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A Cost-Efficient Synthesis of Simvastatin via High-Conversion Methylation of an Alkoxide Ester Enolate

Rajesh K. Thaper,* Yatendra Kumar, S. M. Dileep Kumar, Satyananda Misra, and Jag Mohan Khanna

Ranbaxy Research Laboratories, Plot - 20, Sector - 18, Udyog Vihar Industrial Area, Gurgaon - 122 001, Haryana, India

Abstract:

A cost-efficient synthesis of simvastatin (2), starting from mevinolin (lovastatin) (1a) or its precursor mevinolinic acid (1b), is reported. This synthesis involves the use of a new intermediate, lovastatin cyclopropylamide (3), eliminating two chemical steps of protection and deprotection of the open dihydroxy form of (1a). Synthesis is based on the high-conversion methylation of an alkoxide ester enolate and involves only four chemical steps. Methylation reaction conditions have been optimized to get >99.5% conversion. Process is economical on large-scale and product (2) is obtained in 85% overall yield.

Introduction

Lovastatin, **1a**,[1] a fungal metabolite representing the first of a new class of hypolipaemic agents (HMG CoA reductase inhibitors) brought a significant advance over existing hypolipaemic agents. After the discovery of **1a** as a fermentation product, its more active synthetic analogue, simvastatin (synvinolin), **2**[2] was introduced in the market which led to the need for a high-yielding, economical, and environmentally sound process.

Several methods are available for the synthetic conversion[3] of **1a** to **2** (Figure 1). However, all are not practical on large scale, due primarily to the overall low yields, high costs of reagents, large number of steps involved, or poor conversion of the alkylation. A fundamental problem is the inability to remove even trace amounts of unreacted **1a** from **2** by fractional crystallization or column chromatography.

Thus, the success of any commercial process for synthesising **2** would depend on (i) the potential to reduce unreacted **1a** to very low levels (USP limit of **1a** in **2** is <1%) and (ii) involvement of minimum number of chemical steps.

Simvastatin, **2**, was first prepared by a four-step straightforward strategy[2,3] involving the following distinct steps:

(i) de-esterification of the 2-methylbutyrate side chain,

(ii) protection of the 4-hydroxy group of the pyranone ring,

(iii) re-esterification of the side chain to form the desired 2,2-dimethylbutyrate, and

(iv) deprotection of the 4-hydroxy group.

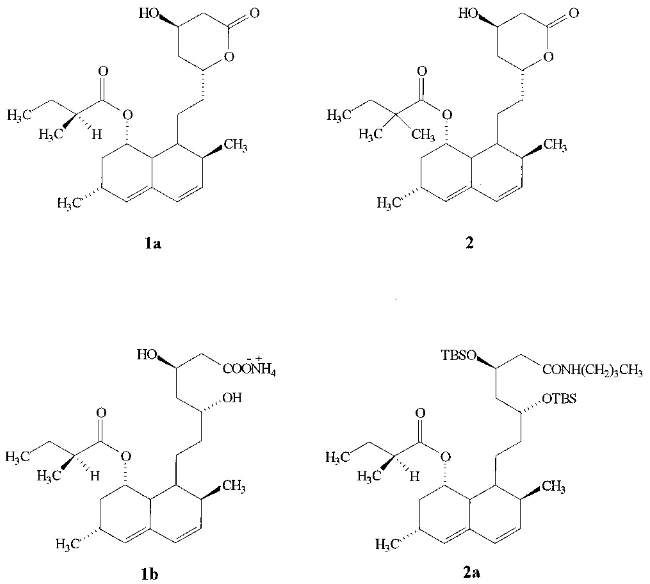

Figure 1. **Structures of lovastatin 1a, simvastatin 2 and derivatives.**

This route is tedious and nonpractical due to poor overall yields (48%).

