(*Z*)-5-(4-Fluorophenyl)pent-4-enoic Acid: A Precursor for Convenient and Efficient Synthesis of the Antihypercholesterolemia Agent Ezetimibe

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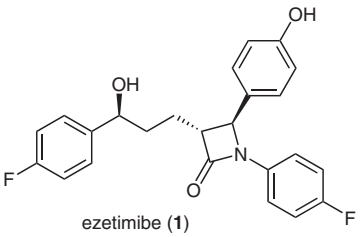
Received 25 May 2010

Abstract: A convenient and efficient total synthesis of ezetimibe, an intestinal cholesterol absorption inhibitor and useful anticholesteremic agent, is described. Based on (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid as a starting compound, and taking the synthesis through further *Z*-configured intermediates, the total yield is remarkably increased, compared with the use of the corresponding *E*-configured starting substances or intermediates.

Key words: cholesterol absorption inhibitor, (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid, Wittig reaction, azetidinone, asymmetric synthesis

Elevated plasma cholesterol levels (hypercholesterolemia) are a major risk factor for the development of cardiovascular disease. Ezetimibe (**1**, Figure 1) has recently been introduced as the first of a new class of LDL-C lowering agents that act by direct inhibition of the uptake of free cholesterol from the small intestine.[1–3] Ezetimibe is absorbed by the intestinal epithelial cells and remains mainly associated with the epithelial cell membrane, where it is believed to interfere with the putative sterol transporter system.[1,2] This appears to prevent both free cholesterol and plant sterols (phytosterols) from being transported into the cell from the intestinal lumen. In addition to its mechanistic novelty, ezetimibe has a long duration of action, low systemic exposure, and an excellent safety profile. Ezetimibe contains three *para*-substituted phenyl rings, a chiral benzylic hydroxyl group, and two additional stereogenic centers on a rigid 2-azetidinone scaffold. The three chiral centers give rise to eight stereoisomers that have been individually characterized and shown to have significantly different profiles for the inhibition of cholesterol absorbtion.[3] In 2009, annual worldwide sales for ZETIA (ezetimibe) were $2.2 billion, and for VYTORIN (ezetimibe/simvastatin combination), $2.1 billion, which puts ezetimibe high on the list of valuable drugs and interesting synthetic targets. To date, several synthetic routes for the preparation of ezetimibe have been described, especially over the last few years.[3–10] In the background section of his patent, Shankar[4] discussed various conventional processes for preparing ezetimibe, and the document itself proposed new processes for the synthesis of ezetimibe.



ezetimibe (**1**)

Figure 1 Chemical structure of ezetimibe (**1**)

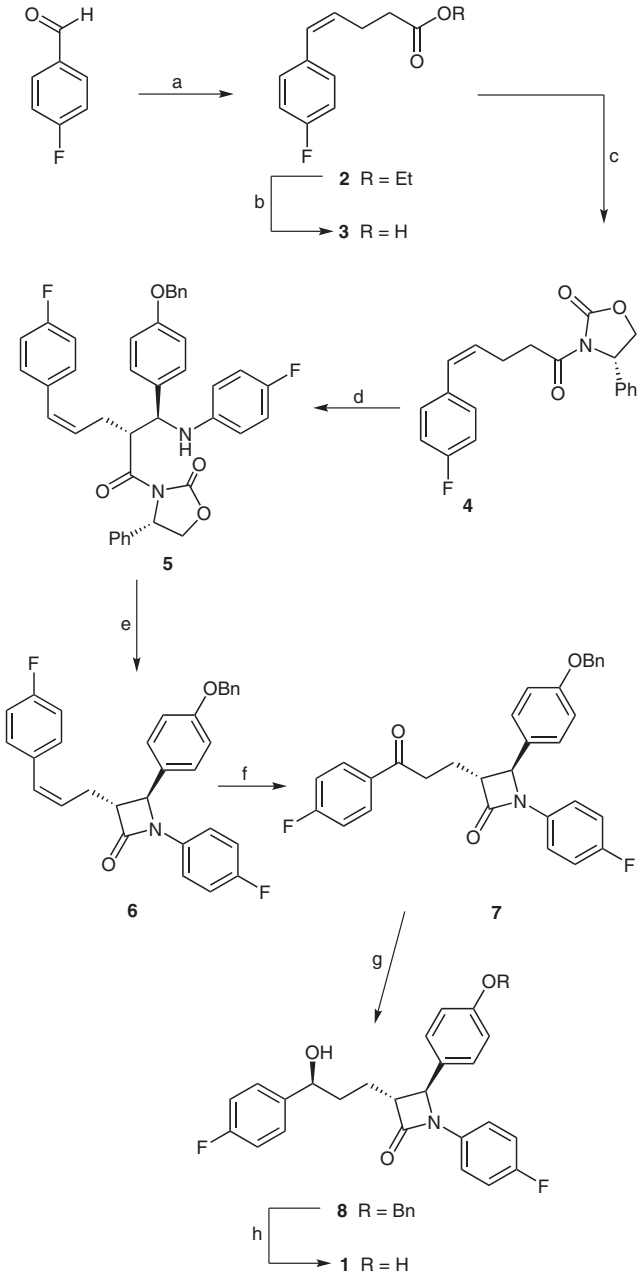
One synthetic route starts from (*E*)-5-(4-fluorophenyl)pent-4-enoic acid and proceeds further via the *E*-configured intermediates. Similar synthetic approaches have been described by Rosenblum et al.[10] The starting compound, (*E*)-5-(4-fluorophenyl)pent-4-enoic acid, has been synthesized by several methods.[10–13] Interestingly, the synthesis of (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid and its use has not been reported yet. Although the synthesis of ezetimibe (**1**) via (*E*)-5-(4-fluorophenyl)pent-4-enoic acid[4,10] appears to be appealing, an overall yield of below 10% and the tedious unselective preparation of the *E*-configured acid precursor makes this approach unsuitable for practical use.

