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Notes

A Catalytic Approach to the Synthesis of (+)-Fluvastatin Analogue

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Statins are a class of drugs that lower the cholesterol level in the blood by blocking hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) in the liver (Figure 1). Statins have become the most frequently prescribed agent for the treatment of hypercholesterolemia due to their effect on reducing the rates of cardiovascular events.[1] Fluvastatin (Lescol^{TM}) inhibits the enzyme that reduces 3-hydroxy-3-methylglutaric acid to mevalonic acid, thus blocking cholesterol biosynthesis and lowers low-density lipoprotein cholesterol levels by 20-30% at a daily dose of 20-40 mg.[2] It has also been shown to exhibit antiviral activity against Hepatitis C.[3]

Due to their potent pharmacological effects and the unique structural features, statins have attracted considerable attention as powerful synthetic targets. The majority of synthetic approaches have focused on efficient construction of the statins side chain.[4] In 1997, the Novartis research group described a practical asymmetric synthesis of fluvastatin *via* a highly selective reduction of optically pure δ-hydroxyl-β-ketoesters with a subsequent Horner-Wadsworth-Emmons reaction.[5] In addition, they developed a manufacturing process for the production of fluvastatin in racemic form.[6] Recently, Hayashi and coworkers reported enantioselective total synthesis of (+)- and (−)-fluvastatin and their analogues through the reaction of an aldehyde with diketene in the presence of $Ti(O^iPr)_4$ and a chiral Schiff base ligand as the key step.[7]

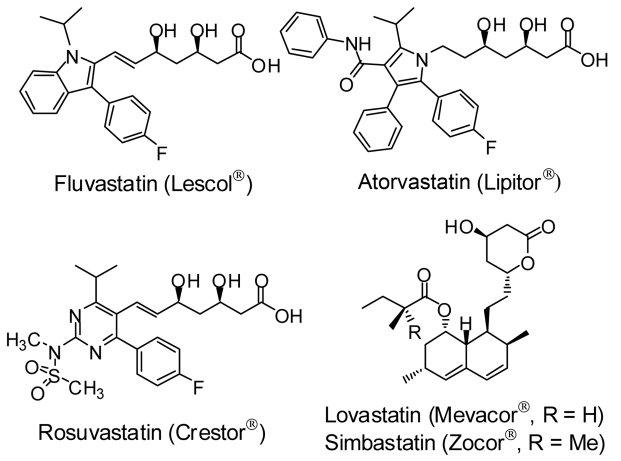
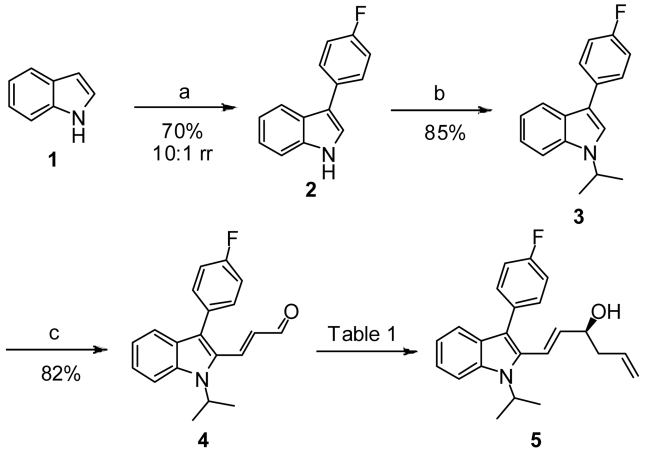


Figure 1. Structure of representative statins.

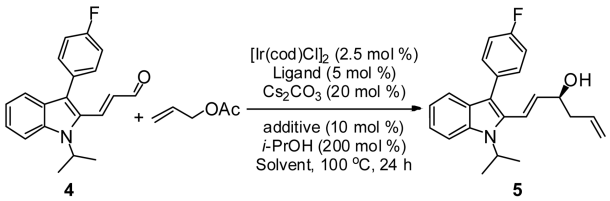
In this paper, we present a new strategy for the asymmetric total synthesis of (+)-fluvastatin analogue, that includes catalytic carbon-carbon bond formations, such as Cu-catalyzed C-3 arylation, Ir-catalyzed asymmetric allylation and Ru-catalyzed intermolecular metathesis, and diastereoselective addition for the preparation of 1,3-*syn*-diol.