Askin[2] et al. in 1991 reported an efficient synthesis of **2** from **1a** via a high-conversion direct methylation of an ester enolate. The strategy involved the protection of the carboxyl and two hydroxyl groups of open dihydroxy acid of **1a** to give bis[*tert*-butyldimethylsilyl)oxy] butylamide, **2a**, which upon methylation followed by deprotection of the silyl functionality and basic amide hydrolysis led to simvastatin. Although the overall yield is good, the process comprises six chemical steps and is not economical and safe on commercial scale due to the protection of two hydroxy groups using an expensive silylating agent (*tert*-butyldimethylsilyl chloride) and deprotection with corrosive acids (HF or MSA).

We herein report an extremely cost-efficient and practical process for the large-scale preparation of simvastatin, **2**, from lovastatin, **1a**, or its open dihydroxy acid form, mevinolinic acid, **1b**. This process is of significance as it involves only four chemical steps, eliminating two expensive chemical steps of protection and deprotection of the open dihydroxy acid form of **1a**. Product **2** is obtained in high overall yield and pharmaceutically acceptable purity, with lesser consumption of reagents, time, and labor.

Results and Discussion

To effect the enolization/methylation of the 2-(s)-methylbutyrate side chain without protection of the dihydroxy

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[1] (a) Kysika, R.; Kren, V. *J. Chromatogr*. **1993**, *630,* 415–417. (b) *Drugs Future* **1987**, *12,* 309. (c) Moore, R. N.; Bigam, G.; Chan, J. K.; Hogg, A. M.; Thomas, T.; Verderas, J. C. *J. Am. Chem. Soc*. **1985**, *107,* 3694–3701 (d) Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42,* 4909–4951.

[2] Askin, D.; Verhoeven, T. R.; Liu, T.M–H; Shinkai, I. *J. Org. Chem*. **1991**, *56,* 4929–4932.

[3] Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chem, J. S.; Smith, R. L.; Willward, A. K. *J. Org. Chem*. **1986**, *29,* 849–852. Also see ref 2.

