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Total Synthesis of Ezetimibe, a Cholesterol Absorption Inhibitor

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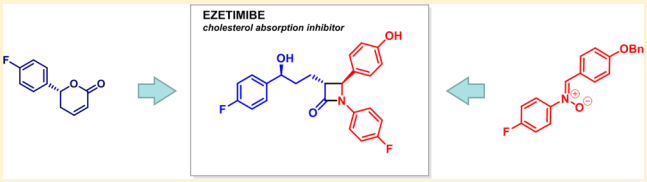
Supporting Information

ABSTRACT: Ezetimibe (**1**), a strong β-lactamic cholesterol absorption inhibitor, was synthesized from (*R*)-6-(4-fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one **7**. Independent pathways were analyzed in order to select the optimal one, which involved 1,3-dipolar cycloaddition with *C*-(4-benzyloxyphenyl)-*N*-(4-fluorophenyl)-nitrone (**8**), intramolecular nucleophilic displacement at the benzylic position of the lactone, cleavage of the N−O bond, elimination of a water molecule, hydrogenation of the double bond, rearrangement of the six-membered lactone ring into a β-lactam moiety, and final deprotection of the phenolic hydroxyl group. Highly stereoselective $Sc(OTf)_3$-catalyzed 1,3-dipolar cycloaddition was the most crucial step of the synthesis. Owing to the rigid transition state of the cycloaddition, the absolute configuration of the starting lactone controlled the formation of other stereogenic centers of the final molecule **1**.



INTRODUCTION

Ezetimibe (**1**) is a strong β-lactamic cholesterol absorption inhibitor that reduces plasma low-density lipoprotein fraction (LDL-C).[1−4] It contains three *para*-substituted phenyl rings, a chiral benzylic hydroxyl, and two additional stereogenic centers at the 2-azetidinone scaffold. The three chiral centers give rise to eight stereoisomers that have been individually characterized and shown to exhibit significantly different CAI profiles.[4] The stereocontrol of the azetidinone stereocenters (3*R*,4*S*) and the installation of the benzylic hydroxyl with absolute (3′*S*) stereochemistry are the most significant synthetic challenges.

Annual worldwide sales of ZETIA for 2010 were $2.3 billion and $2.0 billion for VYTORIN, which puts ezetimibe high on the list of valuable drugs and an interesting synthetic target for many academic and industrial laboratories.[3]

Most of the known methods for the synthesis of **1** assume separate formation of stereogenic centers associated with a β-lactam ring via chiral auxiliary mediated diastereoselective cyclocondensation between diaryl imine **2** and an ester or amide enolate and formation of the center in the side chain via enantioselective reduction of the phenone carbonyl group (Scheme 1).[2−10] Bearing in mind possible industrial applications, the use of a chiral auxiliary is a serious drawback. Strategies starting from a nonracemic substrate with complete atom economy are rare.[11−14]

There has been one controversial patent report on the direct formation of ezetimibe via cyclocondensation between *p*-benzyloxybenzylidene-*p*-fluoroaniline **3** and lactone **4**.[12−14] The authors, however, have not discussed the stereochemical pathway of the reaction and did not provide any proof of the structure or diastereomeric purity of the desired product.[12−14] We repeated the reported procedure and found that an inseparable mixture of two diastereomers **5** and **6** in a ratio of about 55:45 was obtained in 45% yield. Both products were *trans* substituted in the four-membered ring, but the main component had the wrong configuration of both azetidinone stereogenic centers (Scheme 2).

Recently, we described a novel approach for the stereocontrolled formation of ezetimibes' core β-lactam via the copper(I)-catalyzed reaction of *C*-(4-benzyloxyphenyl)-*N*-(4-fluorophenyl)nitrone and L-glyceraldehyde acetonide derived acetylene (Kinugasa reaction).[8] Asymmetric induction was quite good, and moreover two main diastereomeric products can be used for further steps without separation. Subsequently, the obtained β-lactamic derivative was transformed in a three-step sequence into the aldehyde derivative used by Schering-Plough in their method for the synthesis of ezetimibe.[11] Our synthesis of **1** had, however, the same drawback as all other reported approaches to ezetimibe: it required the separate formation of the chiral centers around the β-lactam ring and the stereogenic center in the side chain.

RESULTS AND DISCUSSION

Seeking a more useful method of ezetimibe synthesis, we revisited our work performed 25 years ago.[15] At that time, before the invention of ezetimibe, we investigated 1,3-dipolar cycloaddition reactions of α,β-unsaturated sugar lactones with diaryl nitrones.[15] The reactions were performed in boiling toluene to show, in the case of D-*glycero* and D-*threo* lactones, the exclusive *anti* addition to the terminal acetoxymethyl group in the lactone to afford *anti-exo* and *anti-endo* adducts with prevalence of thermodynamic products *endo*. At that time, using the known Tufariello approach,[16] we have demonstrated the transformation of adducts into *N*,4-diaryl β-lactams.[15b,c] These studies prompted us to reuse this methodology for the synthesis of ezetimibe **1**.

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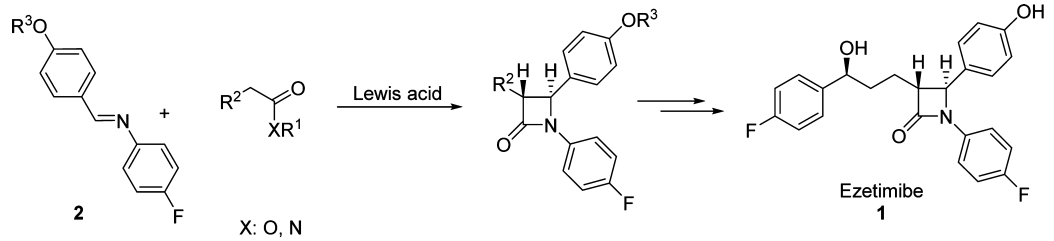
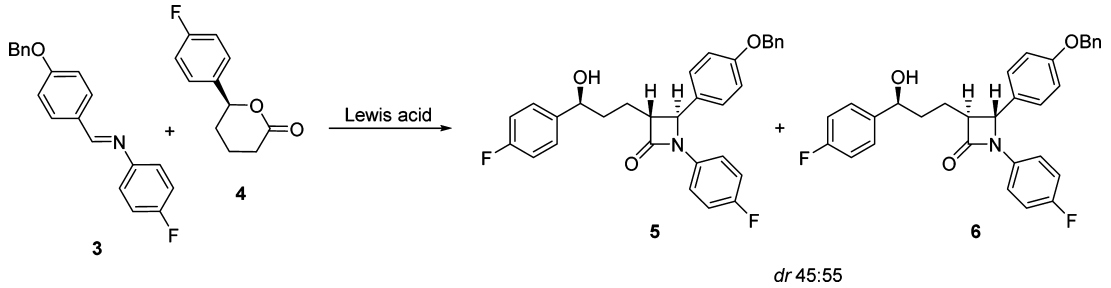
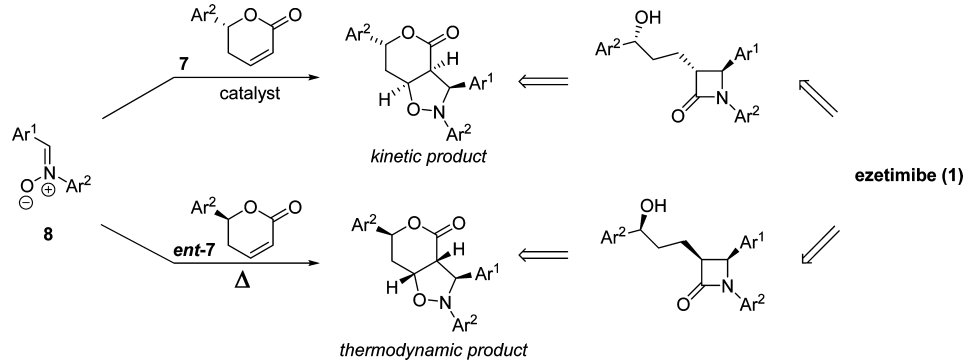
Scheme 1. General Strategy for Synthesis of Ezetimibe 1



Scheme 2. Synthesis of 1 via Cyclocondensation between Imine 3 and Lactone 4[12−14]

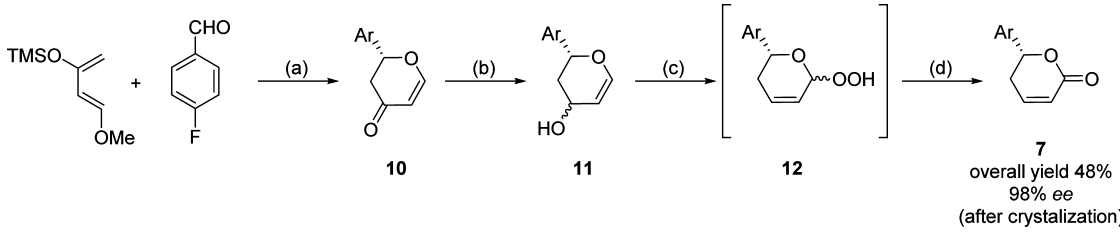


Scheme 3. Possible Synthetic Pathway to Ezetimibe 1 from Lactone 7 and Nitrone 8[a]



[a]Ar^1 = 4-benzyloxyphenyl, Ar^2 = 4-fluorophenyl.

