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A novel and efficient route for the preparation of atorvastatin

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Abstract

A novel and efficient synthetic method of atorvastatin was described. The key step of the synthesis was the construction of the olefin linkage between the chiral side chain and skeleton *via* a Horner–Wadsworth–Emmons reaction, resulting in the advanced intermediate of atorvastatin under hydrogenation of the olefin over Pd/C. This novel method is more useful for the practical synthesis of atorvastatin than its document reported methods.

Keywords: Atorvastatin; Horner–Wadsworth–Emmons reaction; Synthesis; Intermediate

Atorvastatin (**1**, Lipitor®) is the first totally synthesized HMG-CoA reductase inhibitor developed and marketed as a single enantiomer. It becomes the standard of care for treatment of hypercholesterolemia and ranked as one of the most successful drugs of this decade because of its efficacy, safety and long-term benefits [1–3]. Hence, there has been considerable interest in the synthesis of atorvastatin **1**. A number of different routes to this drug have been reported, mostly based on the convergent synthesis using **2** as the advanced intermediate [4–10]. The routine for syntheses of **2** involved a Paal–Knorr condensation of diketoamide **3** with chiral ester **4** as outlined in Scheme 1. However, all of the published methods for the preparation of the atorvastatin side-chain involve several drawbacks such as (a) low overall yields; (b) lengthy and tedious processing steps; and (c) the use of several expensive reagents. Therefore, the development of practical, concise and high yield approaches for the key intermediate **2** of atorvastatin is requisite and significant. Herein we describe a new more convenient and efficient method for the synthesis of the compound **2** as shown in Scheme 2.

Our synthesis of fragment **8** as a key pyrrole precursor was outlined in Scheme 3. We used phthalimide **9** as the starting material which is readily available and inexpensive. The phthalimide **9** was converted to the key precursor diethyl (aminomethyl) phosphonate **8** through four step reactions according to the literature [11,12].

With the phosphonate **8** in hand, we studied its cyclization reaction with diketone **3** and optimized the reaction conditions as shown in Table 1. We found that the reaction conditions under a catalytic amount of acetic acid in anhydrous toluene (Table 1, entries 5 and 6) resulted in good conversion to the desired pyrrole **6**. Comparison of entries 5 and 6 revealed that an excess of diketone **3** (entry 6) afforded slightly improved yields relative to equivalent amount (entry 5).

