylation of the (*S*)-2-methylbutanoyloxy side chain of **4a** was conducted with BuLi, pyrrolidine, and MeI in THF, followed by aqueous workup to give simvastatin β-hydroxyorthoformate derivative **5** in 85% yield. It has to be emphasised that simultaneous removal of the OH protecting group in **4a** occurred during the aqueous workup due to generation of the basic medium in each case. Finally, we have successfully obtained the cholesterol-lowering agent simvastatin (**2**) in 92% yield by removing the C=O protecting group of compound **5** by treatment with dilute HCl in THF.

Scheme. *Synthesis of Simvastatin* (**2**)



We have also obtained simvastatin (**2**) *via* protection of the OH group of **1** with pivaloyl chloride in a manner similar to the benzoate protection (*Scheme*).

The main feature of the new synthesis is in the use of the above-described C=O group protection of the lactone as the orthoester derivatives **4a** and **4b**. This synthesis of **2** involves four simple synthetic steps and overcomes also the formation of a dimer of **2**, as the lactone ring is not opened in contrast to the methods involving lactone opening and closing.

Experimental Part

General. All reactions were carried out under an inert atmosphere of N_2 and with glassware dried in oven (150°) unless otherwise noted. The following solvents and reagents were dried over molecular sieves prior to use: THF, pyrrolidine, DMF, toluene. TLC: *EM Science* (*E. Merck*) plates precoated with silica gel *60* F_{254} (0.25-mm thickness). Spots were visualized by any of the following methods: UV, I_2, phosphomolybdic acid (PMA), anisaldehyde, or $KMnO_4$. Flash column chromatography (FC): with the solvents specified. M.p.: *Electrothermal Thomas-Hoover* cap. melting-point apparatus; uncorrected. IR (KBr for the solids and film for the oil; cm^{-1}): *Jasco FT-IR,* model *5300*. ^{1}H-NMR (δ [ppm], $CDCl_3$): *300-MHz Varian* instrument; TMS as internal standard; the coupling constants *J* are given in Hz. ^{13}C-NMR: at 75 MHz. MS: *VG-Zabspec* double-focusing spectrometer; EI-MS at 70 eV.

*(2*R*,4*R*)-2-[2-((1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-{[(*S*)-2-methylbutanoyl]oxy}-naphthalen-1-yl)ethyl]-3,4,5,6-tetrahydro-6-oxo-2*H*-pyran-4-yl Benzoate* (**3a**). To a soln. of *lovastatin* (**1**; 20 g, 49.63 mmol) in toluene (250 ml) were added pyridine (8.64 g, 109.17 mmol) and then slowly PhCOCl (13.95 g, 99.26 mmol) at r.t. The mixture was stirred at r.t. for 18 h and then diluted with toluene (25 ml). The resulting soln. was washed with 1N HCl soln. (2 × 25 ml), 10% $NaHCO_3$ (30 ml), and H_2O (30 ml). The org. phase was separated and dried (Na_2SO_4). Na_2SO_4 was filtered off, and the filtrate was concentrated *in vacuo*. The product precipitated upon addition of hexane (150 ml), and the filtration afforded **3a** (20.3 g, 91%). White crystalline product. M.p. 114–117°. IR: 2962, 2931, 2877, 1724, 1449, 1265, 1109, 704. ^{1}H-NMR: 0.82 (*t*, *J* = 7.2, Me); 1.04 (*d*, *J* = 6.7, Me); 1.07 (*d*, *J* = 6.6, Me); 1.24–1.76 (*m*, 4 CH_2, CH, Me); 1.81–2.02 (*m*, 3 CH, CH_2); 2.23–2.44 (*m*, CH); 2.88 (*d*, *J* = 4.7, CH_2); 4.59 (*m*, CH); 5.37 (*m*, CH); 5.53 (*m*, 2 CH); 5.78 (*d*, *J* = 9.4, CH); 5.98 (*d*, *J* = 9.4, CH); 7.46 (*t*, *J* = 7.6, 2 CH); 7.65 (*t*, *J* = 7.1, CH); 8.03 (*d*, *J* = 3.5, 2 CH). ^{13}C-NMR: 11.8; 14.2; 16.5; 23.0; 24.5; 27.0; 27.7; 30.9; 33.5; 33.6; 35.7; 36.9; 37.4; 41.6; 42.7; 66.3; 68.1; 76.8; 128.6; 128.8; 129.5; 129.89; 129.97; 131.8; 133.2; 133.8; 166; 168.2; 176.8. EI-MS: 508.6 ($M^{+\cdot}$).