Scheme 4. Synthesis of Lactone 7[a]



[a]Reagents and conditions: (a) 1 mol % (*R*,*R*)-Cr(salen), MTBE, −30°C, yield 97%, 85% ee; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, $MeOH/CH_2Cl_2$; (c) MoO_3, 30% H_2O_2, MeCN; (d) Ac_2O, Py, yield 52% (2 steps); Ar = 4-fluorophenyl.

The assumed synthetic strategy is presented in Scheme 3. For this purpose the 1,3-dipolar cycloaddition reactions of lactones **7**/*ent*-**7** to nitrone **8**, which has been used for synthesis of **1** via the Kinugasa reaction,[8] were considered as a key step. Both lactones contain all of the structural elements corresponding to ezetimibes' side chain and offer an excellent atom economy of the synthesis. By varing the reaction conditions, attractive starting materials suitable for synthesis of **1** should be provided.

On the basis of our previous experience in cycloaddtions to sugar-derived lactones, we expected that the reaction should proceed exclusively *anti* to the substituent at the lactone moiety, and therefore the *endo* addition to (*S*)-lactone (*ent*-**7**) under thermal conditions should provide the correct configuration in the side chain and at the stereogenic center

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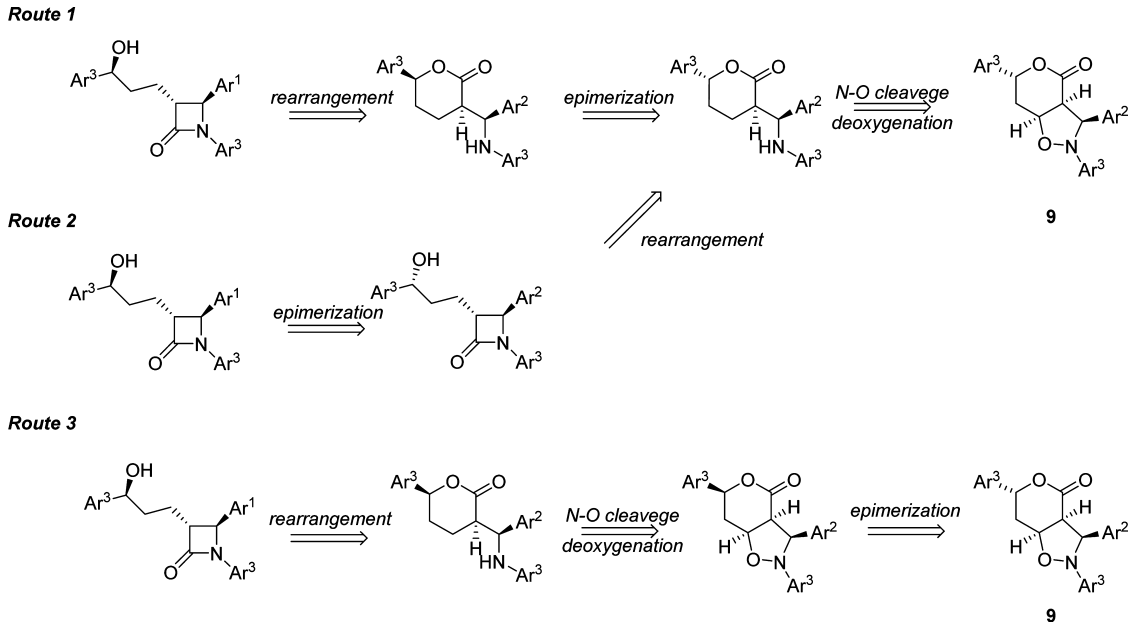
Scheme 5. 1,3-Dipolar Cycloaddition Reaction between Lactone 7 and Nitrone 8 under Thermal and Catalytic Conditions

Scheme 6. Three Strategies for Transformation of Isoxazolidine 9 into Ezetimibe 1[a]



[a]Ar^1 = 4-hydroxyphenyl, Ar^2 = 4-benzyloxyphenyl, and Ar^3 = 4-fluorophenyl.

next to the nitrogen atom (Scheme 3). On the other hand, the *exo* addition to (*R*)-lactone (**7**) through kinetic control should provide the correct configuration at the stereogenic centers that constitute the geometry of the *β*-lactam fragment (Scheme 3). In the first case, the stereogenic center next to the carbonyl group could be epimerized after formation of the *β*-lactam ring, whereas in the second case, the stereogenic center in the side chain should be inverted at a later step of the synthesis.

Although there are several possible methods[17−22] that can be adopted for synthesis of lactone **7**, none of them provided satisfactory yield or enantioselectivity. The most promising, direct formation of lactone **7** via condensation of silyl enol of ethyl crotonate with 4-fluorobenzaldehyde in the presence of (*R*)-TolBINAP/Cu(OTf)$_2$ complex, according to Campagne et al.,[22] gave good ee of 84%, but very low yield of 10%.

We found a four-step procedure involving cyclocondensation between Danishefsky's diene and 4-fluorobenzaldehyde in the presence of the Jacobsen's catalyst to be the most convenient to provide adduct **10** in 97% yield and 85% ee (Scheme 4).[23] Application of modified Jacobsen's catalyst raised the ee to 91% but caused a lower yield of 66%.[24] Subsequent reduction of the carbonyl group to glycal **11**, followed by the oxidative Ferrier rearrangement, provided hydroperoxide **12**, which in the presence of an acetic anhydride/pyridine mixture yielded lactone **7** with 98% ee after crystallization.[25] The assignment of an absolute configuration was done on the basis of the report by Jacobsen et al.[23]

The 1,3-dipolar cycloaddition reaction of lactone **7** and nitrone **8** in boiling toluene led to the *exo* cycloadduct **9** along with its *endo* isomer **13** in ratio 53:47 and yield 41% after 16 h (Scheme 5). The further extension of the reaction time to 72 h increased the content of *endo* adduct to 70% while the reaction yield decreased to 37%. Such a result indicated the reversibility of the cycloaddition reaction, which had been observed earlier for the 2(5*H*)-furanone derivatives.[26] The experiment showed also that under thermal conditions neither pure *endo* adduct (synthesis of **1** from *ent*-**7**) nor pure *exo* (synthesis of **1** from **7**) can be obtained.

Since the *endo* adduct was always accompanied by the *exo* one, we decided to impel the reaction between lactone **7** and nitrone **8** to promote formation of the kinetic product **9** by performing it in the presence of a Lewis acid promoter.