In this study, we report on a significant advance in the efficiency of this process and on new means for the synthesis of ezetimibe. It has been shown that when starting with compounds based on (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid, and proceeding further with the synthesis through the *Z*-configured intermediates, the total yield for the synthesis of the final ezetimibe is remarkably increased, to over 20%.[14] There is a surprisingly higher overall yield when the synthesis route is started and taken through the *Z*-configured precursors and *Z*-configured intermediates[14] than through the respective *E*-configured analogues.[4] In addition, (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid can be prepared in significantly higher yields than (*E*)-5-(4-fluorophenyl)pent-4-enoic acid by the methods reported in the literature.

5-(4-Fluorophenyl)pent-4-enoic acid and its derivatives are important intermediates for the total synthesis of ezetimibe, and here they are provided using a very effec-

SYNTHESIS 2010, No. 20, pp 3433–3438
Advanced online publication: 05.08.2010
DOI: 10.1055/s-0030-1258193; Art ID: P07810SS

tive synthetic approach via a Wittig reaction, generating high yields. In this process step, 4-fluorobenzaldehyde is taken through a Wittig reaction together with (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) $Ph_3P^+(CH_2)_3CO_2Et\ Br^-$, NaHMDS, THF, r.t., 97%; (b) i. NaOH, H_2O, THF, r.t., ii. aq 40% HCl, 94%; (c) i. oxalyl chloride, CH_2Cl_2, r.t., ii. (*S*)-4-phenyloxazolidin-2-one, DIPEA, DMAP, CH_2Cl_2, r.t., 93%; (d) (*E*)-*N*-[4-(benzyloxy)benzylidene]-4-fluoroaniline, $TiCl_4$, DIPEA, CH_2Cl_2, r.t., 59%; (e) i. BSA, ii. TBAF·$3H_2O$, toluene, r.t., 71%; (f) benzoquinone, $Pd(OAc)_2$, 70% aq $HClO_4$, MeCN, H_2O, 86%; (g) $Me_2S{\cdot}BH_3$, (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole, THF, –20 °C, 96%; (h) 5% Pd/C, H_2, 60 psi, EtOH, r.t., 80%.

The mixture of *E*- and *Z*-isomers of 5-(4-fluorophenyl)pent-4-enoic acid or its esters that is obtained can then be isolated as the *E*-isomer and the *Z*-isomer. Use of the Wittig reaction in this process not only significantly contributes to achieve high total yields, but more importantly, it generates predominantly the desired *Z*-isomer, and thus allows the selective isolation to obtain the representative key *Z*-configured intermediate for the synthesis of ezetimibe. Remarkably, yields of over 90% and a *Z*/*E* ratio of 88:12 can be realized using the Wittig reaction. Pure Z-configured acid **3** can be obtained by recrystallization from hexane.

The Wittig reaction proceeds more efficiently if the phosphorylide is an ester, rather than the parent acid, although this includes an additional reaction step – ester hydrolysis is necessary to obtain the corresponding (*Z*)-5-(4-fluorophenyl)pent-4-enoic acid (**3**). The saponification was performed as a one-pot process after the Wittig reaction, without isolation of the ester derivative. (*Z*)-5-(4-Fluorophenyl)pent-4-enoic acid (**3**) was further coupled with (*S*)-4-phenyl-2-oxazolidinone using oxalyl chloride and *N*,*N*-diisopropylethylamine (DIPEA) without intermediate isolation of the unstable acyl chloride. The resulting oxazolidinone product **4** was enolized in the presence of $TiCl_4$ and condensed with (*E*)-*N*-[4-(benzyloxy)benzylidene]-4-fluoroaniline to give **5** in 59% yield. Due to the efficient stereodirecting influence of oxazolidinone chiral auxiliary, compound **5** was obtained in high stereoselectivity (dr = 97:3) as confirmed by NMR analysis.