We first investigated the direct catalytic C-3 arylation of indoles according to the reported literatures.[8] The iridium catalyzed C-3 arylation of heteroarenes with iodoarenes reported by Itami et al.[8a] and the palladium catalyzed C-3 arylation of indoles with bromoarenes reported by Bellina and Rossi[8b] were less effective or ineffective for our system, which is based on the coupling of indole or *N*-isopropyl indole and fluoroiodobenzene. However, Cu(II)-catalyzed site-selective arylation of indole (**1**) reported by Gaunt et al.[8c] afforded our desirable C-3 arylation product **2** in high yield (70%) with a high regioselectivity (C_3:C_2 = 10:1), as shown in Scheme 1. However, in the case of *N*-isopropyl indole, the reaction provided C-3 arylated product in low



Scheme 1. *Reagents and condition*: (a) $Cu(OTf)_2$ (10 mol %), 2,6-di-*tert*-butylpyridine (120 mol %), (4-fluorophenyl)(2,4,6-triisopropylphenyl)iodonium triflate (120 mol %), CH_2Cl_2, 35 °C, 48 h; (b) NaH (150 mol %), isopropyl bromide (300 mol %), DMF, rt, 3 h; (c) 3-(*N*-methyl-*N*-phenylamino)acrolein (300 mol %), $POCl_3$ (300 mol %), CH_3CN, 80 °C, 3 h.

Table 1. Selected optimization of the Krische allylation[a]



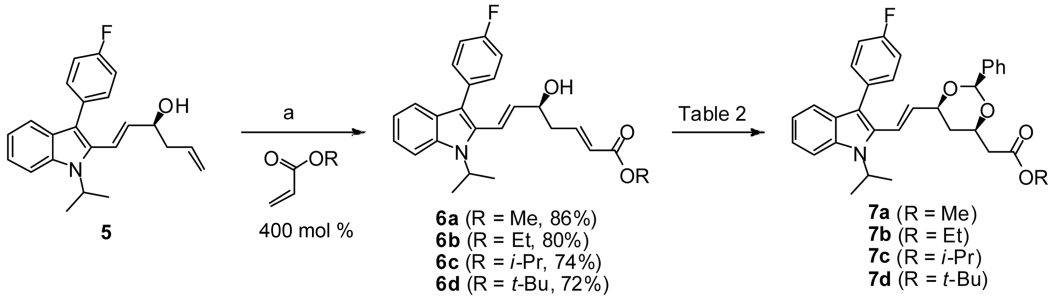
Entry	Ligand	Additive	Solvent	Yield (%)	ee (%)
1	(*S*)-BINAP	*m*-NO_2BzOH	THF	56	85
2	(*S*)-Cl,MeO-BIPHEP	*m*-NO_2BzOH	THF	70	92
3	(*S*)-Cl,MeO-BIPHEP	*p*-Cl-*m*-NO_2BzOH	THF	78	94

[a]All reactions were performed in 13 × 100 mm^2 pressure tubes. The cited yields are of material isolated by silica gel chromatography. Enantiomeric excess (ee) was determined by chiral stationary phase HPLC analysis.

yield (45%) under the identical reaction conditions. Therefore, indole (**1**) was selected as the starting material for the total synthesis of (+)-fluvastatin analogue. The treatment of free (NH)-indole **2** with sodium hydride and isopropyl bromide in DMF furnished compound **3**, which was subjected to a Vilsmeier-Haack type reaction condition using $POCl_3$ and 3-(*N*-methyl-*N*-phenylamino)acrolein (MPAA) in refluxing acetonitrile to give the enal **4** in 82% yield.[9]

