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# An improved process for chiron synthesis of the atorvastatin side chain

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ABSTRACT

An improved and practical synthesis of *tert*-butyl ((4*R*,6*R*)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate **3** has been developed for supplying this key chiral side-chain of atorvastatin by using a Blaise reaction of (*S*)-4-chloro-3-((trimethylsilyl)oxy)butanenitrile **7** and the Raney Ni catalyzed hydrogenation of *tert*-butyl 2-((4*R*,6*R*)-6-(-2-oximeethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate **12** as the key steps. This nine-step route from (*R*)-epichlorohydrin afforded the target compound in 55% overall yield of high chemical and enantiomeric purity.



## 1. Introduction

The industrial asymmetric synthesis of atorvastatin via a direct Paal–Knorr condensation utilizes diketone **2** and enantioenriched primary amine **3** as key building blocks as developed by Warner-Lambert Company in 1989 (Fig. 1).[1] The efficient and convenient preparation of this atorvastatin side chain **3** still represents a major synthetic challenge.

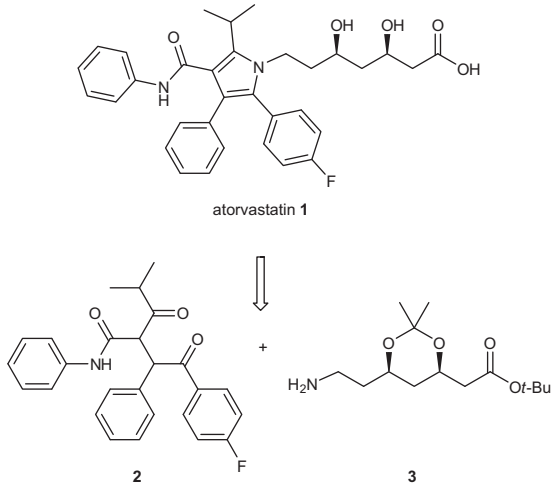


**Figure 1.** Warner-Lambert's industrial strategy for the synthesis of atorvastatin.

Although many strategies for the preparation of **3** have been reported,[2–8] such as Radl's[3] stereoselective synthesis of a C-7 cyano type side chain, a precursor of **3**, the iodolactonization of the homoallylic alcohol involved a seven-step sequence; its poor resolution restricted this procedure in a large-scale preparation. A chemoenzymatic route to **3** described by Wong et al. from Scripps[4] involved a 2-deoxyribose-5-phosphate aldolase (DERA) catalyzed condensation of 3-azidopropanal with acetaldehyde as the key step. However this method suffered from a long reaction time and a very low yield in addition to the lack of availability of mutant DERA. Utilizing a catalytic asymmetric aldol approach, Shibasaki[5] developed an efficient preparation of **3** starting from 3-(benzyloxy)propanal and *N*,*N*-diallylethanethioamide; the major disadvantages of this process were the use of an expensive $[Cu(MeCN)_4]PF_6$/(*S*,*S*)-Ph-BPE catalyst and the low overall yield. Shibasaki et al.[6] recently reported the preparation of an analogue of **3** via the asymmetric intermolecular oxo-Michael addition of benzaldehyde to (*S*)-*tert*-butyl 7-(diallylamino)-5-hydroxyhept-2-enoate derivative from (*S*)-*N*,*N*-diallyl-3-hydroxy-5-(trityloxy)pentanethioamide, which was prepared by an aldol reaction; however the need for chromatographic purification makes this process unamenable to scale-up. Two synthetic methods for the synthesis of **3** via *tert*-butyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (Kaneka alcohol) have been achieved by the formation of a C-7 cyano type side chain[7] or a C-7 nitro type side chain[8] intermediate. Unfortunately, the Kaneka alcohol[9] is not easily accessible in a cost-effective manner. The Chiron approach[7] starting from (*R*)-ethyl 4-cyano-3-hydroxybutanoate is a reliable method for the industrial production of **3**. However, a

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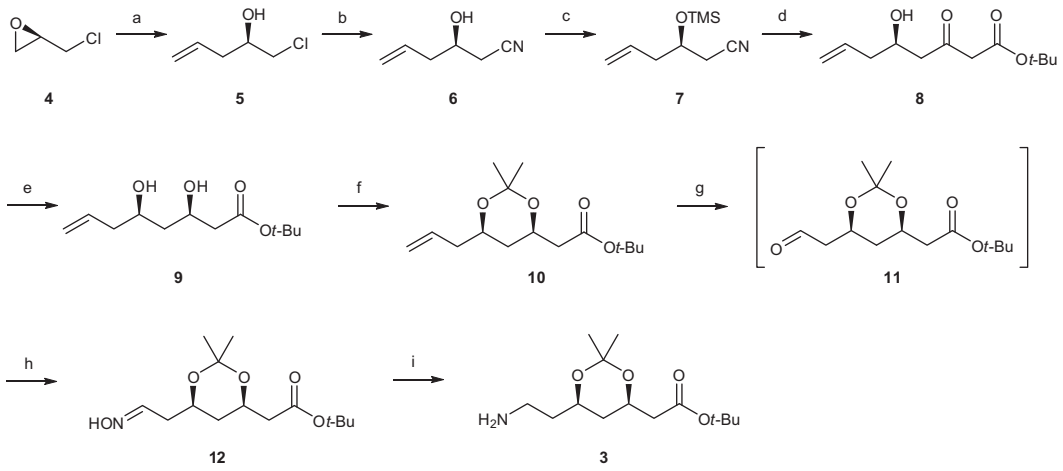