The cyclization of (*S*)-3-((*R*,*Z*)-2-{(*S*)-[4-(benzyloxy)phenyl](4-fluorophenylamino)methyl}-5-(4-fluorophenyl)pent-4-enoyl)-4-phenyloxazolidin-2-one (**5**) was achieved by treatment with a silylating agent, and subsequent treatment with a fluoride ion catalyst. The silylation was performed with *N*,*O*-bistrimethylsilylacetamide (BSA) in anhydrous toluene. This was followed by treatment with tetrabutylammonium fluoride trihydrate (TBAF·$3H_2O$). Different catalytic amounts of TBAF·$3H_2O$ were examined, whereby 5 mol% was shown to be optimal for this type of reaction, to obtain the compound **6** at a 71% yield. The key intermediate, (3*R*,4*S*)-4-[4-(benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]azetidin-2-one (**7**), was then prepared by Wacker-Tsuji oxidation of alkene **6**.[15,16] Miller and Wayner[16] used different acids and palladium (II) salts as catalysts for this type of reaction. However, perchloric acid and palladium acetate were the reagents of choice for our reaction. Different amounts of $HClO_4$ (up to 0.45 M) and $Pd(OAc)_2$ (1.0–3.0 mol%) were investigated. However, optimum conversion of compound **6** to **7** (with 86% yield) was attained with an acid concentration of 0.15 M and 3.0 mol% $Pd(OAc)_2$. Benzoquinone was also used as a reoxidant, and for solubility reasons a mixture of acetonitrile and water (10:1) was used as a solvent. In our hands, oxidation of *Z*-alkene gives an 86% yield of ketone **7**, while *E*-alkene oxidation gives the ketone in 70–80% yield, as described in the patent literature.[4]

Compound **7** was then reduced to an alcohol by reaction with a chiral borane, to obtain and isolate the desired *S*-OH-isomeric product (3*R*,4*S*)-4-[4-(benzyloxy)phenyl]-1-(4-fluorophenyl)-3-{[(*S*)-3-(4-fluorophenyl]-3-hydroxy-

propyl}azetidin-2-one (**8**). The yield of this asymmetric reduction was significantly increased, since compound **8** was obtained in 95% yield, while the reduction step of the ketone derived from the *E*-configured intermediates gives only a 42% yield, as described previously.[4] Subjecting compound **8** to an OH-deprotection reaction finally yielded the target ezetimibe (**1**) in 80% yield. A suitable OH-deprotection reaction included catalytic hydrogenation using palladium on carbon.[17]

In conclusion, we have developed an efficient and practical synthesis route for the antihypercholesterolemia drug ezetimibe. The main feature of our synthetic approach is the use of the *Z*-configured starting and intermediate compounds, which provides the unexpectedly high 20% overall yield for the total synthesis.[14] This compares to the reported use of the corresponding *E*-configured starting substances or intermediates, where ca. an 8% overall yield has been obtained.[4,10,17] This was mainly due to the application of the 'clean' Wittig reaction, which gave the pure *Z*-configured acid **3** starting precursor, while in the previously published reactions,[10–13] a complex mixture of *E*-configured acid and derivatives was obtained. Furthermore, our synthetic design has revealed a conspicuous example that demonstrates that the efficiency of a total synthetic approach can markedly depend on the nature (geometry) of the selected starting precursors, which can themselves be prepared in high yield in a cleaner manner. This ascertains that the subsequent reactions take place with minimum side reactions, which results in a high-yield process and facilitates the isolation of the intermediates. Moreover, the physical properties of the *Z*-configured intermediates allowed more efficient purification, which contributed further to the overall efficiency of the total synthesis of ezetimibe (**1**).

All of the chemicals used were obtained from commercial sources (Acros, Aldrich, Fluka, and Merck) and used without further purification. Solvents used as reaction media were purchased as absolute grades and used as received. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Reactions were monitored using analytical TLC plates (Merck, silica gel 60 F254, 0.25 mm), and compounds were visualized with ultraviolet light and 2,4-dinitrophenylhydrazine or bromocresol green. Circular chromatography was carried out on a Chromatotron® centrifugal thin-layer chromatograph (Harrison Research), using silica gel 60 GP254-containing gypsum. Silica gel grade 60 (70–230 mesh, Merck) was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 instrument operating at 300.13 MHz (^{1}H), and 75 MHz (^{13}C). Chemical shifts (δ) are reported in ppm using TMS as a reference. Mass spectra were obtained with a VG-Analytical Autospec Q mass spectrometer (Centre for Mass Spectrometry, Institute Jožef Stefan, Ljubljana). IR spectra were recorded on a PerkinElmer FTIR 1600 spectrometer. Melting points were determined using a Reichert hot-stage microscope and are uncorrected.