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Scheme 1

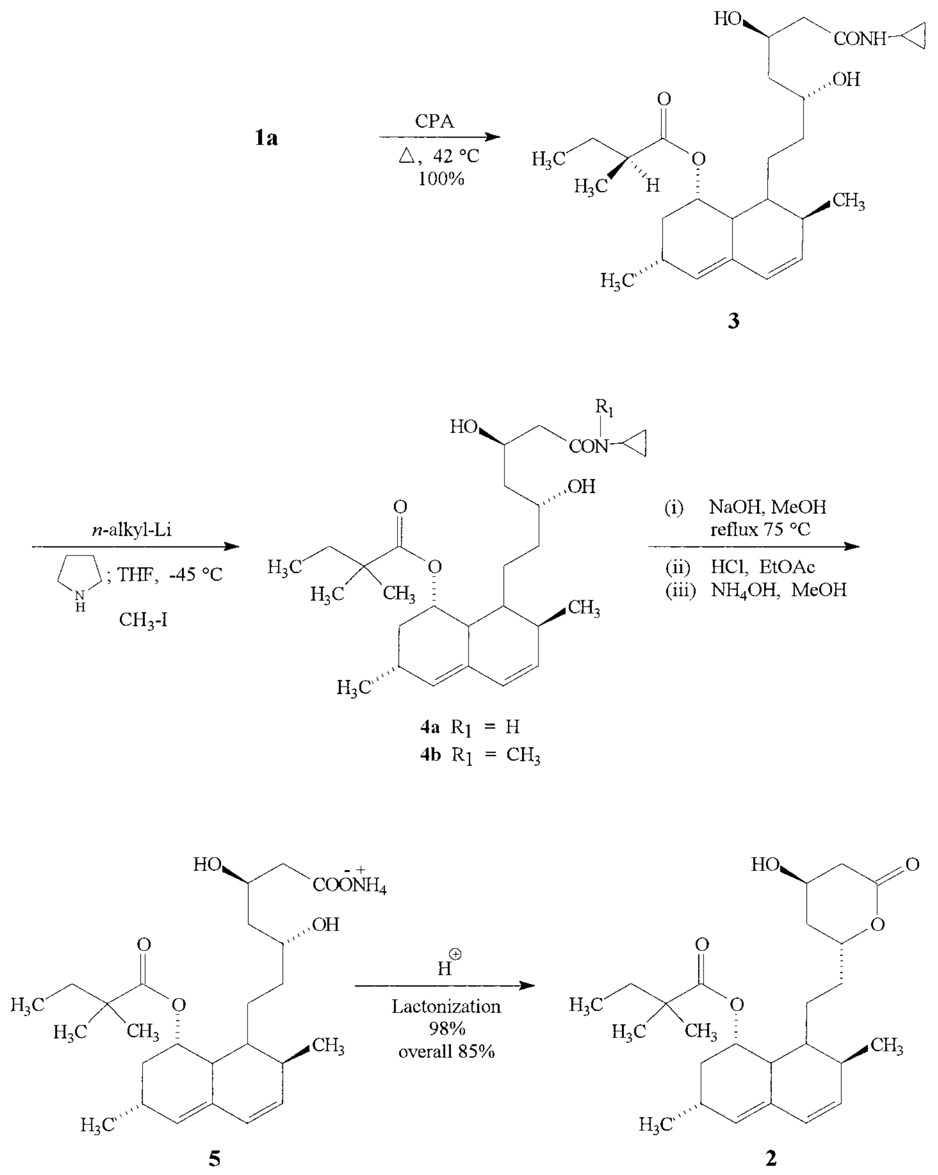

Table 1. **Effect of the quantity of lithium pyrrolidide on the methylation of amide 3**

entry	lithium pyrrolidide (equiv)	conversion (%)	yield of **5** (%)
1	4.0	96−97	90
2	5.0	98	89.5
3	5.5	>98	88
4	7.5−8	>99.5	87
5	8.5	>99.8	80

system, a new intermediate cyclopropylamide **3** was chosen due to the less steric bulk which it offers and the ease with which it can be formed and cleaved. It was interestingly found that treatment of **3** with excess lithium pyrrolidide to an alkoxide ester enolate was desirable and afforded higher degree of methylation (Scheme 1).

Treatment of **1a**[4] with cyclopropyl amine at 42 °C for 8 h led to the formation of amide **3** in quantitative yield. As the reaction is clean, amide **3** did not require isolation and purification prior to methylation. Treatment of **3** with in situ generated lithium pyrrolidide provided an intermediate ester enolate. Subsequent addition of methyl iodide[5] allowed extremely high conversion (>99.5%) to afford methylated product **4**[6] (Scheme 1). Methylation of the enolate was dependent on the quantity of lithium imidate used. Initial experiments with 4 mol equiv of lithium pyrrolidide gave only 96−97% conversion. With an increase in the quantity of lithium imidate from 4 to 8 mol equiv (Table 1) conversion was increased to >99.5%. By using 8.5 mol equiv of lithium imidate, a high conversion of >99.8% was achieved, but the yield of **5** was reduced to 80%. For large-scale production use of 7.5 mol equiv of lithium imidate was standardized

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(4) Mevinolinic acid, **1b**, is isolated as an intermediate in the preparation of lovastatin, **1a**, by a microbial process. **1b** is converted to **1a** in a chemical step incurring ~20% material loss in purification. Direct use of **1b** in the preparation of simvastatin, **2**, was aimed to avoid this loss. This is not, however, being followed in view of wide fluctuations in the assay of **1b**.

(5) No amount of O-methylation of alkoxide ester enolate was observed at the final temperature of −30 °C after addition of MeI. The quantity of MeI has been optimized to about 4 equiv.

(6) Some amount of N-methylation occurred under the present conditions giving rise to about 2−3% (TLC or HPLC) of **4b**.

for reproducibly optimum methylation conversion of >99.5% and 87% yield. Lithium pyrrolidide was prepared by treatment of *n*-butyllithium with pyrrolidine in THF at −20 °C and methylation reaction carried out at −35 to −40 °C. Later, *n*-butyllithium was replaced by hexyllithium. Use of *n*-hexyllithium on large scale has advantages over *n*-butyllithium in terms of greater stability and safety. It does not emit inflammable butane gas as a byproduct, otherwise released by *n*-butyllithium, requiring special scrubbing systems for handling on industrial scale.