Next, we examined the enantioselective iridium-catalyzed carbonyl allylation, described by Krische and coworkers,[10] to obtain the chiral homoallyl alcohol **5**. Reaction of enal **4** with allyl acetate in the presence of $[Ir(cod)Cl]_2$ (2.5 mol %), (*S*)-BINAP (5 mol %), Cs_2CO_3 (20 mol %), *m*-NO_2BzOH (10 mol %) and isopropanol (200 mol %) in THF gave **5** in 56% yield with 85% of enantiomeric excess (Table 1, entry 1). After further optimization, we found that the coupling of the enal **4** and allyl acetate in the presence of $[Ir(cod)Cl]_2$ (2.5 mol %), (*S*)-Cl,MeO-BIPHEP (10 mol %), Cs_2CO_3 (20 mol %), *p*-Cl-*m*-NO_2BzOH (10 mol %) and isopropanol (200 mol %) in THF solvent afforded compound **5** in 78% yield with an excellent level of enantioselectivity (94% ee), as shown in entry 3.

To prepare the 1,3-*syn*-diol moiety of (+)-fluvastatin, we planned to utilize the base-catalyzed intramolecular conjugate addition methodology reported by Evans *et al.* (Scheme 2).[11] With this efficient route to (+)-fluvastatin, our attention was then focused on the synthesis of α,β-unsaturated esters **6a-6d** *via* olefin metathesis using ruthenium catalysts such as a first generation Grubbs catalyst, a second generation Grubbs catalyst, and a Hoveyda-Grubbs catalyst.[12] The best result was obtained when compound **5** was treated with a second generation Grubbs catalyst (1,3-bis(mesityl)-2-imidazolidinylidene substituted ruthenium) in toluene at room temperature, which provided the corresponding products **6a-**

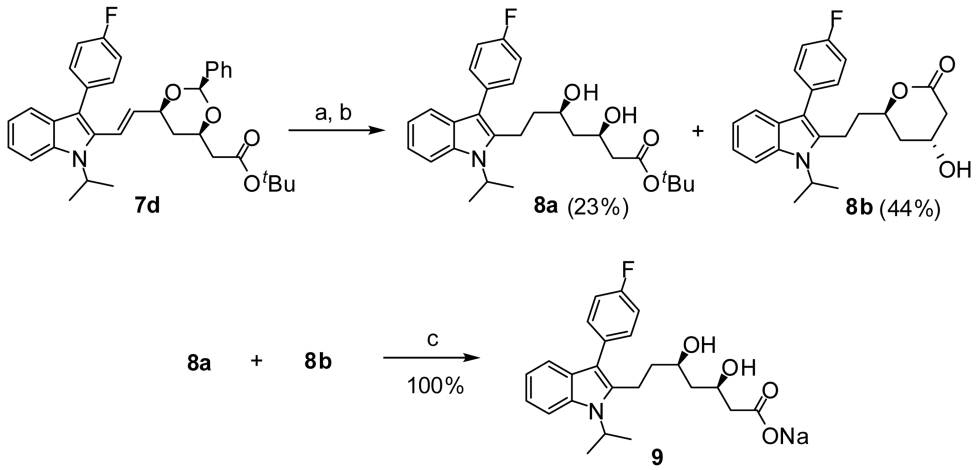


Scheme 2. *Reagents and condition*: (a) second Grubbs catalyst (5 mol %), toluene, rt, 2-4 h.

Table 2. Selected optimization of the intramolecular conjugate addition[a]

Entry	Substrate	Condition	Product (%)	Retro-aldol adduct **4** (%)
1	**6a**	KO^{t}Bu (50 mol %), PhCHO (550 mol %), THF	0	12
2	**6a**	KO^{t}Bu (100 mol %), PhCHO (1100 mol %), THF	0	20
3	**6b**	KO^{t}Bu (100 mol %), PhCHO (1100 mol %), THF	24	22
4	**6c**	KO^{t}Bu (100 mol %), PhCHO (1100 mol %), THF	38	25
5	**6d**	KO^{t}Bu (100 mol %), PhCHO (1100 mol %), THF	44	22
6	**6d**	KHMDS (100 mol %), PhCHO (1100 mol %), THF	25	55
7	**6d**	KO^{t}Bu (100 mol %), PhCHO (1100 mol %), *t*-BuOH (100 mol %), THF	52	23

[a]The cited yields are of material isolated by silica gel chromatography.