Very recently, we demonstrated that Sc(OTf)$_3$ was a highly efficient Lewis acid catalyst of the cycloaddition reaction between *C*,*N*-diarylnitrones and sugar-derived *α*,*β*-unsaturated lactones.[27] In the presence of scandium salt, lactone **7** with nitrone **8** provided almost exclusively product **9** (dr 97:3) in 85% yield (Scheme 5). Additionally, purification of **9** did not

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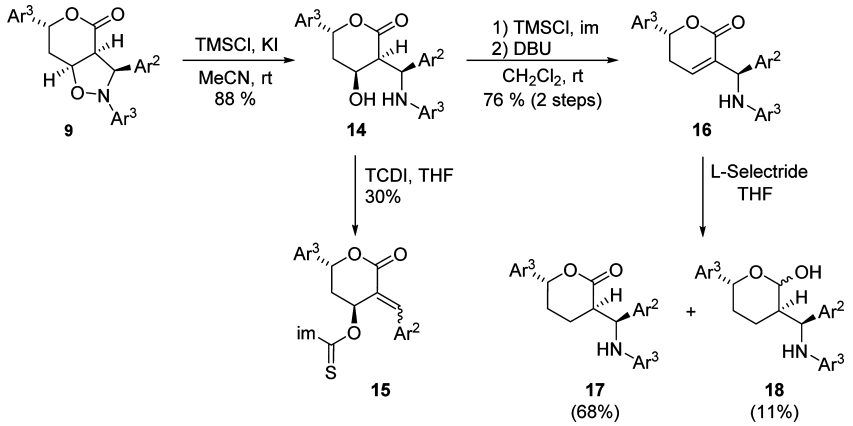
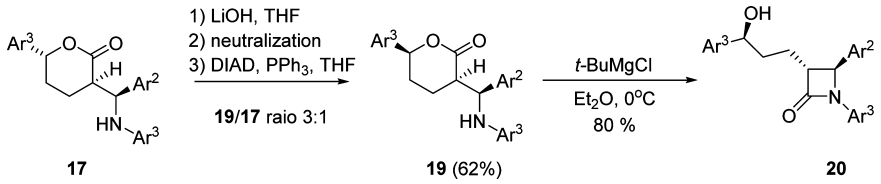
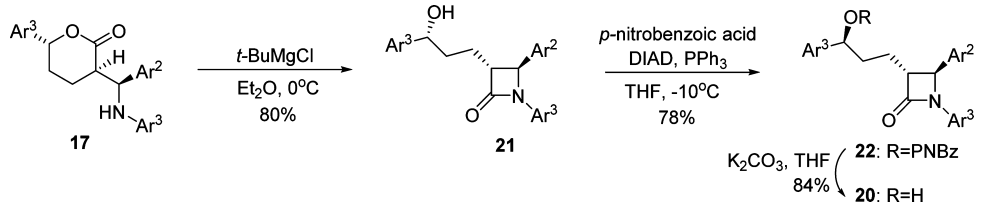
Scheme 7. Synthesis of Aminolactone 17



Scheme 8. Synthesis of 20 through Mitsunobu and Rearrangement Sequence



Scheme 9. Synthesis of 20 via Rearrangement/Mitsunobu Sequence



require any chromatography, and simple crystallization was sufficient. Moreover, when enantiomerically enriched lactone **7** (85% ee) was subjected to cycloaddition, product **9** with 97% ee, after crystallization, was obtained.

With isoxazolidine **9** in hand, its transformations into ezetimibe **1** was investigated. As mentioned above, the choice of (*R*)-lactone (**7**) for cycloaddition reaction resulted in the formation of product **9** with the correct absolute configuration of two carbon atoms of the isoxazolidine ring that corresponded to the stereogenic centers of the target β-lactam. The incorrect absolute configuration at the benzylic position of lactone **7** was inverted in later steps of the synthesis. Three routes were considered for the transformation of **9** into target azetidinone **1** (Scheme 6).

The paths differed in the order of their individual steps involving N−O bond cleavage, deoxygenation, base-mediated rearrangement of the six-membered lactone ring into the β-lactam moiety, and inversion of the configuration at the benzylic position.

Since compound **9** is highly prone to degradation under hydrogenation in the presence of Pd/C due to the presence of multiple benzylic positions, N−O bond cleavage cannot be done by conventional catalytic reductive methods.[28] To overcome this problem, a protocol reported by Kündig et al.[29] was applied, and isoxazolidine **9** was treated with TMSCl and KI in wet MeCN (Scheme 7). The corresponding aminolactone **14** was obtained in 88% yield after extractive workup and was suitable for use in the next step without further purification. Due to the presence of the secondary amine moiety and the double β-substituted carbonyl group, well-known Barton−McCombie reaction, utilized to remove the free hydroxyl group in compound **14**, was not successful, causing β-elimination of the amino group **15**. The other possibility was to use β-elimination of a water molecule to afford **16** followed by reduction of the double bond to afford saturated lactone **17**. Silylation of the hydroxyl group in **14** under standard conditions followed by treatment with DBU provided the desired unsaturated lactone **16** in good yield (76%). The structure of **16** was proved by X-ray analysis (see Supporting Information).

We expected that reduction of the double bond in **16** with hydrides, owing to the carbanion intermediate, should afford thermodynamic product **17** having both substituents of the lactone located *trans* diequatorial. Indeed, the best result was obtained for L-Selectride reduction (1.1 equiv) to provide **17** in 68% yield. The desired product was accompanied, however, with lactol **18**, requiring chromatographical separation. Atempts to eliminate the unwanted subsequent lactone reduction failed. However, it was found that temperature during the reduction of **16** must be maintained below −65 °C; otherwise lactol **18**, along with unreacted substrate, would be the only product of the reaction. Unfortunately, reoxidation of **18** to lactone **17** provided a complicated mixture of products and brought about reduction of the lactone double bond.

Next, epimerization of the stereogenic center at the benzylic position in **17** was made via intramolecular Mitsunobu reaction

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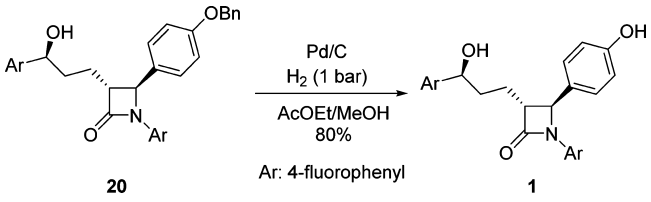
(Scheme 8). Opening of the lactone moiety in **17** with LiOH followed by neutralization to a free carboxylic group and subsequent treatment with Ph_3P and DIAD at 0 °C afforded a mixture of expected **19** in 62% and substrate **17** in a ratio of about 3:1, respectively. Chromatographical separation of **19** followed by rearrangement of the δ-lactone ring into a β-lactam moiety in the presence of *t*-BuMgCl gave benzyl protected ezetimibe (**20**) in 80% yield.

The last two steps could be performed also in reverse order. Such an approach eliminates the disadvantage related to selectivity of the intramolecular Mitsunobu reaction by using the intermolecular procedure, which requires one preparative step more. Accordingly lactone **17** was transformed into azetidinone **21**, which was subjected to the Mitsunobu reaction with *p*-nitrobenzoic acid to afford benzoate **22**. Deprotection of **22** gave **20** in 66% overall yield (2 steps, Scheme 9).

Finally, hydrogenolysis of benzyl protected phenolic hydroxyl in **20** afforded ezetimibe **1** (Scheme 10).

Scheme 10. Synthesis of Ezetimibe 1



20 **1**

It was also found that it was possible to effect hydrogenation of the double bond in **16** over PtO_2 to afford a diastereomer of **17** (**23**), which in the presence of LDA underwent rearrangement to β-lactam and simultaneously epimerization at the α-position to the carbonyl group to provide azetidinone **21** (Scheme 11).

Since routes 1 and 2 (Schemes 7–9) suffer from serious drawbacks such as lack of control during reduction of **16** leading to unwanted lactol **18** and low efficiency of epimerization of **17** into **19** via intramolecular Mitsunobu reaction, and bearing in mind possible industrial applications, the third synthetic strategy toward **1** was considered.

Therefore, the crucial epimerization at the side-chain benzylic position was performed at the beginning of the synthesis just after the cycloaddition step (Scheme 12). In contrast to previous attempts, at the stage of isoxazolidine **9** an intramolecular Mitsunobu reaction to epimerize the stereogenic center at the benzylic position should be the most efficient, since both side chains taking part in the nucleophilic substitution were attached *syn* to the five-membered heterocyclic ring, which should facilitate the displacement.