Amide hydrolysis of **4a** and **4b** without purification with methanolic sodium hydroxide followed by treatment of the resulting dihydroxy carboxylate with ammonium hydroxide afforded ammonium salt **5** as a crystalline solid in a single-pot process. Finally, the lactonization of **5** by acid-catalyzed reaction or by refluxing in toluene gave simvastatin, **2**, in 98% yield. The overall yield of this four-step process (**1a** → **2**) was 87%.

It is worthwhile to note that the rate of methylation of the alkoxide ester enolate is highly dependent on the concentration as well as the hexane/THF ratio that influences the solubility of alkoxide ester enolate. After extensive studies, it became evident that both the concentration of **3** and the hexane/THF ratio influenced the methylation process. The optimum concentration of 4% of **3** in a hexane/THF ratio of 1.3 gave the highest (>99.5%) methylation conversion.

In conclusion, a highly efficient and economical process for the commercial preparation of simvastatin, **2**, starting from lovastatin, **1a**, or its precursor **1b** has been developed. This process involves the use of a new intermediate, amide **3**, and eliminates the need for protection and deprotection of the dihydroxy system of the open pyranone.

Experimental Section

General. Lovastatin, **1a**, and mevinolinic acid, **1b**, were obtained from an in-house source. HPLC analysis were performed on a Waters LC Module-I with detection at 238 nm in acetonitrile/THF/water and orthophosphoric acid (85% w/w HPLC grade). ^{1}H-spectra were obtained at 300 MHz using TMS as an internal standard. All operations were done under an inert atmosphere of nitrogen. Cyclopropylamine (CPA) and THF were used as such, pyrrolidine and MeI were dried prior to use. *n*-Butyllithium and hexyllithium were purchased from Chemetall GmBH.

***N*-Cyclopropyl-7-[1,2,6,7,8,8a(*R*)-hexahydro-2(*s*),6(*R*)-dimethyl-8(*s*)-[[2(*S*)-methyl- butanoyl]-oxy]-1(*S*)-naphthyl]-3(*R*), 5(*R*)-dihydroxyheptanoic Acid Amide (3). From Lovastatin (Method I).** 1a (40 g, 0.098 mol) and CPA (40 mL, 0.57 mol, m.c. 0.3% w/w) were heated at 40−42 °C for 8 h. The excess CPA was distilled off, THF (20 mL, m.c. 0.04% w/w) was added and removed at reduced pressure to give amide 3 as a gum in quantitative yield and 99.8% purity by HPLC; ^{1}H NMR (CDCl$_3$, 300 MHz) $\boldsymbol{\delta}$ 0.495 (m, 2H), 0.50 (m, 2H), 0.86 (m, 6H), 1.08 (m, 6H), 2.3 (d, 2H) $\boldsymbol{\delta}$ 2.6 (m, 1H), 3.7 (m, 1H), 4.18 (m, 1H), 5.4 (m, 1H), 5.5 (bt, J = 3.0 Hz, 1H), 5.7 (dd, J = 6.1, 9.5 Hz, 1H), $\boldsymbol{\delta}$ 5.9 (d, J = 9.6 Hz, 1H) 6.2 (bt, J = 5.3 Hz, 1H); IR (CHCl$_3$) 3500−3000, 3000, 1740, 1660, 1530, 1450, 1210, 860, 760 cm^{-1}.

From Mevinolinic Acid Ammonium Salt (Method II). **1b** (40 g) suspended in toluene (1280 mL) was refluxed at 107 °C under a sweep of nitrogen for 5 h. The clear solution thus obtained was cooled to 60 °C and concentrated by distilling off 1000 mL of toluene in a vacuum. Cyclopropylamine (40 mL, 0.57 mol) was added at 30 °C and the solution heated at 40−42 °C for 12 h. Removal of solvent at reduced pressure afforded the title compound in quantitative yield in gum-like form which was taken to the next step. HPLC purity = 99.6%.