Scheme 3. *Reagents and condition*: (a) Pd/C, H_2, MeOH, rt, 2 h; (b) 80% AcOH, THF, 60 °C, 40 h; (c) 1 M NaOH, EtOH, rt, 1 h, then subsequent lyophilization.

6d in 72-86% yields with high stereoselectivities (*trans*:*cis* ≥ 15:1), respectively.

As shown in Table 2, we first attempted to couple the α,β-unsaturated methyl ester **6a** and benzaldehyde *via* base-catalyzed intramolecular conjugate addition of a hemiacetal-derived alkoxide nucleophile described by Evans.[11] However, these attempts were unsuccessful under standard reaction conditions (50 mol % KO^{t}Bu, 550 mol % PhCHO, THF, 0 °C), and led to the recovery of the starting material **6a** and the production of retro-aldol adduct **4** (Table 2, entry 1). Extended reaction times and the use of an excess amount of reagents (100 mol % KO^{t}Bu, 1100 mol % PhCHO) resulted in decomposition of the starting material and the increase of retro-aldol adduct **4** in 20% yield (entry 2). However, the use of the ethyl ester **6b** with 100 mol % KO^{t}Bu and 1100 mol % PhCHO afforded the desirable product **7b** (24%), the recovered starting compound **6b** (40%) and the retro-aldol byproduct **4** (22%), as shown in entry 3. From these results, we screened the coupling of **6c** or **6d** with benzaldehyde, and obtained the corresponding products **7c** (38%) and **7d** (44%), respectively (entries 4 and 5). The use of KHMDS as the base was ineffective under other identical conditions (entry 6).[13] Finally, when 100 mol % of *tert*-butanol was used as an additive under otherwise identical conditions, homoallyl alcohol **6d** was converted to the corresponding 1,3-*syn*-diol **7d** with a high level of diastereoselectivity (15 > 1) in 52% yield.

To complete the synthesis of (+)-fluvastatin, we first investigated selective deprotection of the benzylidene acetal moiety of **7d** under reported procedures, i.e., i) 80% AcOH, THF,[14] ii) BCl_3, CH_2Cl_2,[15] iii) $Zn(OTf)_2$, EtSH, $NaHCO_3$, CH_2Cl_2,[16] iv) DDQ, THF, H_2O,[17] etc. However, all reactions furnished the complicated reaction mixtures and the recovery of starting material presumably due to the instability of 3,5-dihydroxy hept-6-enoate moiety in our desired product under acidic conditions. Thus our focus moved on the synthesis of (+)-fluvastatin analogue, which contains the reduction of olefin moiety in (+)-fluvastatin (Scheme 3). After hydrogenation of olefin moiety of **7d**, benzylidene acetal moiety was cleanly removed under standard acidic condition (80% AcOH, THF, 60 °C) to afford the diol **8a** (23%) and the lactone **8b** (44%), respectively. Finally, saponification of a mixture of the diol **8a** and the lactone **8b** and subsequent lyophilization provided (+)-fluvastatin analogue (**9**) in quantitative yield as a pale yellow powder.

In conclusion, we describe a catalytic approach to the asymmetric total synthesis of (+)-fluvastatin analogue starting from a readily available indole *via* Cu-catalyzed C-3 arylation, Ir-catalyzed asymmetric allylation, Ru-catalyzed intermolecular metathesis, and diastereoselective intramolecular conjugate addition of hemiacetal alkoxide anion as the key steps. This synthetic strategy can be applied to the synthesis of a broad range of statin family molecules.

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