Indeed, an opening of the lactone moiety in **9** with LiOH followed by neutralization to a free carboxylic function and subsequent treatment with Ph_3P and DIAD at 0 °C afforded compound **24** in high yield (80%) and diastereomeric purity (**24**:**9** dr 9:1). Moreover, the decrease of the reaction temperature to −10 °C led to further improvement of the yield (94%) and diasteroselectivity (**24**:**9** dr 97:3). Initially, product **24** was isolated and purified by chromatography. However, during scale-up experiments it was found that **24** could be easily isolated by fractional crystallization from *i*-PrOH in 63–71% yield. Additionally, the crystallization allowed enhancement of the enantiomeric excess of product **24** from 85% ee (the crude compound) to 98% ee, in the case when substrate **9** with 85% ee was used. The correct absolute configuration of the lactone moiety of **24** was confirmed by X-ray analysis (see Supporting Information).

The N–O bond cleavage in **24** was performed as above using TMSCl and KI in wet MeCN to afford aminolactone **25** in 88% yield, which was suitable for the next step without further purification.

Due to a conformational equilibrium of the lactone, location of elements of silanol, probably close to diequatorial, made the E2-type elimination process difficult in **25**. As a solution we explored elimination using Burgess reagent **27**,[30] which proceeded through E1-type elimination. Treatment of **25** with reagent **27** in toluene at 90 °C provided desired unsaturated lactone **28** in good yield (76%). Hydrogenation of the double bond in **28**, performed over PtO_2, proceeded exclusively *anti* to the aryl substituent of the lactone to provide compound **19** (83%, 98% ee) with three stereogenic centers having absolute configurations identical to those in ezetimibe **1**.

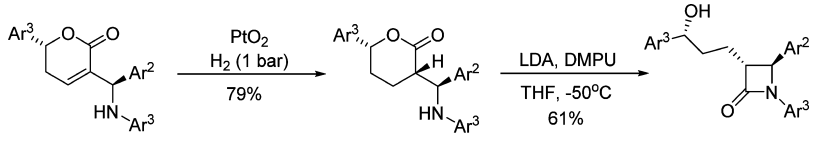
Rearrangement of the six-membered ring into the 2-azetidinone was made, as before, using *t*-BuMgCl according to the standard procedure[15b] and led to product **20** in 80% after extractive workup. The same reaction can also be performed in the presence of LDA or KHMDS.

It should be pointed out that stereoselectivity of hydrogenation of the double bond in **16** and **28** played a secondary role. This was because rearrangement of the six-membered lactone ring into the 2-azetidinone one in the presence of LDA or KHMDS causes epimerization at the stereogenic center next to the carbonyl group to provide, in both cases, exclusively *trans* substituted β-lactams (see Scheme 11).

The final product, ezetimibe (**1**), was obtained by the known debenzylation protocol to provide the product with a very high optical and chemical purity. The structure of the obtained target molecule was confirmed by X-ray analysis (see Supporting Information). The overall yield of **1** was 20%, in 8 steps starting from lactone **7**.

In our opinion, the last presented route is the optimal pathway for the synthesis ezetimibe **1**. In contrast to known syntheses, it did not require chiral auxiliaries for asymmetric induction. In our method, efficient asymmetric induction was provided by the structure of the obtained product through hetero-Diels–Alder reaction, which was the single enantiodifferentiation step for the entire synthetic strategy. All other steps in which formation of new stereocenters or isomerization of existing ones occur were fully controlled by substrate structure

Scheme 11. Synthesis of 21 via Hydrogenolysis/Rearrangement/Epimerization Sequence



16 **23** **21**

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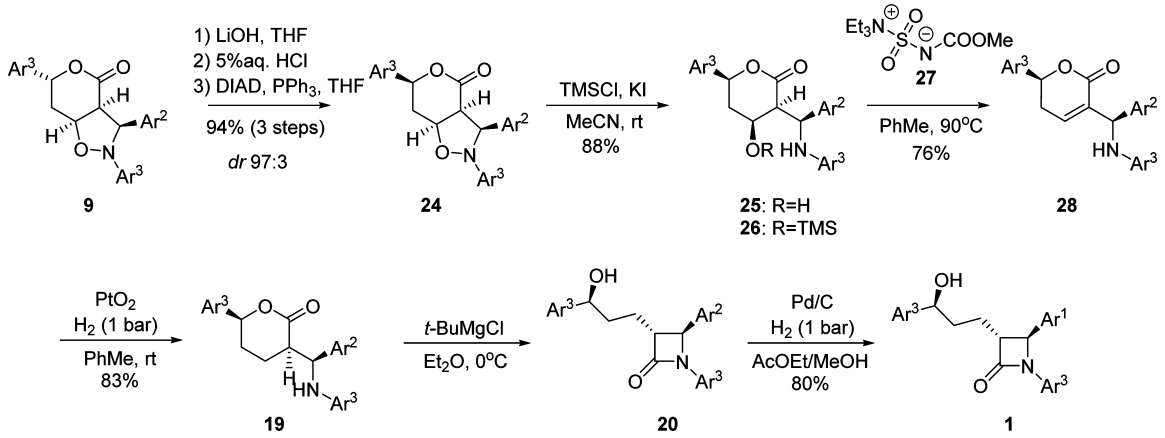
Scheme 12. Synthesis of Ezetimibe 1[a]



[a]Ar^1 = 4-hydroxyphenyl, Ar^2 = 4-benzyloxyphenyl, and Ar^3 = 4-fluorophenyl.

and were completely stereoselective. Additionally the presented reaction sequence did not require chromatographical purification of intermediates but only crystallization at certain steps. Finally, all reactions were performed in an optimal temperature range (mostly at room temperature). These two features are essential when industrial applications of the described synthesis are taken into consideration.

CONCLUSION

We demonstrated a simple, efficient, and stereocontrolled synthesis of ezetimibe (**1**) in which, owing to the rigid transition state of 1,3-dipolar cycloaddition, the absolute configuration of the starting lactone controls the formation of other stereogenic centers of the final molecule. In the optimal reaction sequence epimerization at the benzylic position proceeded effectively at the stage of isoxazolidine via a simple opening and closing of the lactone ring, without any additional protection/deprotection steps. Bearing in mind possible industrial applications, it should be emphasized that purification of intermediates did not require chromatography, and only crystallization at certain steps was sufficient.

EXPERIMENTAL SECTION

(*R*)-2-(4-Fluorophenyl)-2*H*-pyran-4(*3H*)-one (10). Molecular sieves (4 Å, 60 g) were added to a solution of 1.36 g (1% mmol) of [(*R*,*R*)-salen-Cr]BF_4 in MTBE (50 mL), the mixture was cooled to −30 °C, and 4-fluorobenzaldehyde (18.56 g, 200 mmol) was added. Next, Danishefsky's diene (37.84 g, 220 mmol) was added slowly. After 24 h a solution of CF_3COOH (10 mL) in 250 mL of CH_2Cl_2 was added, and the mixture was warmed to room temperature. Molecular sieves were filtered off, and water (10 mL) was added to the residue. After 5 h of stirring, the organic phase was washed with 5% aq $NaHCO_3$ (100 mL) and dried over anhydrous $MgSO_4$. A removal of solvent provided crude product **10** as a yellowish oil (39.91 g 19.4 mmol, 97%, 86% ee (GC)), which was used in the next step. An analytical sample was obtained by chromatography on silica gel (hexanes/AcOEt 4:1 v/v). $[\alpha]^{20}_D$ −83 (*c* 1.1, DCM, ee 91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1 H, dd, *J* 6.0, 0.8 Hz), 7.42−7.37 (2H, m), 7.14−7.08 (2H, m), 5.53 (1H, dd, *J* 6.0, 1.3 Hz), 5.41 (1H, dd, *J* 14.4, 3.5 Hz), 2.89 (1H, dd, *J* 16.8, 14.4 Hz), 2.65 (1H, ddd, *J* 16.8, 3.5, 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 163.9, and 161.9 (d, J_{C-F} 246.6 Hz), 163.0, 133.7, 133.7 (d, J_{C-F} 3.5 Hz), 128.1 and 127.9 (d, J_{C-F} 8.8 Hz), 115.9 and 115.7 (d, J_{C-F} 22.6 Hz), 107.5, 80.4, 43.3; HRMS (EI, TOF) *m*/*z* calcd for $C_{11}H_9FO_2$ [M·+] 192.0586, found 192.0583; IR (film) ν 3073, 1677, 1606, 1594, 1514 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_2$: C 68.75, H 4.72, F 9.89. Found: C 68.71, H 4.69, F 9.83. GC: InertCap CHIRAMIX 160 °C: racemic sample *rac*-**10**: 32.1 min (*S*), 33.2 min (*R*). Assignment was done on the basis of Jacobsen et al. works.[23] Racemic was obtained by reaction of 4-fluorobenzaldehyde with Danishefsky's diene in the presence of $Yb(OTf)_3$. Real sample of **10** (86% ee): 31.8 min (7%, *S*), 32.4 min (93%, *R*). Real sample of **10** after crystallization (91% ee): 32.1 min (4.6%, *S*), 32.4 min (95.4%, *R*).

