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Communications to the Editor

An Improved and Scalable Process for the Synthesis of Ezetimibe: An Antihypercholesterolemia Drug†

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Abstract:

An efficient, cost-effective and large-scale synthesis of ezetimibe 1, an antihypercholesterolemia drug, is described. Chiral oxazolidinone chemistry was used to fix the required stereochemistry of the β-lactam ring, and the chiral oxazaborolidine chemistry was used to fix the hydroxyl group stereochemistry. The synthesis significantly lowers the cost and provides easy access to ezetimibe on large scale.

Introduction

The azetidin-2-one (β-lactam) ring is widely recognized as a key structural motif in several families of antibiotics.[1] Ezetimibe (**1**), has recently been commercialized as an effective acyl-CoA cholesterol acyltransferase inhibitor for lowering cholesterol levels.[2,3] The drug is absorbed into the intestinal epithelial cell and remains associated in great part with the epithelial cell membrane where it is believed to interfere with the putative sterol transporter system.[4] This apparently prevents both free cholesterol and plant sterols (phytosterols) from being transported into the cell from the intestinal lumen. The mechanism is very different from the reduction produced by phytosterol esters and phytostanol esters that have been documented previously as interfering with the micellar presentation of sterols to the cell surface.[5] The drug is rapidly absorbed and glucuronidated in the intestinal cell before secretion into the blood.[6,7] Ezetimibe is avidly taken up by the liver from the portal blood and excreted into the bile, resulting in low peripheral blood concentrations. The glucuronide conjugate is hydrolyzed and absorbed and is equally effective in inhibiting sterol absorption.[8] This enterohepatic recycling is responsible for a half-life in the body of more than 20 h.[9] The medication is effective as a single daily dose due to its long residence time in the body. Combinations of ezetimibe with all available statins have been completed and demonstrate LDLc reductions of approximately 25% as additive effects to any statin dose alone.[10] There are also small additional increases in HDL (2−3%) and reductions in triglycerides (10−15%). Additive effects to statin therapy have also been documented in patients with homozygous familial hypercholesterolemia.[11,12] Reduction of plant sterols has been demonstrated in phytosterolemia, offering the first drug treatment for this rare inherited disease.[13]

The novel structure and potent biological activity of ezetimibe has prompted intense synthetic interest in the synthetic community which led to the development of several syntheses for this molecule.[14] Many of these routes have utilized chiral auxiliary based synthesis and used flash chromatography or chiral HPLC for the purification of the intermediates.[15] To circumvent the above complications in the scale up we have modified the reported process and developed a large-scale synthesis of ezetimibe.

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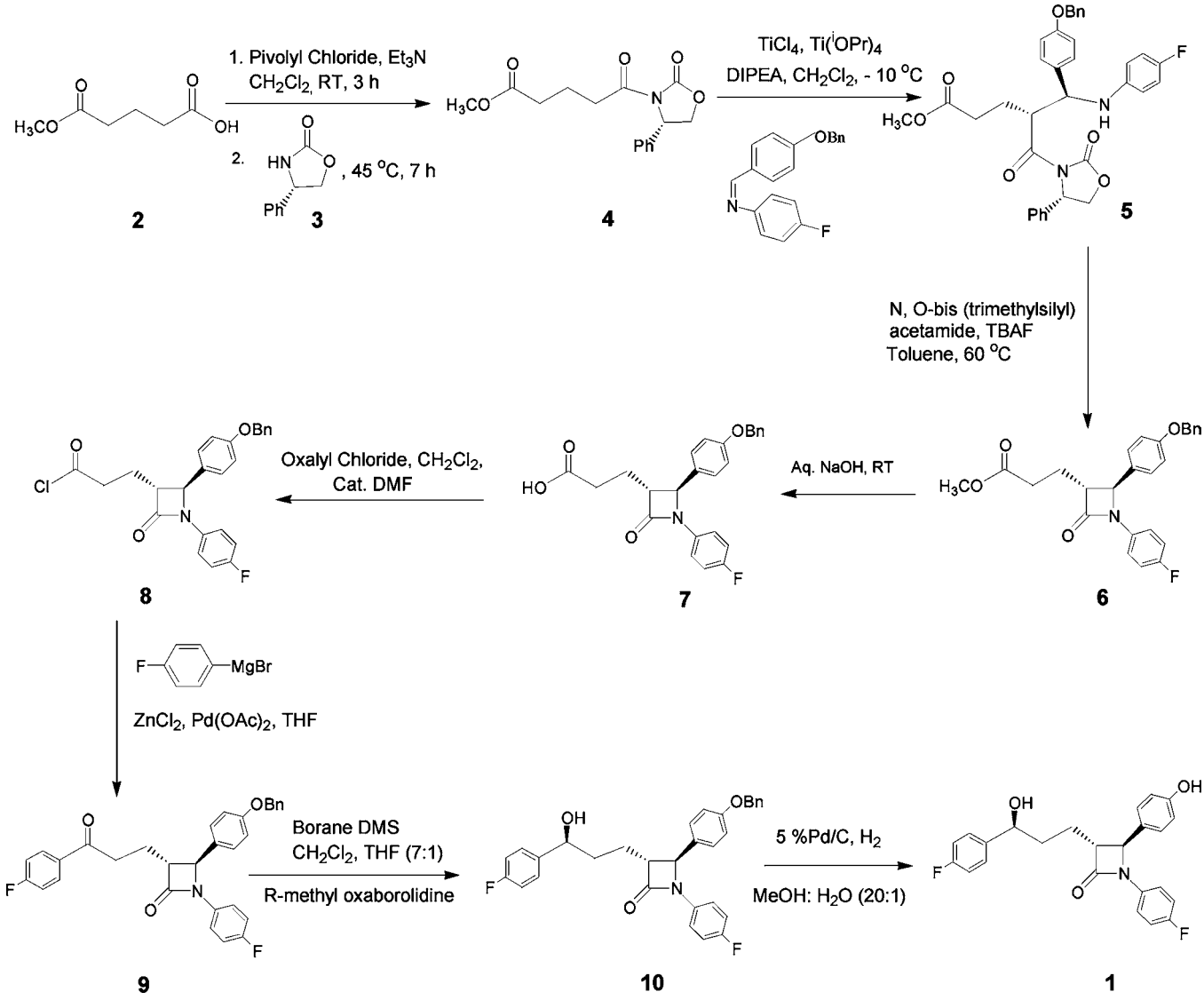
Scheme 1. **Synthesis of ezetimibe**