**Scheme 1.** Reagents and conditions: (a) vinylmagnesium chloride, CuI (5 mol %), tetrahydrofuran, −10 °C, 2 h, (b) NaCN, MeOH, reflux 12 h, 74% (two steps), (c) hexamethyldisilazane, trimethylsilyl chloride (1 mol %), petroleum ether, rt, 8 h, 99%, (d) $BrCH_2COOt$-Bu, Zn, methanesulfonic acid (1 mol %), tetrahydrofuran, reflux, 2 h, then 3 M HCl, rt 3 h, 88%, (e) $Et_2BOMe$, $NaBH_4$, tetrahydrofuran–MeOH (4:1), −60 °C, 2 h, 100%, (f) 2,2-dimethoxypropane, methanesulfonic acid, acetone, rt 8 h, 94%, (g) $O_3$, dichloromethane, −40 °C, 15 min, (h) hydroxylamine hydrochloride, NaOH, MeOH, 24 h, 91% (two steps), (i) $H_2$ (15 atm), Raney-Ni, $NH_3$/MeOH, 50 °C, 5 h, 100%.

large excess of expensive lithium diisopropylamine is required for the Claisen condensation of (*R*)-ethyl 4-cyano-3-hydroxybutanoate with *tert*-butyl acetate in the side chain elongation step. As a result, the development of an efficient route to this important side chain is important. Herein, we report an improved synthesis of **3**, utilizing a Blaise reaction of (*S*)-4-chloro-3-((trimethylsilyl)oxy)butanenitrile and the Raney Ni-catalyzed hydrogenation of *tert*-butyl 2-((4*R*,6*R*)-6-(-2-oximeethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate as the key steps.

## 2. Results and discussion

Our synthetic approach toward **3** is shown in Scheme 1. Cyano alcohol **6** was prepared from (*R*)-epichlorohydrin in an overall yield of 74% over two steps.[10,11] The protection of **6** was performed upon treatment with hexamethyldisilazane in the presence of a catalytic amount of trimethylsilyl chloride in a petroleum ether (60∼90 °C) at room temperature to afford silyl ether **7** in 99% yield, which then underwent Blaise reaction[12] on refluxing with zinc *tert*-butyl bromoacetate derived in situ from Zn dust and *tert*-butyl bromoacetate to provide a keto ester **8** in 88% yield. The diastereoselective reduction of **8** under Narasaka's conditions[13] [$Et_2BOMe$/$NaBH_4$/tetrahydrofuran–MeOH (4:1), −60 °C] gave 3,5-*syn*-diol **9** in almost quantitative yield. The resulting 3,5-*syn*-diol **9** was then protected with 2,2,-dimethyloxypropane to furnish the corresponding acetal **10** in 94% yield and with 99% diastereoselectivity as determined by GC–MS.

The stereochemistry of **10** was confirmed by 2D-NOESY experiments in which NOEs between Ha, Hb, and Hc were observed with each other (Fig. 2).

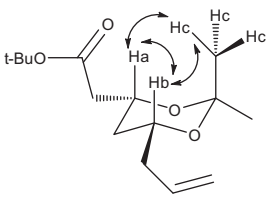


**Figure 2.** Nuclear Overhauser effect between Ha, Hb, and Hc.

Aldehyde **11** was obtained from ozonolysis of terminal olefin **10** and then treated with hydroxylamine hydrochloride and NaOH in methanol to give oxime **12** in 91% yield (*cis*-**12**/*trans*-**12** = 1:1 as determined by $^1$H NMR spectroscopy). The catalytic hydrogenation of **12** over Raney-Ni under 15 bar pressure of $H_2$ at 50 °C for 5 h provided the desired target product **3** in quantitative yield.

## 3. Conclusion

In conclusion we have described an efficient and economical route for the synthesis of atorvastatin side chain **3** starting from readily available (*R*)-epichlorohydrin by using a Blaise reaction as the key step with an overall yield of 55%, in which no expensive reagent or catalyst was used and no chromatographic purification was required.

## 4. Experimental

### 4.1. General

All reagents were obtained from commercial sources and used without further purification. $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as internal standards, IR spectra were recorded on a JASCO FT/IR-4200 spectrometer, Optical rotations were measured with a JASCO P1020 digital polarimeter. EI-MS was recorded on an Agilent 6890N/5975 spectrometer and ESI-MS was recorded on a Waters Micromass Quattro Micro spectrometer. HRMS was recorded on a Bruker micrOTOF spectrometer.

### 4.2. (*R*)-3-((Trimethylsilyl)oxy)hex-5-enenitrile 7

To a stirred suspension of **6**[10,11] (11 g, 0.10 mol) in petroleum ether (100 mL, 60∼90 °C), hexamethyldisilazane (12 g, 75 mmol), and trimethylsilyl chloride (0.10 g, 1 mmol) were added, and the mixture was stirred at rt until it became homogeneous (ca. 8 h). The clear solution was decanted and washed with water (50 mL), dried over $Na_2SO_4$, and the solvent was removed in vacuo to afford **7** (17.9 g, 99%) as a pale yellow oil, relative content 100% (GC area%). $[\alpha]_D^{21} = -2.2$ (*c* 1.0, MeOH). IR (neat): 3080, 2958, 2251, 1642, 1418, 1252, 1098, $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.69–5.80 (m, 1H), 5.15 (d, *J* = 4 Hz, 1H), 5.12 (s, 1H), 3.99 (quint, *J* = 6 Hz, 1H), 2.39–2.50 (m, 2H), 2.32 (t, *J* = 6.4 Hz, 2H), 0.16 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 132.9, 118.9, 117.8, 68.0, 41.6, 25.6, 0.1. MS (EI): *m*/*z* = 183 $[M]^+$. HRMS (ESI) *m*/*z* calcd for $C_9H_{17}NOSiNa$ $[M+Na]^+$ 206.0977, found 206.0977.