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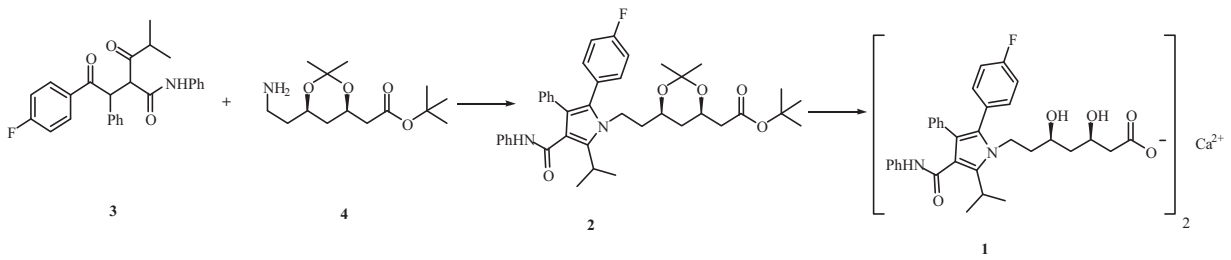
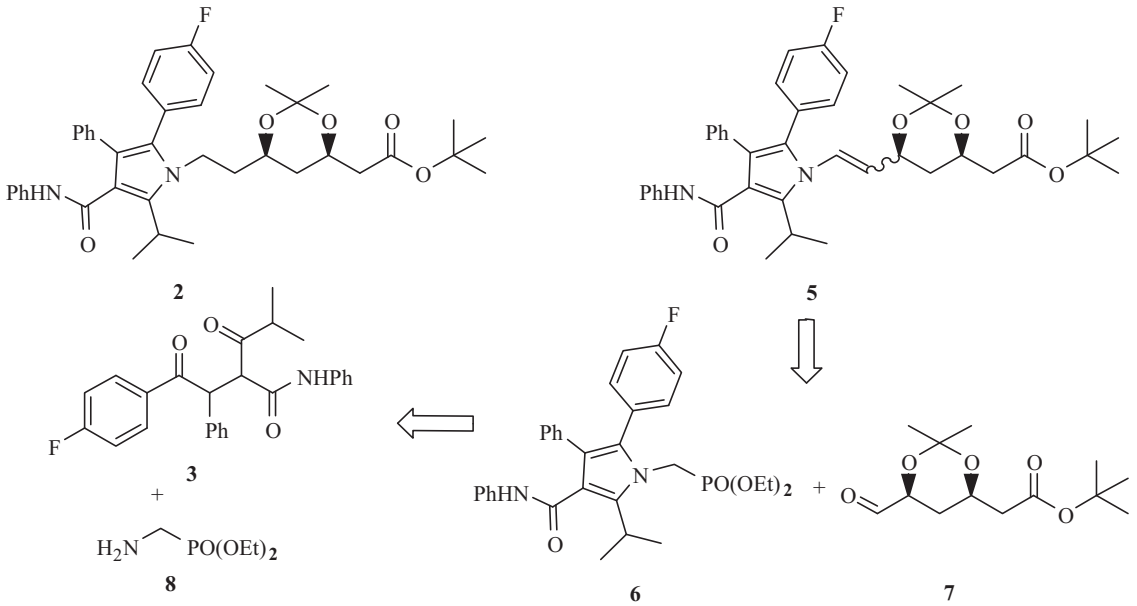
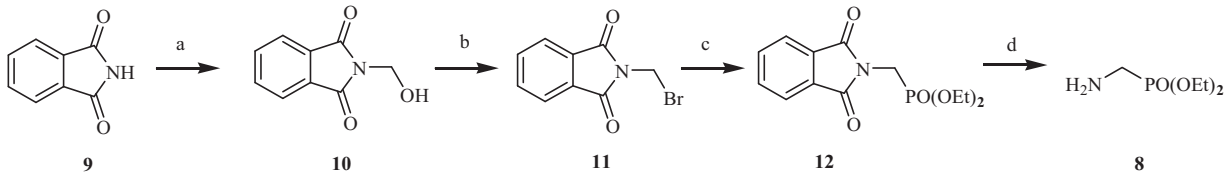


Scheme 1. Document reported synthetic route for atorvastatin **1**.



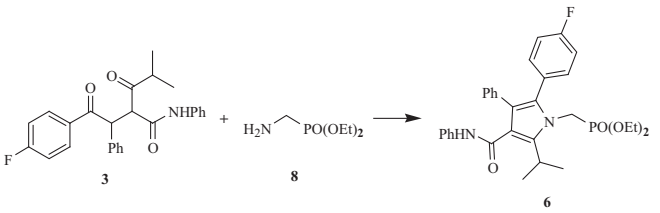
Scheme 2. Our retrosynthetic strategy for the intermediate **2** of atorvastatin.



Scheme 3. Synthesis of precursor **8**. *Reagents and conditions*: (a) formaldehyde solution (36%), 105 °C, 2 h, 94%; (b) HBr (40%), H_2SO_4, 80 °C, 1 h, 90%; (c) triethylphosphite, 90 °C, 1 h, 99%; (d) hydrazine hydrate, EtOH, 25 °C, 1 d.

And then, we focused our attention on the connection of the phosphonate ester **6** to the aldehyde **7** which was the same raw material in the synthesis of rosuvastatin and fluvastatin [13–16] (Scheme 4). A variety of conditions of the Horner–Wadsworth–Emmons reaction were evaluated to prepare olefin **5**. Initial experiment with **6** revealed that the use of several base such as *t*-BuOK, NaH, and LDA failed to afford the desired olefination product. However, BuLi was found to be the right reagent provided compound **5** as a mixture of *cis*/*trans* isomers in a 1/3 proportion as determined by ^{1}H NMR (integration for vinylic protons). Compounds **5a** and **5b** could be separated from each other by the flash chromatography on silica gel (petroleum ether/ethyl acetate, 10:1). The structures of **5a** and **5b** were identified by MS, HRMS, ^{1}H NMR, ^{13}C NMR and 2D NMR. Finally, hydrogenation of the mixture of **5a** and **5b** over 10% Pd/C afforded the key intermediate **2** of atorvastatin in 95% of yield. The compound **2** gave the same analytic data

Table 1
Preparation of phosphonate ester **6** as ylide precursor.