*(2*R*,4*R*)-2,2-(Ethylenedioxy)-6-[2-((1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-8-{[(*S*)-2-methylbutanoyl]oxy}naphthalen-1-yl)ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-yl Benzoate* (**4a**). To a soln. of **3a** (11.4 g, 20 mmol) in dry THF (150 ml) was added ethane-1,2-diol (10.2 g, 200 mmol), $(EtO)_3CH$ (8.9 g, 60 mmol), and 3 drops of H_2SO_4. The mixture was stirred for 48 h at r.t. Then, 150 ml of sat. $NaHCO_3$ soln. was added, and THF was removed under reduced pressure. The aq. phase was extracted with AcOEt (2 × 150 ml). The org. phase was separated and dried (Na_2SO_4). Na_2SO_4 was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by FC with hexane/AcOEt 3:1 to give **4a** (6.05 g, 51% yield). White solid. M.p. 113–115°. IR: 2939, 2924, 1719, 1705, 1460, 1274, 1186, 1111, 703. ^{1}H-NMR: 0.75 (*t*, *J* = 7.62, Me); 0.86 (*d*, *J* = 7, Me); 1.03 (*d*, *J* = 4.1, Me); 1.06 (*d*, *J* = 3.5, Me); 1.25–1.42 (*m*, CH_2, CH); 1.48–1.74 (*m*, CH_2, CH); 1.76–2.10 (*m*, CH_2, CH); 2.16 (*d*, *J* = 3.52, CH_2); 2.23–2.42 (*m*, 2 CH_2, 2 CH); 3.93 (*m*, CH); 4.02–4.16 (*m*, CH_2, 2 CH); 5.31 (*m*, CH); 5.47 (*m*, 2 CH); 5.68 (*d*, *J* = 9.4, CH); 5.94 (*d*, *J* = 9.4, CH); 7.46 (*t*, *J* = 7.6, 2 CH); 7.53 (*t*, *J* = 7.03, CH); 8.14 (*d*, *J* = 7.03, CH). ^{13}C-NMR: 11.7; 14.1; 16.4; 22.9; 24.9; 27.06; 27.7; 30.9; 32.6; 32.9; 34.8; 35.1; 37.3; 37.4; 41.5; 64.2; 64.2; 64.2; 68.2; 70.4; 118.6; 128.4; 128.5; 129.6; 129.9; 130.8; 132.1; 133.1; 133.7; 166.1; 176.9. EI-MS: 552.7 ($M^{+\cdot}$).

*(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-6,6-(Ethylenedioxy)-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-naphthalen-1-yl 2,2-Dimethylbutanoate* (**5**) *from* **4a**. To a stirred soln. of pyrrolidine (3.56 g, 50 mmol) in anh. THF (100 ml) was added BuLi (3.2 g, 50 mmol; 2.5M in hexane) at −20°. The resulting mixture was stirred at −20° for 30 min and then transferred *via* cannula under N_2 pressure to a stirred soln. of **4a** (5.53 g, 10 mmol) in THF (100 ml) cooled to −30° to −35° at such a rate that the temp. was kept below −30°. After completion of the addition, the mixture was stirred at −30° for 2 h, and then MeI (7.1 g, 50 mmol) was added while keeping the temp. at −30°. The mixture was stirred for additional 1.5 h, allowed to warm to −10°, and kept at this temp. for 1 h. The reaction was quenched by careful addition of H_2O

(200 ml). The resulting slurry was stirred for 20 min. at 0°, THF was removed under reduced pressure, and the aq. phase was extracted with AcOEt (2 × 150 ml). The combined org. extracts were washed with H_2O (2 × 150 ml) and dried (Na_2SO_4). Na_2SO_4 was filtered off and the filtrate was concentrated under reduced pressure to give **5** (2.27 g, 85%) as an oily product, which was used directly in the next step. IR: 2963, 1720, 1461, 1372, 1250, 948, 861, 777. ^{1}H-NMR: 0.78 (*t*, *J* = 7.6, Me); 1.03 (*d*, *J* = 7, Me); 1.05 (*s*, 2 Me); 1.22–1.43 (*m*, CH_2, CH); 1.44–1.75 (*m*, 6 H); 1.82–2.03 (*m*, 4 H); 2.04 (*dd*, *J* = 9.6, CH); 2.21 (*d*, *J* = 3.5, CH_2); 2.23–2.41 (*m*, 2 CH_2); 3.82–4.01 (*m*, 2 CH); 4.02–4.22 (*m*, 2 CH_2); 5.77 (*m*, CH); 5.98 (*d*, *J* = 9.2, CH). ^{13}C-NMR: 9.5; 14.3; 23.3; 24.9; 27.5; 30.6; 32.9; 33.2; 37.3; 37.5; 42.4; 37.9; 64.1; 65.4; 68.3; 70.1; 118.9; 128.5; 129.8; 131.9; 133.4; 177.9. EI-MS: 462.6 ($M^{+\cdot}$).

