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# New Synthesis of Simvastatin

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**Abstract:** A noninfringing synthesis of simvastatin **1**, starting from lovastatin **2**, is presented. This synthesis features the protection of the free hydroxyl group of the lovastatin with 3,4-dihydro-2H-pyran (DHP) and opening of the lactone ring with *n*-$BuNH_2$ to afford amide **4** as a key intermediate.

**Keywords:** 3,4-Dihydro-2H-pyran, low-density lipoprotein, methylation, simvastatin

## INTRODUCTION

Simvastatin[1] **1** is a semisynthetic version of a fermentation product **2** of *Aspergillus terreus*. Orally active simvastatin **1** (Fig. 1), a prodrug that gets hydrolyzed in vivo to the corresponding hydroxy acid, which is responsible for eliciting pharmacological effects.[2] Simvastatin **1** targets a specific enzyme that is responsible for catalyzing the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate.

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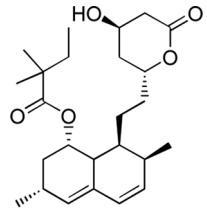



1

*Figure 1.* Structure of simvastatin **1**.



The mode of action involves the inhibition of (HMG-CoA) reductase and eventually lowers the low-density lipoprotein (LDL) level.[2]

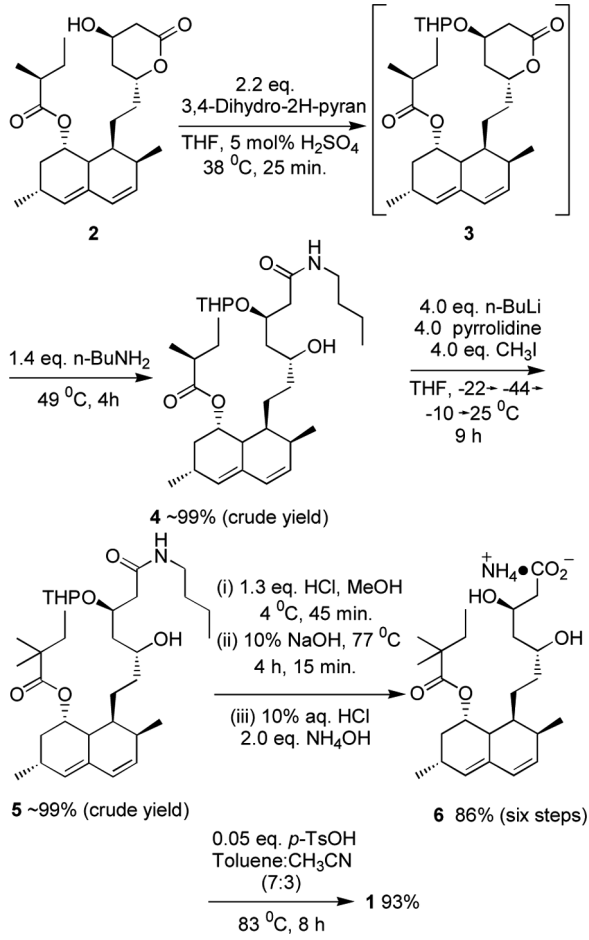
The discovery of lovastatin **2**[3] led to the development of a more potent LDL lowering agent, simvastatin (synvinolin) **1**, way back in 1991 by Merck. Syntheses of lovastatin **2** and simvastatin **1** have been extensively explored.[4] However, most of the developed syntheses except a few appear to be industrially incompatible. Askin et al.[1] reported an elegant synthesis of **1**, although it involves expensive bis-silyloxy protections of naked hydroxy groups. Thaper et al.[5] published a relatively better large-scale preparation method that incorporates four steps, however, the use of more expensive amine (cyclopropyl amine) for amidation appears to be less attractive. Herein we report a cost-effective and noninfringing semisynthetic route for **1** on a large scale.

## RESULTS AND DISCUSSION

Methylation at the 2-position in lovastatin **2** to obtain simvastatin **1**, without a protecting hydroxy group and using excess lithium pyrrolidide and methyl iodide, also allows the formation of side products that make the synthesis cumbersome. However, in the prior process, different protecting groups[1] such as *tert*-butyldimethylsilyl (TBDMS) (expensive), trimethylsilyl (TMS), and dimethoxy propane were successfully employed.