(2*R*)-2-(4-Fluorophenyl)-3,4-dihydro-2*H*-pyran-4-ol (11). To a mixture of $CeCl_3{\cdot}7H_2O$ (80.74 g, 216.7 mmol) in MeOH (700 mL) was added **10** (38 g, 197.9 mmol) in CH_2Cl_2 (700 mL). After cooling to −20 °C, $NaBH_4$ (8.29 g, 216.7 mmol) was added in portions. After 30 min, reaction was quenched by addition of satd NH_4Cl (150 mL). The reaction mixture was adjusted to room temperature and extracted with CH_2Cl_2 (300 mL). After drying over $MgSO_4$ and removal of a solvent, the crude **11** was used in the next step without further purification. Analytical sample: 91% ee; $[\alpha]^{20}_D$ +60 (*c* 1.0, AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.32 (2H, m), 7.09−7.03 (2H, m), 6.52−6.50 (2H, m), 4,97 (1H, dd, *J* 11.9, 2.1 Hz), 4.87 (1H, dt, *J* 6.2, 2.1 Hz), 4.65−4.58 (1H, m), 2.39−2,33 (1H, m), 2.00−1.92 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 and 161.5 (d, J_{C-F} 246.2 Hz), 145.2, 136.1, and 136.1 (d, J_{C-F} 2.9 Hz), 127.8 and 127.7 (d, J_{C-F} 7.8 Hz), 115.5 and 115.3 (d, J_{C-F} 21.4 Hz), 105.8, 76.2, 63.4, 40.0; HRMS (EI, TOF) *m*/*z* calcd for $C_{11}H_{11}FO_2$ [M] 194.0742, found 194.0748. IR (film) ν 3369, 1642, 1607, 1514 cm^{-1}. Anal. Calcd for $C_{11}H_{11}FO_2$: C 68.03, H 5.71, F 9.78. Found: C 68.15, H 5.52, F 9.87.

(*R*)-6-(4-Fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one (7). To a suspension of **11** (37.8 g, 195 mmol) in 30% H_2O_2 (400 mL) was added MoO_3 (5.57, 39 mmol) in MeCN (400 mL). After 24 h the reaction mixture was diluted with water (600 mL) and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were washed with water (5 × 200 mL, to negative result of peroxides test) and dried over anhydrous Na_2SO_4. Then, to a solution of crude hydroperoxide **12** in CH_2Cl_2 was added pyridine dropwise (70 mL) followed by addition of Ac_2O (73 mL), and the mixsture was stirred at room temperature. After 2 h the reaction mixture was poured into a water/ice mixture, and the organic phase was separated. The organic phase was washed with aq Na_2SO_3 (15 g in 50 mL of H_2O), 5% aq HCl (200 mL), 5% aq $NaHCO_3$, water (2 × 150 mL), and finally brine (250 mL). After drying over anhydrous Na_2SO_4 and removal of solvent, crude lactone **7** (86% ee) was obtained as a slightly brown solid. It was dissolved in hot MTBE (50 mL), and heptane (500 mL) was added. The precipitate was filtered off, washed with heptane, and dried in vacuum to afford lactone **7** as a white solid (19.46 g, 52%, 98% ee). An analytical sample was obtained by chromatography on silica gel (hexane/AcOEt 6:4 v/v). Mp 59−60 °C; $[\alpha]^{20}_D$ +220 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.36 (2H, m), 7.11−7.05 (2H, m), 7.00−6.94 (1H, m), 6.15 (1H, ddd, *J* 9.7, 2.4, 1.2 Hz), 5.43 (1H, dd, *J* 11.4, 4.9), 2.70−2.56 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 and 161.8 (d, J_{C-F} 263.8 Hz), 163.7 144.7, 134.3, and 134.2 (d,

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J_{C-F} 3.4 Hz), 128.0 and 127.9 (d, J_{C-F} 7.9 Hz), 121.7, 115.7, and 115.5 (d, J_{C-F} 21.0 Hz), 78.6, 31.7; HRMS (EI, TOF) *m/z* calcd for $C_{11}H_9FO_2$ [M] 192.0587, found 192.0584; IR (film) ν 3071, 1731, 1605, 1511 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_2$: C 68.75, H 4.72, F 9.89. Found: C 68.69, H 4.74, F 9.84. HPLC: Chiralpak OD-H hexane/*i*-PrOH (96:4 v/v), flow 1.0 mL/min, UV 207 nm:. Racemic sample *rac*-**7**: 37.2.2 min (*R*), 39.4 min (*S*). Real sample of **7** (85% ee): 35.6.0 min (91%, *R*-isomer), 39.8 min (9%, *S*-isomer). Real sample of **7** after crystallization (96% ee): 37.7 min (98%, *R*-isomer), 39.6 (2%, *S*-isomer).

Synthesis of *C*-(4-Benzyloxyphenyl)-*N*-(4-fluorophenyl)-nitrone (8). *Step 1:* To a solution of 4-hydroxybenzaldehyde (122 g, 1 mol) in 600 mL of THF was added benzyl chloride (146 mL, 1.4 mol). Next, K_2CO_3 (240 g, 1.75 mol) and KI (49.5 g, 300 mmol) were added. The suspension was refluxed for 20 h. Next, the mixture was cooled to ambient temperature, and the solid was filtered off and washed with 100 mL of THF. The solvent was removed under diminished pressure. The crude product was crystallized from 700 mL of EtOH to afford 145.3 g of aldehyde. A second crystallization provided additional 23 g of 4-benzyloxybenzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 2 H), 7.07 (d, *J* 8.50, 2 H), 7.42 (m, 5H), 7.83 (d, *J* 8.4, 2 H), 9.87 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 163.4, 135.7, 131.7, 129.8, 128.4, 127.4, 114.9, 69.9; MS (EI, TOF) *m/z* 212 [M^+]; IR (KBr) ν 2849, 2745, 1686, 1600, 1509, 1260, 1165,1019 cm^{-1}. *Step 2:* Zinc dust (39 g, 600 mmol) was added portionwise to the suspension of *p*-fluoronitrobenzene (300 mmol, 31.8 mL) in a solution of NH_4Cl (390 mmol, 20.9 g) in water (600 mL) at 60 °C. When the last portion of zinc was added, the reaction mixture was stirred for an additional 15 min. After filtration of zinc oxide, the residue was saturated with sodium chloride and cooled to 0 °C. After 30 min a yellow precipitate was filtered off, washed with cooled water, and dried in vacuo. The crude 4-fluorophenylhydroxylamine was used directly in the next step. *Step 3:* To the solution of crude 4-fluorophenylhydroxylamine (38.0 g, 300 mmol) in acetone (300 mL) were added *p*-benzyloxybenzaldehyde (63.7 g, 300 mmol) and MsOH (12 droplets) at room temperature. After 2 h the precipitate was filtered off, washed with acetone (3 × 100 mL, and dried in vacuo to afford 57.6 g (60%) of nitrone **8** as a white solid. Mp: 193−195 °C (acetone); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49−8.47 (m, 2H), 8.42 (s, 1H), 7.99−7.95 (m, 2H), 7.50−7.45 (m, 2H), 7.44−7.32 (m, 5H), 7.13 (d, *J* 5.0 Hz, 2H), 5.20 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2 (d, J_{C-F} 245.6 Hz), 159.9, 144.8 (d, J_{CF} 2.4 Hz), 136.6, 133.0, 130.9, 128.4, 127.9, 127.8, 124.1, 123.6 (d, J_{C-F} 9.3 Hz), 115.7 (d, J_{CF} 22.9 Hz), 114.7, 69.4; HRMS (ESI, TOF) *m/z* calcd for $C_{20}H_{16}NO_2FNa$ [M + Na]$^+$ 344.1057, found 344.1055. Anal. Calcd for $C_{20}H_{16}FNO_2$: C, 74.75; H, 5.02; F, 5.91; N, 4.36, found: C, 74.76; H, 5.08; F, 6.03; N, 4.40.