*(2*R*,4*R*)-2-[2-((1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-{[(*S*)-2-methylbutanoyl]oxy}-naphthalen-1-yl)ethyl]-3,4,5,6-tetrahydro-6-oxo-2*H*-pyran-4- yl 2,2-Dimethylpropanoate* (**3b**). The reaction was conducted in a manner similar to the preparation of **3a**, with **1** (10 g, 24.8 mmol) as the starting material. The corresponding ester **3b** was obtained as an off-white solid (11.2 g, 92%). M.p. 95–96°. IR: 2968, 2870, 1728, 1708, 1461, 1245, 1154, 1075, 872. ^{1}H-NMR: 0.84 (*t*, *J* = 7.6, Me); 0.95 (*d*, *J* = 7.9, Me); 1.03 (*d*, *J* = 7.8, Me); 1.11 (*d*, *J* = 7.0, Me); 1.24 (*s*, 3 Me); 1.31–1.50 (*m*, CH_2); 1.51–2.03 (*m*, 4 CH_2); 2.22–2.43 (*m*, 4 CH); 2.75 (*m*, CH_2); 2.86 (*d*, *J* = 18.2, CH); 4.45 (*m*, CH); 5.23 (*m*, CH); 5.35 (*m*, CH); 5.54 (*m*, CH); 5.77 (*m*, CH); 5.95 (*d*, *J* = 9.4, CH). ^{13}C-NMR: 11.8; 14.1; 16.5; 23.0; 24.5; 27.0; 27.2; 27.7; 30.9; 32.7; 33.4; 33.5; 35.5; 36.9; 37.4; 39.0; 41.6; 65.4; 68.0; 76.8; 128.6; 129.9; 131.8; 133.2; 169.0; 176.8; 177.7. EI-MS: 488.1 ($M^{+\cdot}$).

*(2*R*,4*R*)-2,2-(Ethylenedioxy)-6-[2-((1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-2,6-dimethyl-8-{[(*S*)-2-methylbutanoyl]oxy}naphthalen-1-yl)ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-yl 2,2-Dimethylpropanoate* (**4b**). The reaction was conducted in a manner similar to the preparation of **4a**, with **3b** (9.77 g, 20 mmol) as the starting material. Yield: 5.11 g (48%). IR: 2958, 2873, 1723, 1461, 1286, 1161, 1039, 950, 733. ^{1}H-NMR: 0.84 (*t*, *J* = 7.6, Me); 0.86 (*d*, *J* = 7.9, Me); 1.02 (*d*, *J* = 7.8, Me); 1.11 (*d*, *J* = 7.0, Me); 1.23 (*s*, 3 Me); 1.24–1.76 (*m*, 3 CH_2); 1.91–2.04 (*m*, 2 CH_2); 2.06–2.51 (*m*, 3 CH); 3.85–4.22 (*m*, 2 CH_2, 2 CH); 4.31 (*m*, CH); 5.05 (*m*, CH); 5.24 (*m*, CH); 5.43 (*m*, CH); 5.85 (*m*, CH); 5.92 (*d*, *J* = 9.3, CH). ^{13}C-NMR: 11.8; 14.1; 16.4; 23.0; 24.9; 27.1; 27.2; 27.7; 29.9; 30.8; 32.6; 32.9; 34.8; 37.3; 37.4; 39.0; 41.6; 64.0; 64.1; 67.4; 68.2; 70.3; 118.5; 128.4; 129.6; 132.1; 133.7; 176.9; 178.1. EI-MS: 532.2 ($M^{+\cdot}$).

Compound **5** *from* **4b**. The reaction was conducted in a manner similar to the preparation of **5** from **4a**. Compound **5** was obtained in 84% yield (2.76 g), which was used directly in the next step. Spectroscopic data were identical with those of compound **5** obtained from **4a**.

*(1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-[(2*R*,4*R*)-3,4,5,6-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl]naphthalen-1-yl 2,2-Dimethylbutanoate* (= *Simvastatin*; **2**). To a soln. of **5** (4.63 g, 10 mmol) in THF (50 ml) was added 1N HCl (10%, 10 ml) at r.t. The mixture was stirred at r.t. for 3 h. THF was removed under reduced pressure, and the aq. phase extracted with AcOEt (2 × 50 ml). The combined org. extracts were washed with sat. $NaHCO_3$ (2 × 25 ml) and dried (Na_2SO_4). Na_2SO_4 was filtered off, and the filtrate was concentrated under reduced pressure. The residue was crystallized from toluene/hexane to give **2** (3.85 g, 92%). White solid. M.p. 132–134°. IR: 2945, 2930, 1701, 1389, 1255, 1162, 1076,1056. ^{1}H-NMR: 0.83 (*t*, *J* = 7.3, Me); 1.04 (*d*, *J* = 7.1, Me); 1.10 (*s*, 2 Me); 1.20–1.73 (*m*, Me, 4 CH_2); 1.83–2.03 (*m*, CH_2, CH); 2.24–2.44 (*m*, CH_2, CH); 2.65–2.81 (*m*, 2 CH); 4.32 (*m*, CH); 4.63 (*m*, CH); 5.33 (*m*, CH); 5.43 (*m*, CH); 5.84 (*m*, CH); 5.98 (*d*, *J* = 9.4, CH). ^{13}C-NMR: 9.6; 14.1; 23.3; 24.5; 24.9; 25.0; 27.5; 30.8; 33.1; 33.2; 36.3; 36.8; 37.6; 38.8; 43.2; 62.7; 68.3; 76.7; 128.6; 129.9; 131.7; 133.1; 170.8; 178.3. EI-MS: 418.2 ($M^{+\cdot}$).

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