Results and Discussion

As mentioned in Scheme 1, our approach began with the coupling of monomethyl glutarate **2** with (*S*)-4-phenyl-2-oxazolidinone **3** which was done by the mixed anhydride method using pivaloyl chloride and triethylamine to obtain the oxazolidinone **4**.[16] This method avoids the need for isolating the unstable, corrosive acyl chloride and seems to offer advantages in terms of practicality. The crucial enolate condensation of oxazolidinone **4** with 4-benzyloxybenzylidene(4-fluoro)aniline in the presence of $TiCl_4$ and $Ti(OiPr)_4$ delivered the compound **5** in excellent diastereoselectivity (dr = 97:3), demonstrating the impressive stereodirecting power of chiral auxiliary.[17] Compound **5** on reaction with *N*,*O*-bis-trimethylsilyl)acetamide and tetrabutylammonium fluoride in toluene at 60 °C gave the cyclized β-lactam product **5**. β-Lactam product **6** on ester hydrolysis followed by treating the resultant acid with oxalyl chloride in presence of cat. DMF delivered the acid chloride **8**.[18] The acid chloride **8** is unstable and also is difficult to handle in large-scale productions. Hence, the reaction mass proceeds to the next step in the same reactor without isolating the product. Negishi coupling of acid chloride **8** with 4-fluorophenylmagnesiumbromide in the presence of $ZnCl_2$ and $Pd(OAc)_2$ gave the ketone **9**.[19] This type of reaction is already

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known in the literature using $Pd(PPh_3)_4$, and the main disadvantage of using $Pd(PPh_3)_4$ is to purify the product by using column chromatography, which is not preferable on large scale. We have replaced the $Pd(PPh_3)_4$ with $Pd(OAc)_2$ to get the ketone **9** with good quality and without doing any column chromatography. By this modification there is no need to purify the product by column chromatography. *R*-Methyloxazaborolidine-mediated reduction of ketone **9** with borane dimethylsulfide delivered the compound **10** with the required stereochemistry.[20] The final deprotection of the benzyl group by using 5% Pd/C in methanol−water (20:1) gave the ezetimibe **1** as a white solid.

Conclusion

In conclusion we have developed an improved and practical synthesis of ezetimibe **1**, the first example of a cholesterol-lowering drug that inhibits cholesterol absorption in the small intestine. The present synthesis is free of column chromatography in all stages.

Experimental Section

The ^{1}H NMR spectra were measured using Varian Gemini FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 ev) was recorded on HP- 5989A LC/MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The solvents and reagents were used without further purification.