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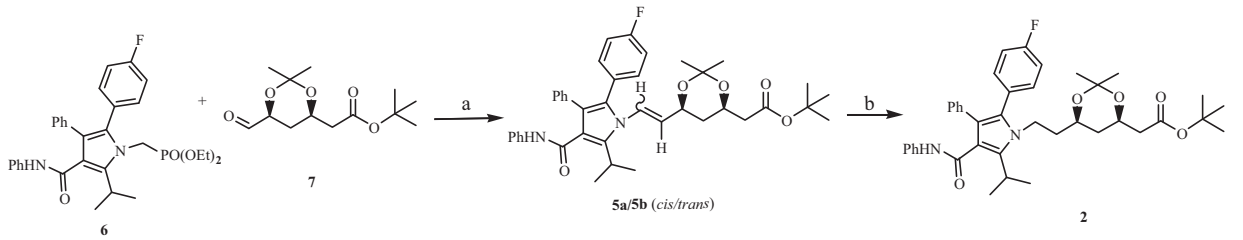
Entry	Ratio of **3/8**	Addition	Solvent	Temp (°C)	Yield (%)
1	1:1	$TiCl_4$	CH_2Cl_2	30	0
2	1:1	$ZnCl_4$	DMSO	90	0
3	1:1	TsOH	Toluene	90	33
4	1:1	$BF_3(Et_2O)$	Toluene	90	46
5	1:1	AcOH	Toluene	90	68
6	1.4:1	AcOH	Toluene	90	76
7	1.4:1	–	AcOH	90	0



Scheme 4. Synthesis of the advanced intermediate **2**. *Reagents and conditions*: (a) BuLi, THF, −78 to 70 °C, 3 h, 68%; (b) 10% Pd/C, H_2, 97%.

as reported in the literature [7,10]. The protective intermediate **2** could easily be translated to the atorvastatin according to the literature [17]. At last, the prepared compounds gave satisfactory analytical data [18].

In conclusion, we developed a convenient, efficient and economical synthetic approach for compound **2** from available low cost raw material and reagents with good total yields of 42.0%. Furthermore, our strategy should change the way of atorvastatin producing in industry.