***N*-Cyclopropyl-7-[1,2,6,7,8,8a (*R*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2,2-dimethyl- butanoyl]oxy-1(*S*)-naphthyl]-3(*R*), 5(*R*)-dihydroxyheptanoic Acid Amide (4a) and (4b).** THF (343 mL, m.c. 0.02% w/w) and pyrrolidine (54.86 g, 0.77 mol, m.c. 0.2% w/w) were cooled to −30 °C, and *n*-butyllithium (464 mL, 1.6 M solution in hexane) was added via a cannula, maintaining temperature of −20 °C. The reddish clear solution was stirred for 30 min at −20 °C. Amide **3** in THF (262 mL) was added at −45 to −40 °C, and the mixture was stirred for 1 h at the same temperature. Methyl iodide (24.6 mL, 0.392 mol) was syringed in, maintaining the temperature below −30 °C. The cloudy solution thus obtained was stirred for 1 h at −35 to −30 °C. Reaction was quenched by addition of water (350 mL). The mixture was stirred for 5 min, and the lower aqueous layer was separated. The organic layer was washed with 2 N HCl (150 mL, chilled). To the combined aqueous layers and acid wash was added NH$_4$Cl (100 g) and the mixture was extracted with hexane (200 mL). The combined organic phases were concentrated under vacuum to give an oil. It contains the titled compound **4a** along with some traces of **4b**.[6]

6(*R*)-[2-[8(*S*)-(2,2-dimethylbutyryloxy)-2(*S*),6(*R*)-dimethyl-1,2,6,7,8,8a(*R*)-hexahydro-1(*S*)-naphthyl]ethyl-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Simvastatin) (2). To the concentrated solution from the previous step containing amides **4a** and **4b** was added NaOH solution (2 N, 400 mL) and MeOH (700 mL). The mixture was refluxed at 75−78 °C for 3 h, cooled to 50 °C, and MeOH (about 500 mL) was removed by rotary evaporation. The concentrate was diluted with water (300 mL) followed by acidification with 2 N HCl to pH 4 at 10−15 °C. Material was extracted with EtOAc (500 mL). To the ethyl acetate extract a solution of NH$_4$OH and methanol (1:1, 40 mL) was slowly added at 22−25 °C. The precipitates were stirred at 25 °C for 1.5 h and then cooled to 5 °C. Filtration, followed by washing with EtOAc and drying in a vacuum at 35 °C afforded the ammonium salt **5** (39 g, 97.6% HPLC purity).

^{1}H NMR (MeOH-d_3 + D$_2$O, 300 MHz) δ 0.831 (m, 6H, 2-Me gps), 1.075 (m, 9H, 3-Me gps), 1.53 (m, 6H), 1.97 (m, 2H), 2.27 (m, 5H), 3.68 (m, 1H), 4.07 (m, 1H), 5.52 (m, 1H), 5.50 (bt, J = 3.0 Hz, 1H), 5.77(dd, J = 6.1, 9.5 Hz, 1H), 5.96 (d, J = 9.6 Hz, 1H); IR (KBr): δ 3380, 2995, 1720, 1560, 1450, 1150, 1100, 870, 860 cm^{-1}

The ammonium salt **5** (10 g, 0.022 mol) was suspended in toluene (350 mL). The mixture was heated and stirred at 105 °C for 5 h, activated charcoal (0.5 g) was added and stirred for 0.5 h, and then the mixture was filtered through Hyflo bed. The filtrate was concentrated in vacuo to a volume of 40 mL at 60 °C bath temperature. Cyclohexane (125 mL) was added and the solution again refluxed for 15 min, cooled for 1 h to 25 °C, and further cooled to 10−12 °C for 30 min. The crystallized product was stirred at 10−12 °C for 30 min, filtered, and washed with cold cyclohexane (50 mL) and dried in a vacuum oven at 40 °C to give a white crystalline product **2** (9 g, HPLC purity > 99%). Analytical data is consistent with that of literature.[2]

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