(*Z*)-Ethyl 5-(4-Fluorophenyl)pent-4-enoate (2) and (*Z*)-5-(4-Fluorophenyl)pent-4-enoic Acid (3)

Powdered (4-ethoxy-4-oxobuthyl)triphenylphosphonium bromide (10.5 g, 23.7 mmol) in anhyd THF (30 mL) was treated with sodium hexamethyldisilazide (12.5 mL, 25 mmol; 2 M solution in THF) at 18 °C with stirring under an argon atmosphere. After 20 min, 4-fluorobenzaldehyde (2.61 g, 21.0 mmol) was added at 18 °C, rapidly decolorising the red-orange mixture. After stirring at r.t. for 4 h, a sample of 100 mg was taken from the reaction mixture and purified by flash chromatography (hexane–EtOAc, 10:1), to get the pure ethyl ester **2** as a colorless oil. The reaction mixture was cooled down in an ice bath, and NaOH (1.6 g, 40 mmol) in H_2O (10 mL) was added. The resulting solution was stirred at r.t. for an additional 12 h, followed by the addition of H_2O (100 mL) and Et_2O (200 mL). The phases were separated and the aqueous phase was rinsed with Et_2O (2 × 50 mL), acidified with 4 M aq HCl, and extracted with EtOAc (4 × 50 mL). The combined EtOAc extracts were dried (Na_2SO_4), and concentrated. Kugelrohr distillation (124 °C/0.11 Torr) gave 3.52 g (91%) of pure **3** as white crystals, containing 88% of the *Z*-isomer, which was obtained in pure form after recrystallization from hexane.

(*Z*)-Ethyl 5-(4-Fluorophenyl)pent-4-enoate (2)

R_f = 0.42 (hexane–EtOAc, 10:1).

IR (NaCl): 2982, 1735, 1602, 1508, 1373, 1224, 1158, 1096, 1055, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.42–2.47 (m, 2 H, CH_2), 2.60–2.68 (m, 2 H, CH_2CO), 4.15 (q, *J* = 7.1 Hz, 2 H, $COOCH_2$), 5.63 (td, *J* = 7.2, 11.6 Hz, 1 H, =CH), 6.44 (d, *J* = 11.6 Hz, 1 H, ArC*H*=), 7.00–7.08 (m, 2 H, ArH), 7.22–7.28 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 23.8, 34.2, 60.2, 114.9 (d, $^2J_{C,F}$ = 21.3 Hz), 128.9, 130.1 (d, $^3J_{C,F}$ = 7.8 Hz), 130.2, 133.1 (d, $^4J_{C,F}$ = 3.4 Hz), 161.5 (d, $^1J_{C,F}$ = 246.2 Hz, C-3), 172.7 (C=O).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}FO_2$ + Na: 245.0954; found: 245.0958.

(*Z*)-5-(4-Fluorophenyl)pent-4-enoic Acid (3)

Mp 43–45 °C; R_f = 0.49 (Et_2O–PE–AcOH, 3:1:3‰).

IR (KBr): 2904, 1894, 1730, 1636, 1604, 1509, 1401, 1322, 1278, 1244, 1175, 1161, 1101, 1051, 1030, 1012, 966, 842 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46–2.51 (m, 2 H, CH_2), 2.59–2.66 (m, 2 H, CH_2CO), 5.64 (td, *J* = 7.0, 11.6 Hz, 1 H, =CH), 6.44 (d, *J* = 11.6 Hz, 1 H, ArC*H*=), 7.00–7.08 (m, 2 H, ArH), 7.22–7.27 (m, 2 H, ArH), 9.99 (br s, 1 H, CO_2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 34.1, 115.1 (d, $^2J_{C,F}$ = 21.4 Hz), 129.3, 129.7 (d, $^5J_{C,F}$ = 1.3 Hz), 130.2 (d, $^3J_{C,F}$ = 7.9 Hz), 133.1 (d, $^4J_{C,F}$ = 3.4 Hz), 161.6 (d, $^1J_{C,F}$ = 246.3 Hz, C-3), 179.4 (C=O).

HRMS-ESI: *m*/*z* [M – H]$^-$ calcd for $C_{11}H_{10}FO_2$: 193.0665; found: 193.0672.

(*S*,*Z*)-3-[5-(4-Fluorophenyl)pent-4-enoyl]-4-phenyloxazolidin-2-one (4)

To a solution of **3** (2.3 g) in CH_2Cl_2 (40 mL) were added slowly oxalyl chloride (1.81 g) and DMF (2 drops) at 0 °C. The solution was warmed to r.t. and refluxed for 1 h. The solvent was evaporated under reduced pressure and the excess of oxalyl chloride was removed azeotropically with CH_2Cl_2 (2 × 50 mL). The resultant acid chloride was redissolved in CH_2Cl_2 (40 mL) and the solution was added dropwise to a cooled solution of (*S*)-(+)-4-phenyl-2-oxazolidone (1.99 g), DIPEA (3.07 g), and DMAP (0.05 g) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at r.t. for 2 h. Then, CH_2Cl_2 (100 mL) was added, and the organic layer was washed with aq 0.5 M HCl (2 × 40 mL), H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. The product **4** was recrystallized from EtOAc–hexane and collected by filtration.

Yield: 3.7 g (93%); mp 65–67 °C; R_f = 0.42 (EtOAc–hexane, 1:2); $[\alpha]_D^{25}$ +0.088 (*c* 5.0, MeOH).

