A Convenient Procedure for the Methylation of Lovastatin: Synthesis of Simvastatin

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Abstract:

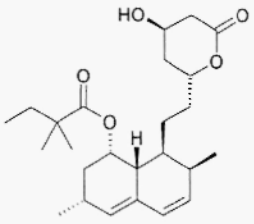
A new synthetic method for the preparation of the cholesterol lowering drug simvastatin **1** from the naturally occurring lovastatin **2** is reported. The synthesis relies upon deactivation of the α-carbon of the δ-lactone via conversion of the lactone group of lovastatin **2** to its carboxylic acid-amine salt derivative and then methylation of the 2-methylbutyrate-side chain of **3**.

Introduction:

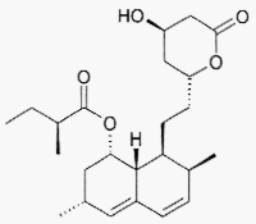
Many people suffer from coronary heart diseases which arise from high cholesterol values. For a successful therapy, besides dietary measures, modern therapeutic drugs are also available, and their use helps to normalise the high cholesterol values (1). Thus, the number of studies on the preparation of the cholesterol-lowering drugs and new synthetic methods for their preparations (2-6) are enhanced.

Simvastatin **1**, like other statins (lovastatin **2**, pravastatin, mevastatin, atorvastatin, fluvastatin, cervastatin, etc., derivatives and analogs thereof) is a hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitor and is used as an antihypercholesterolemic agent (7-11).

Simvastatin **1** is prepared by organic synthesis from a fermentation product, lovastatin **2**.



Simvastatin (**1**)



Lovastatin (**2**)

It has been reported (12) that lovastatin **2** cannot be converted directly to simvastatin **1** by a methylation 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 **2**. One involves a deacylation/reacylation procedure, comprising de-esterification of 2-methylbutyrate-side chain of **2** and re-esterification with 2,2-dialkylbutyric acid (13-14). 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 **1** from **2** (15-23).

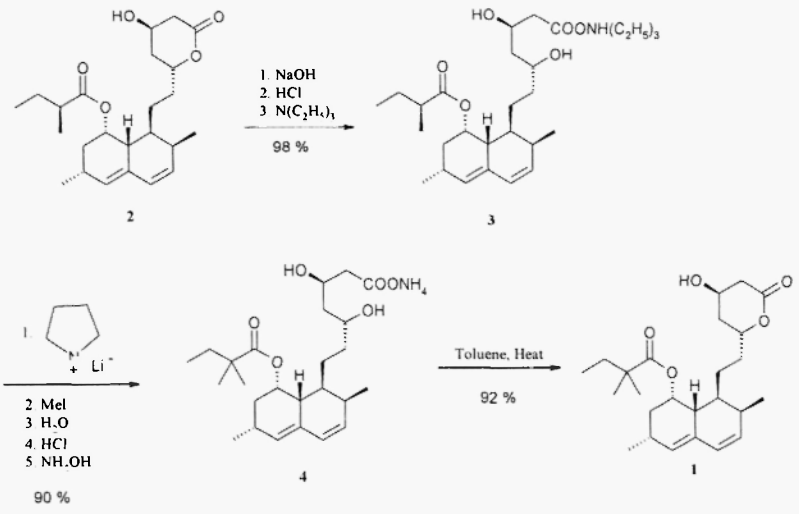
All synthetic approaches to prepare simvastatin **1** suffer from severe disadvantages, such as excessive steps, including those involved with the ring opening of the lactone group of **2**, the insertion and removal of protecting groups and use of expensive reagents. One of our study describes the synthesis of simvastatin (**1**) via novel intermediates (24), however it was still suffering from relatively low overall yield.

We report here a less expensive, safe, reliable and direct method to synthesise simvastatin **1** from lovastatin **2**. Since the protection and the removal of the protecting groups are not involved, the overall yield is higher than the described process (13-24). Methylation reaction is easy to handle and simvastatin **1** is obtained in only three main steps with inexpensive reagents.

Results and Discussions:

Our synthesis started with the conversion of **2** to the amine salt **3**. Then, **3** was treated with n-BuLi, pyrrolidine and MeI in THF, followed with HCl and NH_4OH. Lactonization of **4** gave simvastatin **1** in 81% overall yield (*Scheme*).

Scheme. Synthesis of Simvastatin **1** from Lovastatin **2**.



The main feature of the new synthesis is in the use of above-described deactivation of the α-carbon of the δ-lactone via conversion of the lactone group of lovastatin **2** to its carboxylic acid-amine salt derivative. The described amine salt formation prevents a spontaneous lactone back formation. Thus, complicated protection and deprotection reactions are eliminated and this makes our method superior compared with the other reported methods.

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, 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, phospomolybdic acid (PMA), anisaldehyde, or $KMnO_4$. 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], $CDCl_3$, unless otherwise noted): *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.