In our efforts to develop a robust and scaleable route for simvastatin **1** as shown in Scheme 1, we chose lovastatin **2**, a commercially available starting material. Use of 3,4-dihydro-2*H*-pyran (DHP), one of the suitable protecting groups in hydroxyl protection, was found to be cost-effective, nonhazardous, and easy to handle, and overall the transformation was high yielding.

Parallel to the development of the synthesis of **1**, we also prepared all the reported impurities **7**–**10** (Fig. 2) in significant quantities. The spectroscopic data of these impurities are in complete agreement with the related known values.




***Scheme 1.*** Synthesis of simvastatin **1**.

Tetrahydro pyran (THP) protection in the first step was found to be concentration dependent. The reaction time in this step was less at lower dilution, and the transformation was also efficient.

It was also observed that 2.2 eq. of DHP with respect to **3** was more than sufficient to achieve better yield and purity. Optimization studies of hydroxy protection stage revealed that the 1.4 to 1.8 eq. of DHP was not enough to effect the optimal conversion. Eventually ~2.0 eq. of the same was found to be ideal for this transformation as shown in Table 1 (entry 4).

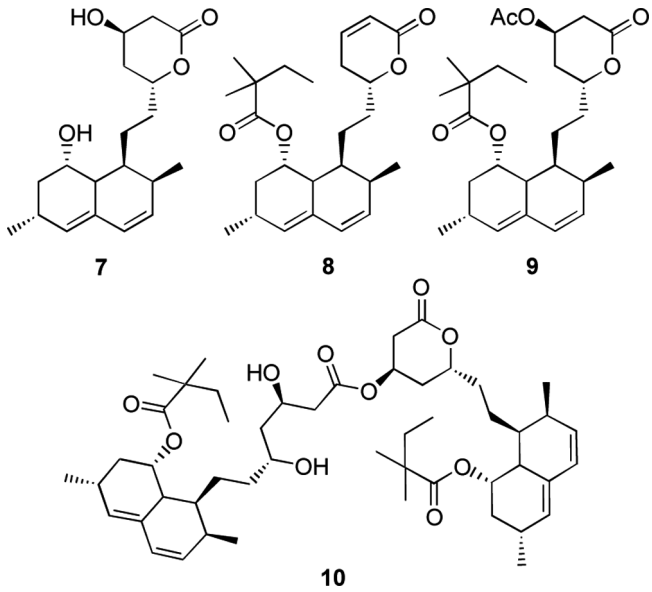



*Figure 2.* Structure of reported impurities **7–10**.

The number of equivalence of *n*-butyl amine was also investigated. An amount of 1.4 eq. of *n*-butyl amine was optimal for the preparation of amide **4**. Optimization results are summarized in Table 2 (see entry 2).

In further transformation, a solution of 4.0 eq. *n*-BuLi and pyrrolidine each was added to a solution of **4** in THF. After stirring for 1 h, methyl iodide was added slowly to the reaction mass and subsequently quenched upon completion of reaction. The pyrrolidine hydrochloride salt was removed by extraction, and the organic layer was concentrated

**Table 1.** Quantification of DHP in the conversion of **2** to **3**

| | | | | Purity by HPLC (%) | |
|---|---|---|---|---|---|
| Entry | Input **2** (g) | $H_2SO_4$ (eq.) | DHP (eq.) | **3** | **2** |
| 1 | 5.0 | 0.05 | 1.4 | 71.27 | 27.82 |
| 2 | 5.0 | 0.05 | 1.6 | 94.48 | 4.34 |
| 3 | 5.0 | 0.05 | 1.8 | 96.98 | 2.72 |
| **4** | **5.0** | **0.05** | **2.0** | **98.93** | **0.46** |
| 5 | 10.0 | 0.05 | 2.2 | 97.46 | 0.09 |

**Table 2.** Optimization of n-butyl amine quantity in the conversion of **3** to **4**

| Entry | Input **2** (g) | Residue (g) | *n*-Butyl amine (eq.) | Purity by HPLC (%) | |
|---|---|---|---|---|---|
| | | | | **4** | **3** |
| 1 | 5.0 | 7.1 | 1.2 | 93.33 | 3.18 |
| 2 | 5.0 | 7.8 | 1.4 | 97.72 | 0.21 |

to afford amide **5** as syrup with excellent yield (>99%) and purity (high pressure liquid chromatography [HPLC]). Optimization results regarding number of equivalence of bases, alkylating agent, and solvent are summarized in Table 3 (entry 6; best result at 100-g scale).