IR (KBr): 3390, 3039, 2965, 1790 (C=O), 1704 (C=O), 1601, 1506, 1457, 1430, 1388, 1331, 1222 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55–2.70 (m, 2 H, CH_2), 3.05–3.15 (m, 2 H, CH_2CO), 4.29 (dd, *J* = 8.9, 3.7 Hz, 1 H, CH_aO), 4.69 (t, *J* = 8.8 Hz, 1 H, NCH), 5,43 (dd, *J* = 8.7, 3.6 Hz, 1 H, CH_bO), 5.57–5.66 (m, 1 H, =CH), 6.40 (d, *J* = 11.6 Hz, 1 H, ArC*H*=), 6.95–7.04 (m, 2 H, ArH), 7.20–7.43 (m, 7 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 35.5, 57.5, 70.0, 115.0 (d, $^2J_{C,F}$ = 21.3 Hz), 125.8, 128.6, 128.9, 129.1, 130.1, 130.2 (d, $^3J_{C,F}$ = 7.9 Hz), 133.1 (d, $^4J_{C,F}$ = 3.3 Hz), 139.0, 153.6, 161.5 (d, $^1J_{C,F}$ = 246.1 Hz, C15), 171.8 (C=O).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}FNO_3$ + Na: 362.1168; found: 362.1165.

(*S*)-3-((*R*,*Z*)-2-{(*S*)-[4-(Benzyloxy)phenyl](4-fluorophenylamino)methyl}-5-(4-fluorophenyl)pent-4-enoyl)-4-phenyloxazolidin-2-one (5)

To a stirred solution of **4** (1.0 g, 3 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added slowly a 1 M solution of $TiCl_4$ in CH_2Cl_2 (3.25 mL). After 15 min, DIPEA (0.97 mL) was added, and the mixture was stirred for 30 min at –20 °C. A solution of (*E*)-*N*-[4-(benzyloxy)benzylidene]-4-fluoroaniline (1.53 g) in CH_2Cl_2 (30 mL) was added to the solution keeping the temperature below –20 °C. After 1.5 h, the reaction was quenched with glacial AcOH (1 mL) in CH_2Cl_2 (3 mL) at –20 °C and stirred for 30 min. The mixture was poured into 1 M aq H_2SO_4 (40 mL) and stirred for another 30 min. Then, EtOAc (150 mL) was added, and the organic layer was washed with sat. aq $NaHCO_3$ (3 × 40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. The product was recrystallized from EtOAc–hexane and collected by filtration. The crystals were washed with cold MeOH (5 mL).

Yield: 1.15 g (59%); mp 175–179 °C; R_f = 0.20 (EtOAc–hexane, 1:2); $[\alpha]_D^{25}$ +0.054 (*c* 5.0, DMF).

IR (KBr): 3381, 3035, 1754 (C=O), 1698, 1607, 1511, 1456, 1422, 1388, 1317, 1229, 1110, 1012 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31–2.40 (m, 1 H, CH_aH), 2.65–2.75 (m, 1 H, CH_bH), 4.22 (dd, *J* = 8.8, 3.1 Hz, 1 H, CH_aO), 4.39 (t, *J* = 9.4 Hz, 1 H, CH) 4.36–4.60 (m, 1 H, CHNH), 4.69 (t, *J* = 8.7 Hz, 1 H, NCH), 4.95 (d, *J* = 10.3 Hz, 1 H, NH), 5.03 (s, 2 H, CH_2Ph), 5.43 (dd, *J* = 8.5, 3.1 Hz, 1 H, CH_bO), 5.51–5.60 (m, 1 H, =CH), 6.24–6.42 (m, 1 H, ArC*H*=), 6.69–6.81 (m, 2 H, ArH), 6.84–6.96 (m, 4 H, ArH), 7.08–7.18 (m, 10 H, ArH), 7.38–7.50 (m, 7 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2, 48.7, 58.1, 60.8, 70.0, 114.9, 115.0 (d, $^2J_{C,F}$ = 21.4 Hz), 115.0, 115.4 (d, $^2J_{C,F}$ = 22.3 Hz), 125.2, 127.5, 128.0 (d, $^3J_{C,F}$ = 7.8 Hz), 128.2, 128.6, 128.9, 130.1 (d, $^3J_{C,F}$ = 7.8 Hz), 130.4, 132.7 (d, $^4J_{C,F}$ = 3.5 Hz), 132.8, 133.8 (d, $^4J_{C,F}$ = 2.6 Hz), 136.6, 154.3, 155.9 (d, $^1J_{C,F}$ = 235.3 Hz), 158.2, 161.6 (d, $^1J_{C,F}$ = 246.1 Hz), 174.6 (C=O).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{35}F_2N_2O_4$: 645.2565; found: 645.2575.

(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(*Z*)-3-(4-fluorophenyl)allyl]azetidin-2-one (6)

A suspension of **5** (0.484 g, 0.75 mmol) in anhyd toluene (5.0 mL) was deoxygenated with argon, and after 15 min, BSA (1.50 mmol, 0.37 mL) was added. After stirring for 30 min at r.t., TBAF·3H_2O (5.0 mol%, 0.0375 mmol, 11.8 mg) was added, and the mixture was left stirring for 4 h. Then glacial AcOH (0.027 mL) and MeOH (4.0 mL) were added. After 5 min, the reaction mixture was concentrated under reduced pressure, and then EtOAc (50 mL) was added. The organic layer was washed with 5% aq $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc–hexane (1:4) as the eluent to afford compound **6**.