Acknowledgments

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[18] Representative data of **2**: $[\alpha]_D^{25}$ + 4.9 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (m, 1H), 1.32 (s, 3H), 1.38 (s, 3H), 1.45 (s, 9H), 1.55 (d, 3H, *J* = 7.2 Hz), 1.55 (d, 3H, *J* = 7.2 Hz), 1.68 (m, 2H), 2.26 (dd, 1H, *J* = 15.2 Hz, 6.4 Hz), 2.40 (dd, 1H, *J* = 15.2 Hz, 7.2 Hz), 3.59 (sept, 1H, *J* = 7.2 Hz), 3.71 (m, 1H), 3.84 (m, 1H), 4.09 (m, 1H), 4.17 (m, 1H), 6.88 (s, 1H), 6.99–7.03 (m, 3H), 7.08 (d, 2H, *J* = 8.0 Hz), 7.18–7.28 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 164.8, 163.5, 161.0, 141.5, 138.4, 134.7, 133.2, 133.1, 130.5, 128.8, 128.7, 128.3, 128.2, 126.5, 123.5, 121.8, 119.6, 115.4, 115.3, 115.2, 98.7, 80.7, 66.4, 65.9, 42.5, 40.9, 38.1, 36.0, 29.9, 28.1, 26.1, 21.7, 21.5, 19.6; ESI-MS *m/z*: 655.4 $[M+H]^+$; HR-MS 655.3575 ($[M+H]^+$, $C_{40}H_{47}FN_2O_5$; calcd. 655.3547);
Compound **5a**(*cis*): ^1H NMR (400 MHz, $CDCl_3$): δ 0.85–0.91 (m, 1H), 1.26 (s, 3H), 1.38 (s, 3H), 1.44 (s, 9H), 1.46 (d, 3H, *J* = 6.4 Hz), 1.46 (d, 3H, *J* = 6.4 Hz), 1.47 (m, 2H), 2.39 (dd, 1H, *J* = 15.2 Hz, 6.4 Hz), 2.43 (dd, 1H, *J* = 15.2 Hz, 7.2 Hz), 3.63 (sept, 1H, *J* = 7.2 Hz), 4.22 (m, 1H), 4.35 (m, 1H), 5.57 (t, 1H, *J* = 8.0 Hz), 6.62 (d, 1H, *J* = 7.6 Hz), 6.88–6.93 (m, 3H), 6.96–7.00 (m, 1H), 7.04–7.08 (m, 4H), 7.16–7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 164.1, 163.0, 160.6, 138.5, 138.3, 134.4, 132.7, 132.6, 131.3, 130.9, 129.3, 129.1, 128.7, 127.9, 127.5, 127.4, 127.2, 123.6, 123.3, 121.6, 119.9, 115.8, 115.7, 115.5, 115.1, 98.9, 80.7, 65.5, 42.4, 34.5, 32.0, 29.5, 28.1, 26.8, 26.0, 22.7, 22.4, 21.1, 19.6; ESI-MS *m/z*: 653.1 $[M+H]^+$; HR-MS 653.3367 ($[M+H]^+$, $C_{40}H_{45}FN_2O_5$; calcd. 653.3391);
Compound **5b**(*trans*): ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (m, 1H), 1.26 (s, 3H), 1.38 (s, 3H), 1.44 (s, 9H), 1.46 (d, 3H, *J* = 6.4 Hz), 1.46 (d, 3H, *J* = 6.4 Hz), 1.47 (m, 2H), 2.39 (dd, 1H, *J* = 15.2 Hz, 6.4 Hz), 2.43 (dd, 1H, *J* = 15.2 Hz, 7.2 Hz), 3.82 (sept, 1H, *J* = 7.2 Hz), 4.22 (m, 1H), 4.35 (m, 1H), 5.19 (dd, 1H, *J* = 14.0 Hz, 5.6 Hz), 6.77 (d, 1H, *J* = 14.0 Hz), 6.88–6.93 (m, 3H), 6.96–7.00 (m, 1H), 7.04 − 7.08 (m, 4 Hz), 7.16–7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 163.2, 162.1, 159.6, 141.6, 137.3, 133.4, 132.3, 132.2, 131.1, 129.7, 127.9, 127.8, 127.7, 127.4, 127.0, 126.9, 126.0, 123.8, 122.6, 121.1, 118.5, 114.8, 114.0, 113.8, 97.9, 79.7, 66.2, 64.8, 41.4, 35.3, 30.9, 28.9, 28.7, 27.1, 25.1, 21.7, 20.4, 20.3, 18.7; ESI-MS *m/z*: 653.1 $[M+H]^+$; HR-MS 653.3367 ($[M+H]^+$, $C_{40}H_{45}FN_2O_5$; calcd. 653.3391);
Compound **6**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2 Hz), 1.27 (t, 3H, *J* = 7.2 Hz), 1.55 (d, 6H, *J* = 7.2 Hz), 3.46 (sept, 1H, *J* = 7.2 Hz), 3.95–4.07 (m, 4H), 4.25 (d, 2H, *J* = 10.8 Hz), 6.90 (s, 1H), 6.97–7.01 (m, 3H), 7.07–7.10 (d, 2H, *J* = 8 Hz), 7.16 − 7.20 (m, 7H), 7.31–7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 161.3, 141.7, 138.3, 134.4, 134.0, 133.9, 130.3, 129.2, 128.7, 128.4, 127.7, 127.6, 126.7, 123.7, 122.6, 119.8, 116.4, 115.4, 115.1, 62.7, 62.6, 42.3, 40.7, 26.6, 21.4, 16.4, 16.3; ESI-MS *m/z*: 549.1 $[M+H]^+$; HR-MS 548.2295 ($[M]^+$, $C_{31}H_{34}FNO_4P$; calcd. 548.2240).