Cycloaddtion between Nitrone 8 and Lactone 7 under Thermal Conditions. A solution of nitrone **8** (321 mg, 1 mmol) and lactone **7** (192 mg, 1 mmol, 98% ee) in toluene (10 mL) was refluxed for 72 h. After cooling to room temperature and removal of solvent, the residue was chromatographed on silica gel (30% AcOEt in hexane) to afford 130 mg of **13** and 60 mg of **9** and (ratio 69:31 overall yield 37%).

(3*S*,3a*S*,6*R*,7a*S*)-3-(4-(Benzyloxy)phenyl)-2,6-bis(4-fluorophenyl)tetrahydro-2*H*-pyrano[3,4-*d*]isoxazol-4(6*H*)-one (9). Mp: 64−66 °C; 98.5% ee; $[\alpha]^{20}_D$ −96 (*c* 1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.49 (2H, m), 7.41−7.30 (5H, m), 7.14−6.97 (10H, m), 5.42 (1H, d, *J* 9.1 Hz), 5.06 (2H, dd, *J* 11.9, 1.4 Hz), 5.04 (2H, s), 4,81 (1H, ddd, *J* 9.1, 3.8, 1.4 Hz), 3.95 (1H, t, *J* 9.1 Hz), 2.30−2.27 (1H, m) 2.10−2.05 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 163.5, and 161.9 (d, J_{C-F} 246 Hz), 159.8 and 158.2 (d, J_{C-F} 242 Hz), 158.7, 145.1, 145.0, 136.7, 133.9, and 133.8 (d, J_{C-F} 2.9 Hz), 128.7, 128.6, and 128.6 (d, J_{C-F} 15.5 Hz), 128.0, 127.9, 127.5, 116.6, 116.5, 116.0, and 115.9 (d, J_{C-F} 22.5 Hz), 115.7 and 115.5 (d, J_{C-F} 21.1 Hz), 114.9, 75.7, 73.5, 71.5, 70.0, 53.2, 34.4; HRMS (ESI, TOF) *m/z* calcd for $C_{31}H_{25}F_2NO_4Na$ [M + Na]$^+$ 536.1644, found 536.1656. Anal. Calcd for $C_{31}H_{25}F_2NO_4$: C 72.50, H 4.91, F 7.40, N 2.73. Found: C 72.74, H 4.93, F 7.61, N 2.51; IR (film) ν 3033, 1729, 1609, 1513, 1501 cm^{-1}.

(3*R*,3a*S*,6*R*,7a*S*)-3-(4-(Benzyloxy)phenyl)-2,6-bis(4-fluorophenyl)tetrahydro-2*H*-pyrano[3,4-*d*]isoxazol-4(6*H*)-one (13). Not isolated in pure form; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.32 (10H, m), 7.24−6.88 (7H, m), 5.76 (1H, dd, *J* 11.4, 1.8 Hz), 5.06 (2H, dd, *J* 11.9, 1.4 Hz), 5.04 (2H, s), 4.89−4.87 (1H, m), 4.34 (1H, d, *J* 7.6 Hz), 3.61 (1H, t, *J* 7.6 Hz), 2.42 (1H, dt, *J* 15.2, 2.4 Hz), 2.21−2.15 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 163.6, and 161.9 (d, J_{C-F} 246.4 Hz), 160.6, 159.1, 159.1, 143.8, 136.7, 134.1, and 134.0 (d, J_{C-F}3.5 Hz), 129.8, 128.8, and 128.6 (d, J_{C-F} 25.4 Hz), 128.0, 127.9, 127.8, 127.5, 120.7, 120.6, 115.8, 115.7, 115.5, 115.4, and 115.3 (d, J_{C-F} 16.2 Hz), 75.9, 74.5, 71.9, 70.6, 56.3, 33.9; HRMS (ESI, TOF) *m/z* calcd for $C_{31}H_{25}F_2NO_4Na$ [M + Na]$^+$ 536.1644, found 536.1650; IR (film) ν 1729 cm^{-1}; HPLC: Chiralpak AD-H hexane/*i*-PrOH (50:50 v/v), flow 0.4 mL/min, UV = 231 nm. Racemic sample *rac*-**13**: 56.1 min (*ent*-**13**) and 82.5 min (**13**).

Cycloaddtion between Nitrone 8 and Lactone 7 under Catalytic Conditions. A mixture of $Sc(OTf)_3$ (180 mg, 0.37 mmol) and MS 4 Å (1.46 g) in dry PhMe (28 mL) was stirred for 30 min at room temperature. Then, solid lactone **7** (0.70 g, 3.66 mmol) and solid nitrone **8** (1.86 g, 5.48 mmol) were added, and reaction mixture was kept at 30 °C for 72 h. Molecular sieves were filtered off, and solvent was removed under diminished pressure. The residue was chromatographed to afford isoxazolidine **9** (dr 97:3, yield 90%, 98.5% ee) was obtained.

Cycloaddtion between Nitrone 8 and Lactone 7 under Catalytic Conditions: Scale-up. The mixture of $Sc(OTf)_3$ (3.48 g, 7 mmol) and MS 4 Å (28 g) in PhMe (300 mL) was stirred for 30 min at room temperature. Then, solid lactone **7** (13.6 g, 70.8 mmol, 85% ee) and solid nitrone **8** (34.2 g, 106.3 mmol) was added and reaction mixture was kept at 30 °C for 72 h. Molecular sieves were filtered off and resulting organic solution was washed with water (250 mL) and dried ($MgSO_4$). After removal of solvent crude isoxazolidine **9** (39 g, dr 97:3, yield 85%, 85% ee) was obtained. Crude **9** was used in the next step without further purification.

(3*S*,4*S*,6*R*,1′*S*)-[(4-Benzyloxyphenyl)-(4-fluorophenylamino)-methyl]-6-(4-fluorophenyl)-4-hydroxy-tetrahydro-2*H*-pyran-2-one (14). To a mixture of the isoxazolidine **9** (1.00 g, 1.94 mmol) and KI (0.97 g, 5.85 mmol) in 20 mL of wet acetonitrile at room temperature was added TMSCl (0.83 mL, 5.85 mmol). After 35 min, 10 mL of saturated aq Na_2SO_4 was added, and then the product was extracted with ethyl acetate. After drying of the resulting organic extracts ($MgSO_4$), the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate 9:1 to 1:1) to provide 0.89 g (1.72 mmol, yield 88%) of aminolactone **14** as a pale yellow solid. Mp 63−65 °C; $[\alpha]_D$ +8,8 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.27 (9H, m), 7,08−6.69 (8H, m), 5.81 (1H, dd, *J* 11.1, 3.6 Hz), 5.42−5,13 (1H, bs), 5,00 (2H, s), 4.72 (1H, d, *J* 2.4 Hz), 4.63−4.62 (1H, m), 2.37 (1H, dt, *J* 14.3, 4.0 Hz,) 2.07−2.00 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 163.4, 161.8, 158.2, 156.6, 141.7, 136.8, 135.1, 131.9, 128.6, 128.3, 128,0, 127.7, 127.6, 127.5, 117.7, 117.6, 115.9, 115.8, 115.7, 115.5, 114.8, 78.3, 70.1, 70.0, 60.5, 53.1, 39.1; HRMS (ESI, TOF) *m/z* calcd for $C_{31}H_{27}F_2NO_4Na$ [M + Na]$^+$ 538.1800, found 538.1810; IR (film) ν 3374, 1727, 1609, 1511 cm^{-1}.