Yield: 0.256 g (71%); mp 45–49 °C; R_f = 0.5 (hexane–EtOAc, 2:1); $[\alpha]_D^{25}$ +32.8 (*c* 0.5, MeOH).

IR (KBr): 3455, 3014, 2900, 1888, 1733 (C=O), 1611, 1510, 1452, 1428, 1291, 1221, 1158, 1142, 1105, 1044, 1012 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.95 (m, 1 H, CH_2), 3.13–3.19 (m, 1 H, CHCO), 4.52 (d, *J* = 2.3 Hz, 1 H, CHN), 5.07 (s, 2 H, OCH_2Ph), 5.63–5.71 (m, 1 H, =CH), 6.52 (d, *J* = 11.5 Hz, 1 H, ArC*H*=), 6.86–7.04 (m, 6 H, ArH), 7.15–7.24 (m, 6 H, ArH), 7.30–7.41 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 60.1, 60.3, 70.06, 115.3 (d, $^2J_{C,F}$ = 21.4 Hz), 115.5, 115.7 (d, $^2J_{C,F}$ = 22.6 Hz), 118.4 (d, $^3J_{C,F}$ = 7.8 Hz), 127.0, 127.1, 127.4, 128.0, 128.6, 129.5, 130.3 (d, $^3J_{C,F}$ = 7.9 Hz), 130.6, 132.8 (d, $^4J_{C,F}$ = 3.3 Hz), 133.8 (d, $^4J_{C,F}$ = 2.6 Hz), 136.6, 158.7 (d, $^1J_{C,F}$ = 208.9 Hz), 159.0, 161.9 (d, $^1J_{C,F}$ = 212.3 Hz), 166.6 (C=O).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{26}F_2NO_2$: 482.1932; found: 482.1930.

(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]azetidin-2-one (7)

$Pd(OAc)_2$ (3.0 mol%, 0.042 mmol, 9.43 mg), benzoquinone (2.1 mmol, 227 mg), and 70% aq $HClO_4$ (0.15 M, 0.100 mL) were dissolved in MeCN (3.5 mL) and deoxygenated by purging with argon for at least 20 min. H_2O (0.7 mL), which was deoxygenated with argon, was then added. The reaction mixture was stirred vigorously for another 5 min under argon, and then a solution of **6** (1.40 mmol) in MeCN (3.5 mL) (also previously deoxygenated by purging with argon for 30 min) was added. After 4 h, an additional amount of 70% aq $HClO_4$ (0.100 mL) was added. The resulting solution was stirred for 48 h and then diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with H_2O (2 × 40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with EtOAc–hexane (1:4) to obtain compound **7** as a white stable foam with physical and spectroscopic properties in agreement with those reported in the literature.[17]

Yield: 0.600 g (86%); R_f = 0.63 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +4.9 (*c* 1.0, MeOH).

IR (KBr): 3448, 3066, 2928, 1744, 1685, 1598, 1508, 1453, 1409, 1386, 1367, 1290, 1227, 1175, 1155, 1136, 1104, 1012, 990, 833 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21–2.47 (m, 2 H, CH_2), 3.10–3.21 (m, 2 H, $COCH_2$), 3.24–3.35 (m, 1 H, CHCO), 4.68 (d, *J* = 2.3 Hz, 1 H, CHN), 5.05 (s, 2 H, OCH_2Ph), 6.90–6.99 (m, 4 H, ArH), 7.09–7.17 (m, 2 H, ArH), 7.22–7.27 (m, 4 H, ArH), 7.33–7.44 (m, 5 H, ArH), 7.96–8.02 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 35.5, 59.8, 61.1, 70.0, 115.5, 115.6 (d, $^2J_{C,F}$ = 21.9 Hz), 115.7 (d, $^2J_{C,F}$ = 22.6 Hz), 118.4 (d, $^3J_{C,F}$ = 7.8 Hz), 127.2, 127.4, 128.0, 128.6, 129.5, 130.6 (d, $^3J_{C,F}$ = 9.3 Hz), 133.0 (d, $^4J_{C,F}$ = 3.0 Hz), 133.9 (d, $^4J_{C,F}$ = 2.7 Hz), 158.9 (d, $^1J_{C,F}$ = 243.4 Hz), 159.0, 165.8 (d, $^1J_{C,F}$ = 254.9 Hz), 167.1, 197.3 (C=O).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{26}F_2NO_3$: 498.1881; found: 498.1883.