Deprotection, hydrolysis, and ammonium salt formation to obtain **6** were accomplished in one pot with an overall yield of 86%, and the optimization results are summarized in Table 4. Optimization of number of equivalents of HCl involved in the deprotection was essential to effect transformation efficiently. An amount of 1.3 eq. of HCl was optimal for the preparation of **6** (see Table 4, entry 7).

Finally, *p*-TsOH-catalyzed lactonization of **6** in toluene and acetonitrile afforded **1**, with 93% yield and 99% purity.

## EXPERIMENTAL

The $^{1}H$ and $^{13}C$ NMR spectra were recorded in DMSO-d6 at 400 MHz, on a Varian Gemini NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The mass spectrum (70 eV) was recorded on HP-5989a LC-MS spectrometer. The solvents and reagents were used without any purification.

**Table 3.** Quantification of reagents and solvent

| Entry | Input **4** (g) | Residue (g) | *n*-Buli (eq.) | Pyrrolidine (eq.) | MeI (eq.) | THF (volumes with respect to **4**) | Conversion of **5** (%) |
|---|---|---|---|---|---|---|---|
| 1 | 10.0 | 11.0 | 7.5 | 8.8 | 7.16 | 13.0 | 99.67 |
| 2 | 10.0 | 11.5 | 7.5 | 7.5 | 7.16 | 13.0 | 99.67 |
| 3 | 10.0 | 11.4 | 4.5 | 5.8 | 7.16 | 10.0 | 99.57 |
| 4 | 10.0 | 11.1 | 4.0 | 5.3 | 7.16 | 10.0 | 99.32 |
| 5 | 10.0 | 11.0 | 3.5 | 4.8 | 5.0 | 6.0 | 98.90 |
| **6** | **100.0** | **115.0** | **4.0** | **4.0** | **4.0** | **6.0** | **99.60** |

**Table 4.** Optimization of acid/base on THP deprotection and amide hydrolysis

| Entry | 5 (g) | Quantity/yield | HCl (eq.) | NaOH (eq.) | HPLC purity (%) |
|---|---|---|---|---|---|
| 1 | 5.0 | 1.7/49 | 4.0 | 4.0 | 94.97 |
| 2 | 5.0 | 0.4/11 | 0.53 | 4.0 | 94.97 |
| 3 | 5.0 | 1.9/54 | 0.45 | 4.0 | 93.16 |
| 4 | 5.0 | 2.7/77 | 1.0 | 4.0 | 95.37 |
| 5 | 5.0 | 1.2/34 | 1.0 | 3.6 | 97.58 |
| 6 | 5.0 | 2.8/80 | 1.3 | 4.0 | 98.11 |
| **7** | **50.0** | **30.5/87** | **1.3** | **4.0** | **98.09** |



### 2-Methyl-butyricacid-8-[6-butylcarbamoyl-3-hydroxy-5-(tetrahydro-pyran-2-yloxy)-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl Ester 4

A solution of sulphuric acid (0.06 mL) in THF (10 mL) was added to a solution of 3,4-dihydro-2H-pyran (0.54 mol 49.4 mL) in THF (40 mL). After the addition over a period of 10 min and stirring for 5 min, lovastatin **2** (0.25 mol, 100 g) was added at 28 °C. After stirring for 45 min at 36 °C, *n*-$BuNH_2$ (0.32 mol, 34 mL) was added. After additional stirring for 4 h at 49 °C, the reaction mixture was concentrated under reduced pressure to afford crude material **4** as brown syrup. Crude yield: 148.3 g (>100%); purity by HPLC: 98%; $^1$H NMR (400 MHz, DMSO-d6): δ 7.77 and 7.69 (t, $J = 6.4$ Hz, 1H), 5.94 (d, $J = 9.6$ Hz, 1H), 5.78 (dd, $J = 9.6$, 6.0 Hz, 1H), 5.48 (s, 1H), 5.24–5.18 (m, 1H), 4.63–4.59 (m, 1H), 4.36 (d, $J = 6.0$ Hz, 1H), 4.26 (d, $J = 5.6$ Hz, 1H), 4.12–4.00 (m, 1H), 3.82–3.70 (m, 1H), 3.10–2.94 (m, 2H), 2.50 (t, $J = 4.0$ Hz, 1H), 2.44–2.20 (m, 4H), 1.98–1.22 (m, 22H), 1.03–1.00 (m, 6H), 0.88–0.80 (m, 9H); MS: m/e = 584.4 ($M + Na^+$).