Preparation of 1-[(5-Methoxy-1,5-dioxopenta)yl]-4(*S*)-phenyloxazolidi-2-one 4. To a solution of monomethyl glutarate (300 g, 2.05 mol) in dichloromethane (1500 mL) was added triethyl amine (496 g, 4.92 mol) and pivaloyl chloride (299.8 g, 2.48 mol) at room temperature and stirred for 3 h at the same temperature. To the above reaction mixture *S*-4-phenyloxazolidinone (267 g, 1.74 mol) and DMAP (17 g, 0.137 mol) were added and heated to 45 °C. The reaction mixture was maintained for 7 h at 45 °C. After cooling to room temperature water was added, and the organic layer was separated. The aqueous layer was washed with dichloromethane, and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound. Hexane was added to the oily compound, and the mixture stirred for 60 min and was filtered to give 448.5 g (75%) of compound **4** as a crystalline solid. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 1.8−2.0 (m, 2H), 2.3 (m, 2H), 2.8−3.2 (m, 2H), 3.6 (s, 3H), 4.3−4.4 (m, 1H), 4.6−4.8 (m, 1H), 5.65 (m, 1H), 7.2−7.4 (m, 5H, Ar); IR (KBr pellet) 1781.89, 1736.61, 1701.56 cm^{-1}. MS: *m*/*z* 596.2 (M^+).

Preparation of 1-{2-[3-(Methoxy)-3-(oxo)-propyl]-3-(4-fluorophenylamino)-3-(4-benzyloxyphenyl)-1-oxo-propyl}-4-(*S*)-phenyloxazolidin-2-one 5. To a solution of oxazolidinone compound **4** (100 g, 0.34 mol) in dichloromethane (1000 mL) at −10 °C were added titanium chloride (65.18 g, 0.34 mol), titanium tetra(isopropoxide) (19.5 g, 0.068 mol), and diisopropylethylamine (66.5 g, 0.514 mol), and this mixture stirred for 1 h at the same temperature. 4-Benzyloxybenzylidene(4-fluoro)aniline (157.4 g, 0.514 mol) was added to the above reaction mixture and stirred for 6 h at −10 °C. The reaction mixture was quenched with a mixture of acetic acid (100 mL) and dichloromethane (200 mL) and 2 N H_2SO_4 solution (300 mL), and stirred at 30 °C for 1 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layer was washed with water (600 mL), dried, and concentrated to get the crude **4**. Methanol was added to the above crude product, stirred for 1 h, and then filtered to get 98.3 g (48%) of compound **5**. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 1.4−2.6 (m, 6H), 3.7 (s, 3H), 3.92−4.78 (m, 3H), 5.1 (s, 2H), 5.47 (m, 1H), 6.4−7.4 (m, 18H, Ar); IR (KBr pellet): 3383.97, 1767.4, 1736.98 cm^{-1}, 1699.9; MS: *m*/*z* 596.2 (M^+).

Preparation of (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(methoxy)-3-oxopropyl]-4-(4-benzyloxyphenyl)-2-azetidinone 6. To a solution of compound **5** (200 g, 0.336 mol) in toluene (1400 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (119.46 g, 0.587 mol) at 60 °C and was maintained at the same temperature for 30 min. TBAF (3.7 g, 0.012 mol) was added to the reaction mixture, and the reaction mixture was stirred at 60 °C until the completion of reaction. The reaction mixture was cooled to 40 °C and neutralized with acetic acid (20 mL), and the solvent was distilled to get the crude compound. Toluene (200 mL) was added to the above crude compound and stirred at 0 °C for 30 min and filtered. The combined filtrates were distilled, and the crude compound was crystallized from methanol to get 110.3 g (76%) of pure compound **6** as a crystalline solid. ^{1}H NMR (200 MHz, $CDCl_3$, δ) 1.72−1.94 (m, 2H), 2.4−2.7 (m, 2H), 3.65 (m, 2H), 3.7 (s, 3H), 4.68 (m, 1H), 5.0 (s, 2H), 6.4−7.4 (m, 13H, Ar); IR: 1736.13 cm^{-1}; MS: *m*/*z* 433 (M^+).

Preparation of (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(hydroxy)-3-oxopropyl]-4-(4-benzyloxyphenyl)-2-azetidinone 7. To a solution of ester **6** (250 g, 0.576 mol) in acetone was added 4 N NaOH (625 mL) and stirred at room temperature for 4 h. Water was added to the above reaction mixture, and the pH was adjusted to 6.6 with 1 N hydrochloric acid. The reaction mixture was extracted with ethyl acetate, dried over sodium sulphate, and concentrated to afford the 217.7 g (90%) of crude acid **7**, which was used as such for the next reaction. ^{1}H NMR ($CDCl_3$, δ) 1.6−1.8 (m, 2H), 2.4−2.8 (m, 2H), 3.65 (m, 1H), 4.64 (m, 1H), 5.1 (s, 2H), 6.8−7.6 (m, 13H, Ar); IR (KBr pellet) 3518.23, 1740.274 cm^{-1}; MS: *m*/*z* 419.1 (M^+).