(3*R*,4*S*)-4-[4-(Benzyloxy)phenyl]-1-(4-fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]azetidin-2-one (8)

(*R*)-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborole (96 mg, 0.346 mmol) and **7** (760 mg, 1.528 mmol) were dissolved in anhyd THF (2 mL) under argon. The solution was cooled to –22 °C, and after stirring for 5 min, $Me_2S·BH_3$ complex (2 M solution in THF, 0.864 mL, 1.728 mmol) was added dropwise over 2 h. After stirring for a total of 5 h at –22 °C, the reaction was

quenched by the addition of MeOH (3 mL). EtOAc (30 mL) and 1 M aq HCl (15 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined EtOAc extracts were dried (Na_2SO_4), and concentrated to a stable foam (0.900 g). The resulting crude product was purified by flash chromatography using EtOAc–hexane (1:3) as the mobile phase, to obtain the title compound **8** as a white stable foam with physical and spectroscopic properties in agreement with those reported in the literature.[17]

Yield: 0.731 g (96%); R_f = 0.50 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ –15.8 (*c* 1.0, MeOH).

IR (KBr): 3482, 2937, 2406, 2348, 2293, 1742, 1609, 1509, 1387, 1223, 1156, 1013, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.84–2.05 (m, 4 H, CH_2CH_2), 3.07–3.17 (m, 1 H, CHCO), 4.59 (d, *J* = 2.4 Hz, 1 H, CHN), 4.71–4.76 (m, 1 H, ArC*H*), 5.07 (s, 2 H, O*CH*$_2$Ph), 6.91–7.06 (m, 6 H, ArH), 7.22–7.46 (m, 11 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 36.5, 60.2, 61.0, 70.0, 72.8, 115.2 (d, $^2J_{C,F}$ = 21.3 Hz), 115.5, 115.7 (d, $^2J_{C,F}$ = 22.7 Hz), 118.3 (d, $^3J_{C,F}$ = 7.8 Hz), 127.1, 127.2, 127.4 128.0, 128.5, 129.5, 133.8 (d, $^4J_{C,F}$ = 2.7 Hz), 136.6, 140.1 (d, $^4J_{C,F}$ = 3.1 Hz), 158.9 (d, $^1J_{C,F}$ = 243.4 Hz), 159.0, 162.0 (d, $^1J_{C,F}$ = 245.4 Hz), 167.6.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{31}H_{27}F_2NO_3$ + Na: 522.1857; found: 522.1864.

Ezetimibe (1)

To a solution of **8** (618 mg, 1.24 mmol) in EtOH (3 mL) was added 5% Pd/C (13 mg, 0.5 mol%). The resulting suspension was stirred under a H_2 gas atmosphere at an elevated pressure of 60 psi, until all of the starting material **7** had been consumed. The catalyst was removed by filtration. The solution obtained was concentrated under reduced pressure and recrystallized, to provide the title compound **1** (406 mg, 80%), with specific rotation and physical and spectroscopic properties in agreement with those reported in the literature.[17]

Acknowledgment

The authors gratefully acknowledge Lek Pharmaceuticals, d.d., for financial support of this work and Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for mass spectrometry analyses.

References

(1) Knopp, R. H.; Gitter, H.; Truitt, T.; Bays, H.; Manion, C. V.; Lipka, L. J.; LeBeaut, A. P.; Suresh, R.; Yang, B.; Veltri, E. P. *Eur. Heart J.* **2003**, *24*, 729.

(2) Bays, H. E.; Moore, P. B.; Drehobl, M. A.; Rosenblatt, S.; Toth, P. D.; Dujovne, C. A.; Knopp, R. H.; Lipka, L. J.; LeBeaut, A. P.; Yang, B.; Mellars, L. E.; Cuffie-Jackson, C.; Veltri, E. P. *Clin. Ther.* **2001**, *23*, 1209.

(3) Rosenblum, S. B. In *The Art of Drug Synthesis*; Johnson, D. J.; Li, J. J., Eds.; Wiley-Interscience: New Jersey, **2007**, 183–196; and references cited therein.

(4) Shankar, B. B. US Patent 5856473, **1999**; *Chem. Abstr.* **1999**, *130*, 110148.

(5) Thiruvengadam, T. K.; Sudhakar, A. R.; Wu, G. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, **1999**, 221–242; and references cited therein.

(6) Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Browne, M. E.; Davis, H. R. Jr.; Clader, J. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 311.

(7) Xu, X.; Fu, R.; Chen, J.; Chen, S.; Bai, X. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 101.