***O*-[(4*S*,6*R*)-3-(4-Benzyloxybenzylidene)-6-(4-fluorophenyl)-tetrahydro-2*H*-pyran-2-on-4-yl]-1*H*-imidazol-1-carbotiol, *E*/*Z* Mixture (15).** A solution of **14** (513 mg, 1 mmol) and of TCDI (178 mg, 1 mmol) was refluxed for 4 h. After cooling, solvent was removed under diminished pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate 7:3) to afford 159 mg (0.3 mmol, yield 30%) of **15** (*E*/*Z* mixture) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (0.4 × H, s) 8.08 (0.6 × H, s), 7.70−7.65 (2H, m), 7.45−7.30 (8H, m), 7.08−7.00 (6H, m), 5.83 (1H, m), 5.11 (2H, s), 5.04 (1H, m), 2.15−2.13 (1H, m), 2.07−2.11 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 164.6, 161.7, 160.8, 147.5, 147.4, 136.2, 135.1, 132.9, 128.7, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 126.4, 123.2, 116.6, 116.5, 115.6, 115.5, 115.4, 75.1, 75.0, 70.1, 62.9, 39.1; IR (KBr) ν 3456, 1693, 1598, 1509, 1172 cm^{-1}.

(1′*R*,6*R*)-3-[(4-Benzyloxyphenyl)-(4-fluorophenylamino)-methyl]-6-(4-fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one (16). A solution of amicolactone **14** (420 mg, 0.82 mmol) and imidazol

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(114.8 mg, 1.64 mmol) in CH_2Cl_2 (20 mL) was treated with TMSCl (295 μL, 2.05 mmol). After 30 min the solid was filtred off, and DBU (245 μL, 1.64 mmol) was added. After 15 min the reaction mixture was portioned between water (10 mL) and CH_2Cl_2 (50 mL). The aqueous phase was additionally washed with CH_2Cl_2 (30 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After removal of drying agent, MeOH (100 mL) was added, and solvents were removed under diminished pressure (350 mbar, 55 °C). Remaining methanolic solution was slowly cooled to an ambient temperature, and the precipitate was collected after 5 h. Yield of **16**, 298 mg (0.60 mmol, 73%) as a colorless crystals. Mp 170−172 °C (MeOH); $[\alpha]_D$ −60.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.31 (9H, m), 7.08−6.79 (8H, m), 6.51−6.47 (2H, m), 5.29 (1H, dd, *J* 12.1, 3.9 Hz), 5.05 (2H, s), 2.73−2.66 (1H, m) 2.67−2.58 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 163.7, 161.7, 158.7, 138.5, 136.8, 134.1, 134.0, 132.7, 128.8, 128.6, 128.1, 128.0, 127.5, 115.8, 115.7, 115.6, 115.5, 115.2, 78.2, 70.1, 57.9, 31.9; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{25}F_2NO_3Na$ $[M + Na]^+$ 520.1695, found 520.1710; IR (film) ν 3395, 1714, 1609, 1509 cm^{-1}.

(1′*S*,3*R*,6*R*)-3-[(4-Benzyloxyphenyl)-(4-fluorophenylamino)-methyl]-6-(4-fluorophenyl)-tetrahydro-2*H*-pyran-2-one (17). A solution of the lactone **16** (480 mg, 0.96 mmol) in dry THF (100 mL) was cooled to −78 °C, and then 0.96 mL (0.96 mmol) of L-Selectride was slowly added. After 2 h the reaction was quenched by addition of aq NH_4Cl (10 mL). Then, the mixture was adjusted to room temperature and alkalized (to pH about 8) with aq $NaHCO_3$. After extraction with ethyl acetate (2 × 30 mL), the organic layer was dried over anhydrous $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel (hexane/ethyl acetate 8:2) to afford 328 mg of **17** (0.66 mmol, yield 68%, white solid) and 52 mg (11%) of lactol **18** and unreacted **16** (47 mg, 9%). Compound **17**: mp 51−53 °C; $[\alpha]_D$ +30 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, C_6D_6) δ 7.25−7,18 (4H, m), 7.19−6.68 (13H, m), 6.46−6.43 (2H, m), 4.88 (1H, d, *J* 5.3 Hz) 4.63 (2H, s), 4.40−4.37 (1H, m), 1.32−1,17 (4H, m) 1.09−1.03 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 163.3, 161.7, 158.6, 137.0, 135.7, 128.8, 128.3, 115.7, 115.5, 115.5, 115.1, 114.9, 96.1, 80.8, 69.7, 59.5, 46,1, 30.6, 22,1; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{27}F_2NO_3Na$ $[M + Na^+]$ 522.1851, found 522.1878; IR (film) ν 3349, 1610, 1512 cm^{-1}. Compound **18** (mixture): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.26 (10H, m), 7.21−7.16 (3H, m), 7.01−6.98 (3H, m), 6.94−6.90 (3H, m), 6.80−6.75 (3H, m), 6.55−6.52 (1H, m), 6.46−6.42 (2H, m), 5.03−4.98 (4.5 × H, m), 4.81 (0.6 × H, d, *J* 8.1 Hz), 4.42−4.36 (1.5 × H, m), 4.22 (0.4 × H, d, *J* 8.1 Hz), 2.15−2.04 (2H, m), 1.89−1.84 (1.4 × H, m), 1.77−1.72 (0.4 × H, m), 1.62−1.44 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$), δ 162.9, 161.3, 158.2, 157.9, 138.2, 136.9, 136.8, 128.6, 128.6, 128.5, 128.0, 127.9, 127.7, 127.6, 127.6, 127.5, 127.4, 116.6, 115.6, 115.5, 115.2, 115.0, 114.9, 114.8, 110.3, 92.8, 77.4, 70.3, 70.1, 70.0, 46.5, 45.6, 34.1, 33.2, 25.7, 22.6; MS (ESI, TOF) *m*/*z* 524.2 $[M + Na]^+$, 540.1 $[M + K]^+$.

(1′*S*,3*R*,6*S*)-3-[(4-Benzyloxyphenyl)-(4-fluorophenylamino)-methyl]-6-(4-fluorophenyl)-tetrahydro-2*H*-pyran-2-ol (19). *Method 1.* To a solution of the lactone **17** (100 mg, 0.2 mmol) in 5 mL of THF were added LiOH (6 mg, 0.22 mmol) and 0.5 mL of water. After 18 h, the solvent was evaporated, and 3 mL of 5% aq HCl was added. Next, the mixture was neutralized with $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 10 mL). After drying of the organic layer with anhydrous Na_2SO_4 and removal of the solvent, the residue (80 mg of a yellowish solid) was dissolved in 10 mL of THF. Next, 50 mg (0.19 mmol) of Ph_3P was added. The reaction mixture was cooled to 0 °C, and then 40 μL (0.19 mmol) of DIAD was added. After 3 h, the solvent was removed, water was added to the obtained residue, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). Then, the organic layer was dried ($MgSO_4$), solvent was removed, and the residue was chromatographed on silica gel (hexane/ethyl acetate 7:3) to afford 74 mg (62%, white solid) of **19** and 20 mg of **17** (**19**/**17** ratio 3.7:1). Compound **19**: mp 52−54 °C; $[\alpha]^{20}_D$ −8.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.28 (8H, m), 7.19−6.68 (6H, m), 6.55−6.52 (2H, m), 5.31 (1H, dd, *J* 10.0, 3.6 Hz) 5.02 (2H, s), 4.66 (1H, d, *J* 6.5 Hz), 3.10−3.06 (1H, m), 2.10−2.03 (1H, m), 1.99−1.90 (1H, m), 1.89−1.78 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 163.3, and 161.7 (d, J_{C-F} 250 Hz), 158.3, 157.0, and 155.4 (d, J_{C-F} 237 Hz), 143.2, 136.8, 134.7, 134.6, 132.6, 128.6, 128.5, 128.0, 127.6, and 127.5 (d, J_{C-F} 13.8 Hz), 127.5, 116.1, 116.0, 115.7, 115.63, and 115.48 (d, J_{C-F} 22.8 Hz), 115.60 and 115.45 (d, J_{C-F} 21.5 Hz), 115.3, 115.2, 114.9, 79.5, 70.1, 58.8, 45.1, 29.3, 20.8. HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{25}F_2NO_3Na$ $[M + Na]^+$ 522.1851, found 522.1864; IR (film) ν 3349, 1610, 1512 cm^{-1}. Anal. Calcd for $C_{31}H_{27}F_2NO_3$: C 74.53, H 5.45, N 2.80, F 7.61. Found: C 74.42, H 5.51, N 2.76, F 7.54.