### 2,2-Dimethyl-butyricacid-8-[6-butylcarbamoyl-3-hydroxy-5-(tetrahydro-pyran-2-yloxy)-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl Ester 5

To a solution of pyrrolidine (1 mol, 82 mL) in THF (278 mL), 1.6 M *n*-BuLi (1 mol, 622 mL) was added at −25 °C. After the addition over a period of 1 h and stirring for 25 min, a solution of **4** (0.25 mol, 139 g) in THF (556 mL) was added. After stirring for additional 1 h at −45 °C, methyl iodide (1 mol, 63 mL) was added to the reaction mixture and stirred for 1.5 h. The reaction mixture was quenched with 1 N aq. HCl (915 mL), and the organic layer was separated, concentrated, and dried under

reduced pressure to afford crude material **5** as a thick brown syrup. Crude yield: 154 g (>100%); $^1$H NMR (400 MHz, DMSO-d6): δ 7.77 and 7.69 (t, $J = 6.4$ Hz, 1H), 5.94 (d, $J = 9.6$ Hz, 1H), 5.77 (dd, $J = 9.6$, 6.0 Hz, 1H), 5.48 (s, 1H), 5.20–5.18 (m, 1H), 4.63–4.59 (m, 1H), 4.36 (d, $J = 6.0$ Hz, 1H), 4.27 (d, $J = 5.6$ Hz, 1H), 4.10–4.02 (m, 1H), 3.79–3.71 (m, 1H), 3.04–2.95 (m, 2H), 2.50 (t, $J = 4.0$ Hz, 1H), 2.39–2.23 (m, 4H), 1.99–1.20 (m, 21H), 1.26–1.00 (m, 9H), 0.88–0.75 (m, 9H); MS: m/e = 598.4 ($M + Na^+$).



(3R,5R)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-Dimethylbutanoyl]oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoicacidammonium Salt 6[5]

HCl (0.15 mol, 15 mL) was added to a solution of **5** (0.12 mol, 67.6 g) in methanol (149 mL) at 2 °C. After stirring for 4 °C at 45 min to afford in situ amide intermediate, 10% aq. NaOH (0.5 mol, 188 mL) was added to the reaction mixture. After additional stirring for 4 h at 77 °C, the reaction mixture was cooled to 33 °C and water (135 mL) was added. After adjusting the pH to 4.7 (by adding 10% HCl) at 15 °C, the reaction mixture was extracted with EtOAc (338 mL), and 28% ammonium hydroxide solution (0.24 mol, 30 mL) in methanol (30 mL) was added to the organic layer. After stirring for 30 min at 28 °C, the reaction mixture was cooled to 3 °C and stirred additionally for 1 h to afford **6** as a light-brown-colored solid in 87% isolated yield (39.5 g) and 98% purity (HPLC). $^1$H NMR was found to be satisfactory as per literature.

2,2-Dimethylbutanoicacid(1S,2R,7S,8S,8aR)1,2,3,7,8a-hexahydro-3,7,dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl Ester 1[5]

A solution of *p*-TsOH (0.003 mol, 0.5 g) in toluene (421 mL) was added to a solution of **6** (0.055 mol, 25 g) in acetonitrile (173 mL) after stirring for 8 h at 83 °C, water, a by-product, was azeotropically distilled out. The reaction mixture was cooled to 43 °C and filtered. The solvent was completely distilled from the filtrate at 60 °C under vacuum, and methanol (300 mL) was added to the residue at 45 °C. After stirring for 20 min, activated carbon (2.5 g) was added and stirred for an additional period of 0.5 h. The reaction mixture was filtered, washed with methanol (50 mL), and heated to 38 °C. Water (350 mL) was added to the filtrate and cooled to 13 °C over a period of 2 h. The obtained solid mass was filtered, followed by washing with a precooled mixture (110 mL) of

methanol/water (1:1). The wet material was dried over a period of 2 h at 54 °C to afford **1** (21.5 g) in 93% yield and 99% purity (HPLC). $^1$H NMR was found to be satisfactory as per literature.

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