Preparation of 3 from lovastatin 2. To a soln. of *lovastatin* **2**; (20 g, 49.63 mmol) in methanol (250 ml) was added a soln. of NaOH (2.18 g, 54.59 mmol) in water (25 ml). The mixture was stirred at r.t. for 2 h and TLC showed no starting material (eluent: hexane/ethyl acetate: 1/1). Methanol was removed *in vacuo*. Water (200 ml) was added and pH was adjusted to 3.0 with 1 N HCl. The resulting soln. was extracted with ethyl acetate (2 x 250 ml). The org. phase was washed with water (2 x 200 ml). Phases were separated and org. phase was dried (Na_2SO_4). Na_2SO_4 was filtered off, and triethylamine (13.82 ml, 99.26 mmol) was added. The mixture was stirred at r.t. for 4 h. TLC showed no starting material (eluent: methanol). The soln. was concentrated under reduced pressure to give **3** (25 g, 98%) as an oily product, which was used directly in the next step. IR: 3440, 2966, 2933, 2488, 1766, 1716, 1677, 1572, 1455, 1394, 1261, 1238, 1188, 1155, 1122, 1050, 972, 855, 750. ^{1}H-NMR: 0.81-0.86 (6H, *m*), 1.02-1.08 (5H, *m*), 1.24 (9H, *t*, J=7.6) 1.30-1.40 (4H, *m*), 1.50-1.73 (3H, *m*), 1.81-2.02 (5H, *m*), 2.18-2.42 (6H, *m*), 3.04 (6H, *q*, J=7.6) 3.71-3.80 (1H, *m*), 4.05-4.15 (1H, *m*), 5.32 (1H, *m*), 5.48 (1H, *s*), 5.73-5.79 (1H, *m*), 5.95 (1H, *d*, J=9.3). ^{13}C-NMR: 8.7, 11.9, 14.0, 14.4, 16.4, 21.3, 21.5, 21.6, 22.2, 23.0, 24.7, 27.0, 30.8, 32.7, 35.0, 36.8, 37.5, 41.6, 42.8, 43.0, 45.2, 60.6, 68.2, 70.1, 72.9, 128.3, 129.5, 132.2, 133.8, 177.0, 178.7. EI-MS: 422.5 ($M^+ - N(C_2H_5)_3$).

Preparation of Simvastatin ammonium salt **4**. To a stirred soln. of pyrrolidine (3.56 g, 50 mmol) in anhydrous THF (100 ml) was added n-BuLi (3.2 g, 50 mmol, 2.5 M) in hexane at –20°. The resulting mixture was stirred at –20° for 30 min. and then transferred *via* a cannula by N_2 pressure to a stirred soln. of **3** (5.38 g, 10 mmol) in THF (100 ml) cooled to –30° to –35° at such a rate that the temperature was kept below –30°. After completion of the addition, the mixture was stirred at –30° for two h and then MeI (7.1 g, 50 mmol) was added while keeping the temperature at –30°. The mixture was stirred for an additional 1.5 h, allowed to warm to –10° and kept at this temperature 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 (pH=11.5). Water (100 ml) was added and pH was adjusted to 3.0 with 1 N HCl. The resulting soln. was extracted with ethyl acetate (2 x 250 ml). The org. phase was washed with water (2 x 200 ml). Phases were separated and org. phase was dried (Na_2SO_4). Na_2SO_4 was filtered off, and a soln. of NH_4OH (10 ml, 25% in water) in methanol (10 ml) was added. The mixture was stirred at r.t. for 2 h. During the stirring, a white precipitate was formed. Solid product was filtered off and washed with ethyl acetate (100 ml), dried in the vacuum oven to give **4** (4 g, 90%). IR: 3444, 2966,

2955, 1766, 1727, 1711, 1694, 1677, 1550, 1505, 1516, 1450, 1405, 1305, 1244, 1155, 1122, 1055, 861, 838. ^{1}H-NMR (DMSO-D6): 0.67-0.76 (5H, *m*), 0.93-0.98 (6H, *m*), 1.10-1.40 (6H, *m*), 1.74-1.92 (5H, *m*), 2.03-2.09 (4H, *m*), 2.16-2.29 (5H, *m*), 3.35-3.42 (1H, *m*), 3.62-3.75 (1H, *m*), 5.11 (1H, *s*, CH), 5.43 (1H, *s*, CH), 5.73 (1H, *m*, CH), 5.88 (1H, *d*, J=9.4, CH), ^{13}C-NMR: 9.8, 14.7, 23.4, 24.8, 25.0, 25.1, 27.4, 30.8, 32.6, 33.2, 35.1, 37.2, 37.3, 43.0, 45.5, 67.2, 68.4, 69.5, 128.8, 129.6, 132.4, 133.9, 177.2. EI-MS: 436.5 (M^+ - NH_3).

Preparation of Simvastatin 1: Compound **4** (2 g, 4.4 mmol) was suspended in toluene (50 ml) and stirred at 90^0 for 4 h. Toluene was removed under reduced pressure. The residue was crystallised from toluene/hexane mixture to give **1** as a white solid (1.69 g, 92%). Mp: 132-134°. IR: 2945, 2930, 1701, 1389, 1255, 1162, 1076,1056. ^{1}H-NMR: 0.83 (3H, *t*, *J*= 7.3, CH_3), 1.04 (3H, *d*, *J*= 7.1, CH_3), 1.10 (6H, *s*, 2 x CH_3), 1.20-1.73 (11H, *m*, CH_3 and 4 x CH_2), 1.83-2.03 (3H, *m*, CH_2 and CH), 2.24-2.44 (3H, *m*, CH_2 and CH), 2.65-2.81 (2H, *m*, 2 x CH), 4.32 (1H, *m*, CH), 4.63 (1H, *m*, CH), 5.33 (1H, *m*, CH), 5.43 (1H, *m*, CH), 5.84 (1H, *m*, CH), 5.98 (1H, *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^+).

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