Preparation of (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]-4-(4-benzyloxyphenyl)-2-azetidinone 9. To a clean and dry round-bottom flask were added magnesium turnings (14.5 g, 0.60 mol) and a catalytic amount (1.2 g) of iodine and tetrahydrofuran (187.5 mL), and this mixture was heated to 48 °C. 1-Bromo-4-fluorobenzene (105.7 g, 0.60 mol) was added to the above solution. After 5 min of stirring extra 1-bromo-4-fluorobenzene (85 mL) was added slowly and stirred at 48 °C. The reaction mass was then cooled to 0 °C, and 580 g of zinc chloride (81.75 g, 0.60 mol) was added to the above reaction mass.

In a separate round-bottom flask, the intermediate acid **6** (125 g, 0.298 mol) was dissolved in dichloromethane (625 mL), and

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dimethylformamide (2.5 mL) was added and stirred at room temperature. To the above reaction mixture oxalyl chloride (56.0 g, 0.445 mol) was added and stirred at the same temperature. After completion of the reaction, the solvent was distilled at 63 °C. Toluene (25 mL) was added to the reaction mass and again distilled off completely. The residue obtained was dissolved in toluene (625 mL) and cooled to 10 °C. Palladium acetate (6.25 g, 0.015 mol) and 4-fluorophenyl zinc chloride (prepared as above) were added to the reaction mass and stirred at 10 to 11 °C for 20 min. After completion of the reaction (TLC), 1 N hydrochloric acid (625 mL) and ethyl acetate (625 mL) were added to the reaction mixture. The organic layer was separated and washed with water (625 mL) followed by 10% sodium bicarbonate solution (625 mL). The organic layer was distilled completely at 65 °C. To the crude residue were added dichloromethane (125 mL) and cyclohexane (750 mL), and 50% of the solvent was distilled from the reaction mass. Cyclohexane (375 mL) was added to the reaction mass, and again 50% of the solvent was distilled. Another 375 mL of cyclohexane was added to the reaction mass and kept for stirring. The reaction mass was stirred at 30 °C for 4 h, and then the cyclohexane layer was decanted. Another 500 mL of cyclohexane was added to the reaction mass and stirred for 30 min. The cyclohexane layer was decanted, and the residue was distilled at 70 °C to remove the solvent completely to yield 127.5 g (68.5%) of the title compound **9**. ^{1}H NMR (DMSO-d_6, δ) 1.6−1.8 (m, 2H), 2.0−2.2 (m, 1H), 3.2−3.4 (m, 1H), 4.05 (m, 1H), 4.68 (m, 1H), 5.1 (s, 2H), 7.0−8.0 (m, 17H, Ar); IR: 1743.43, 1683.82 cm^{-1}; MS: *m*/*z* 497.4 (M^+).

Preparation of (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4-(4-benzyloxyphenyl)-2-azetidinone 10. To the mixture of dichloromethane (1050 mL) and THF (150 mL) at 0 °C were added borane dimethylsulfide (28.7 mL, 0.45 mol) and *R*-methyloxazaborolidine (12.4 g, 0.04 mol). To this reaction mixture was added keto compound **9** (150 g, 0.30 mol) in dichloromethane and was stirred at the same temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with 5% aqueous hydrogen peroxide and the organic layer was separated. The organic layer was successively washed with hydrochloric acid and brine solution and then treated with activated charcoal and filtered. The filtrate was concentrated to give the crude product, which on crystallization in diisopropylether gave 94.1 g (62.5%) of compound **9** as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6, δ) 1.6−1.9 (m, 4H), 2.0−2.2 (bs, 1H), 3.0−3.2 (m, 1H), 4.4−4.6 (m, 1H), 4.74 (m, 1H), 5.05 (s, 2H), 6.95−7.9 (m, 17H, Ar); IR: 3492, 2922, 2852, 1719 cm^{-1}; MS: *m*/*z* 499.3 (M^+).

Preparation of 1-(4-Fluorophenyl)-3-(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone 1 (Ezetimibe). To a solution of compound **10** (150 g, 0.34 mol) in methanol was added 5% Pd−C (50 g, 50% water) and stirred under H_2 atmosphere employing 3 bars of pressure at 25 °C. The reaction mixture was hydrogenated until no H_2 was consumed. The reaction mixture was filtered, and the filtrate was concentrated to give the ezetimibe. The obtained product was purified using isopropanol and water to afford 69.0 g (49.5%) of compound **1**. ^{1}H NMR (300 MHz, DMSO-d_6, δ) 1.72−1.84 (m, 4H), 3.08 (m, 1H), 4.45 (m, 1H), 4.8 (d, 1H, J = 2.0 Hz), 5.25 (d, 1H, J = 4.8), 6.75 (d, 2H, J = 8.4 Hz), 7.05−7.4 (m, 10H, Ar), 9.48 (s, 1H); IR: 3270.0, 2918, 1862, 1718.4, 1510 cm^{-1}. MS: *m*/*z* 409.2 (M^+). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 70.41; H, 5.17; N, 3.42. Found: C, 70.38; H, 5.27; N, 3.34.

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