(8) (a) Sawant, M. S.; Pillai, B. K. G.; Bhirud, S. B.; Sharma, K. PCT Int. Appl. WO 2007017705, **2007**; *Chem. Abstr.* **2007**, *146*, 229083. (b) Escude, A. G. I.; Llado, J. B. I.; Nettekoven, U. PCT Int. Appl. WO 2007144780, **2007**; *Chem. Abstr.* **2007**, *148*, 78871. (c) Kansal, K. K.; Ahmad, S.; Mariappan, S.; Tyagi, B.; Perlman, N.; Le Paih, J.; Zanotti-Gerosa, A. PCT Int. Appl. WO 2007120824, **2007**; *Chem. Abstr.* **2007**, *147*, 486269. (d) Bodi, J.; Eles, J.; Szoeke, K.; Vukics, K.; Gati, T.; Temesvari, K.; Kiss-Bartos, D. PCT Int. Appl. WO 2007072088, **2007**; *Chem. Abstr.* **2007**, *147*, 95527. (e) Ramakrishnan, A.; Shrigadi, N. B.; Prabhavalkar, T. S.; Thorat, A. N. PCT Int. Appl. WO 2007108007, **2007**; *Chem. Abstr.* **2007**, *147*, 385762. (f) Uppala, V. B. R.; Vaddadi, P. R.; Sunkara, V. V.; Cheemalapati, V. A. S.; Padaga, K. S. K. US Pat. Appl. Publ. US 2007049748, **2007**; *Chem. Abstr.* **2007**, *146*, 295763. (g) Perlman, N.; Fishman, A. PCT Int. Appl. WO 2008151324, **2008**; *Chem. Abstr.* **2008**, *150*, 19943. (h) Srinivasan, C. V.; Saxena, R.; Gupta, P.; Wadhwa, L. PCT Int. Appl. WO2008096372, **2008**; *Chem. Abstr.* **2008**, *149*, 267891. (i) Slavikova, M.; Vesilek, P.; Obadalova, I.; Hajicek, J. PCT Int. Appl. WO 2008106900, **2008**; *Chem. Abstr.* **2008**, *149*, 355683. (j) Allegrini, P.; Naldini, D.; Razzetti, G.; Taddei, M. Ital. Appl. IT 2007MI2013, **2008**; *Chem. Abstr.* **2008**, *152*, 168785. (k) Štimac, A.; Mohar, B.; Stephan, M.; Bevc, M.; Zupet, R.; Gartner, A.; Krošelj, V.; Smrkolj, M. Eur. Pat. Appl. EP 1953140, **2008**; *Chem. Abstr.* **2008**, *149*, 224075. (l) Satyanarayana Reddy, M.; Sahadeva Reddy, M. PCT Int. Appl. WO 2008032338, **2008**; *Chem. Abstr.* **2008**, *148*, 355561. (m) Szabo, L.; Toth, L.; Perlman, N. PCT Int. Appl. WO 2009032264, **2009**; *Chem. Abstr.* **2009**, *150*, 304851. (n) Stepankova, H.; Hajicek, J.; Slavikova, M.; Zezula, J. PCT Int. Appl. WO 2009106021, **2009**; *Chem. Abstr.* **2009**, *151*, 313529. (o) Huang, Z.; Dai, L.; Han, Y. Chin. Pat. Appl. CN 101423511, **2009**; *Chem. Abstr.* **2009**, *151*, 8510. (p) Venkateswaran, S. C.; Gurdeep, S. S.; Gupta, P.; Wadhwa, L. PCT Int. Appl. WO 2009157019, **2009**; *Chem. Abstr.* **2009**, *152*, 97325. (q) Du, H.; Zheng, L.; Chen, X. Chin. Pat. Appl. CN 101423515, **2009**; *Chem. Abstr.* **2009**, *150*, 563526. (r) Slavikova, M.; Stepankova, H.; Zezula, J.; Hajlcek, J. PCT Int. Appl. WO 2009140932, **2009**; *Chem. Abstr.* **2009**, *152*, 12131. (s) Stepankova, H.; Hajicek, J.; Slavikova, M.; Zezula, J. PCT Int. Appl. WO 2009067960, **2009**; *Chem. Abstr.* **2009**, *151*, 33290. (t) Selič, L. PCT Int. Appl. WO 2009150038, **2009**; *Chem. Abstr.* **2009**, *152*, 62067. (u) Reddy, R. B.; Reddy, G. M.; Sahadev, K.; Nagaraju, M. Indian Pat. Appl. IN 2007CH02953, **2009**.

(9) Sasikala, C. H. V. A.; Padi, P. R.; Sunkara, V.; Ramayya, P.; Dubey, P. K.; Uppala, V. B. R.; Praveen, C. *Org. Process Res. Dev.* **2009**, *13*, 907.

(10) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R. Jr. *Tetrahedron* **2000**, *56*, 5735.

(11) Lamb, R. C.; Spadafino, L. P.; Webb, R. G.; Smith, E. B.; McNew, W. E.; Pacifici, J. G. *J. Org. Chem.* **1966**, *31*, 147.

(12) Murakami, M.; Ishida, N.; Miura, T. *Chem. Commun.* **2006**, 643.

(13) Lemhadri, M. L.; Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2007**, *692*, 2270.

(14) Mravljak, J.; Sova, M.; Kovač, A.; Gobec, S.; Časar, Z. PCT Int. Appl. WO 2010012775, **2010**; *Chem. Abstr.* **2010**, *152*, 215003.

(15) Tsuji, J. *Synthesis* **1984**, 369.

(16) Miller, D. G.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 2924.

(17) (a) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. *J. Med. Chem.* **1998**, *41*, 973. (b) Wu, G.; Wong, Y.; Chen, X.; Ding, Z. *J. Org. Chem.* **1999**, *64*, 3714.