Method 2. PtO_2 (109 mg) was added to the solution of the lactone **28** (4.80 g, 9.65 mmol) in toluene (100 mL), and the resulting suspension was saturated with hydrogen for 24 h. A filtration through Celite and removal of solvent under diminished pressure provided lactone **19** (4.29 g, 89%) as white solid.

(3*R*,4*S*,3′*R*)-1-(4-Fluorophenyl)-4-(4-hydroxyphenyl)-3-[3′-(4-fluorophenyl)-3′-hydroxy-propyl]-azetidin-2-one (21). *Method 1.* To a cooled (0 °C) solution of the lactone **17** (100 mg, 0.2 mmol) in 8 mL of dry diethyl ether was added 100 μL (0.4 mmol) of a 2 M solution of *t*-BuMgCl in Et_2O. After 15 min 3 mL of aq NH_4Cl was added. The aqueous layer was extracted with ether (10 mL), then the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate 7:3) to afford 81 mg (0,16 mmol, yield 80%) of **21** as a white solid. Mp 129−132 °C $[\alpha]_D$ +10.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.20 (11H, m), 7.02−6.90 (6H, m), 5.04 (2H, s), 4.72−4.68 (1H, m) 4.55 (1H, d *J* 2.2 Hz), 4.55 (1H, dt *J* 7.1, 2.2 Hz) 2.05−1.93 (3H, m) 1.89−1.82 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 163.0, 161.4, 159.8, 159.0, 158.1, 140.0, 139.9, 136.6, 133.9, 129.6, 128.6, 128,1, 127.5, 127.4, 127.4, 127.2, 118.4, 118.3, 115.8, 115.7, 115.5, 115.4, 115.3, 73.3, 70,1, 61,1, 60.3, 36.5, 25,0; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{27}F_2NO_3Na$ $[M + Na]^+$; 522.1851, found 522.1870; IR (KBr) ν 3441, 1743, 1609, 1510 cm^{-1}.

Method 2. A solution of the lactone **23** (350 mg, 0.7 mmol) and DMPU (4 mL) in 10 mL of dry THF mL was cooled to −50 °C, and 1 mL of a 0.7 M solution of LDA in THF was added. After 15 min solution was warmed to −20 °C. After 3 h aq NH_4Cl (5 mL) was added. The aqueous layer was extracted with ether (60 mL). Organic phase was washed with satd $NaHCO_3$ (50 mL) and dried ($MgSO_4$), and the solvent was removed under diminished pressure. The residue was chromatographed on silica gel (hexanes/AcOEt 7:3) to afford 213 mg (61%) of **21**.

(3*S*,6*RL*)-3-(*S*)-(4-Benzyloxyphenyl)-(4-fluorophenyl)amino-methyl-6-(4-fluorophenyl)-tetrahydro-2*H*-piran-2-one (23). PtO_2 (2 mg, 5 mol %) was added to the solution of the lactone **16** (100 mg, 0.2 mmol) in toluene (5 mL), and the resulting suspension was saturated with hydrogen for 24 h. A filtration through Celite and removal of solvent under diminished pressure provided lactone **23** (79 mg, 79%) as white solid. An analytical sample was obtained by chromatography on silica gel (hexane/AcOEt 4:1). Mp 65 °C; $[\alpha]_D$ +14.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.28 (8H, m), 7.19−6.65 (6H, m), 6.65 (2H, bs), 5.39 (1H, dd, *J* 7.3, 4.4 Hz), 5.02 (2H, s), 4.61 (1H, d, *J* 3.7 Hz), 3.40 (1H, bs), 2.13−2.08 (1H, m), 1.99−1.90 (1H, m), 1.81−1.70 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 158.7, 136.7, 134.7, 129.4, 128.6, 128.1, 127.5, 127.3, 127.2, 115.8, 115.6, 115.5, 115.3, 115.0, 79.7, 70.1, 44.5, 30.9, 29.6, 19.8; HRMS (EI, TOF) *m*/*z* calcd for $C_{31}H_{27}F_2NO_3$ [M] 499.1959, found 499.1938; IR (film) ν 3384, 1609, 1510 cm^{-1}.

(3*S*,3a*S*,6*S*,7a*S*)-3-(4-(Benzyloxy)phenyl)-2,6-bis(4-fluorophenyl)tetrahydro-2*H*-pyrano[3,4-*d*]isoxazol-4(6*H*)-one (24). To a solution of isoxazolidine **9** (150 mg, 0.29 mmol) in 5 mL THF were added LiOH·H_2O (7 mg, 0.30 mmol) and 0.5 mL of water. After 18 h, the solvent was removed, 3 mL of 5% aq HCl was added, and then the mixture was neutralized with aq $NaHCO_3$. Subsequently, the mixture was extracted with methylene chloride (3 × 10 mL). The combined organic solutions were dried (Na_2SO_4). Removal of solvent provided 114 mg of pale yellow solid, which was dissolved in 10 mL of THF. Then 56 mg (0.21 mmol) of PPh_3 was added, and the obtained mixture was cooled to 0 °C. Next, 45 μL (0.21 mmol) of DIAD was added. After 3 h, the solvent was removed, water was added to the obtained residue, and the mixture was extracted three times with

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CH_2Cl_2. After drying ($MgSO_4$), solvent was removed, and the residue was chromatographed on silica gel (hexane/AcOEt 7:3) to provide 94 mg (0.18 mmol, 62%) of isoxazolidine **24** as a white solid; mp 152−154 °C; $[\alpha]^{20}_D$ −111 (*c* 1.84, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.49 (2H, m), 7.41−7.30 (5H, m), 7.14−6.97 (10H, m), 5.23 (1H, d, *J* 8.2 Hz), 5.09 (2H, dd, *J* 12.6, 2.1 Hz), 5.06 (2H, s), 4.81 (1H, m), 3.80 (1H, dt, *J* 9.6, 8.4 Hz), 2.37 (1H, ddd, *J* 13.9, 6.2, 2.1 Hz) 1.97−1.90 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 163.6, and 161.9 (d, J_{C-F} 248 Hz),159.9 and 158.3 (d, J_{C-F} 245 Hz), 158.5, 146.3, 146.3, 136.8, 133.9, and 133.8 (d, J_{C-F} 3.5 Hz), 129.5, 128.9, 128.6, 128.0, and 127.9 (*d*, J_{C-F} 8.7 Hz), 127.5, 116.9, 116.8, 115.8, and 115.66 (d, J_{C-F} 22.6 Hz), 115.72 and 115.6 (d, J_{C-F} 21.9 Hz), 114.7, 77.5, 73.2, 71.5, 70.0, 50.5, 35.7; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{25}F_2NO_4Na$ $[M + Na]^+$ 536.1644, found 536.1631. Anal. Calcd for $C_{31}H_{25}F_2NO_4$: C 72.50, H 4.91, F 7.40, N 2.73. Found: C 72.01, H 5.00, F 7.36, N 2.63.

Large Scale Synthesis of 24. Crude **9** (39 g, 57 mmol, 85% ee) was dissolved in 400 mL of THF and treated with $LiOH·H_2O$ (4.9 g, 117 mmol) and water (10 mL). After 18 h solvent was removed. The residue was treated with 5% aq HCl (30 mL), extracted with 300 mL AcOEt, and washed with water (20 mL with 200 mg $NaHCO_3$). The combined organic phases were dried over anhydrous Na_2SO_4. After removal of AcOEt, the residue was dissolved in 500 mL of THF, PPh_3 was added (18.34 g, 70 mmol), and the mixture was cooled to −10 °C. Then, DIAD (14.15 g, 70 mmol) was added slowly. After 3 h, 500 mL of wet *i*-PrOH was added, and THF was removed under diminished pressure (550 mbar) at 55 °C. The obtained mixture was left for 16 h at room temperature. The precipitation was collected, washed with cold *i*-PrOH (10 °C, ∼100 mL), and dried to afford 19.39 g of isoxazolidine **24** (62%, >99% ee, dr 98:2) as a off-white solid.

(3*S*,4*S*,6*S*)-3-((*S*)-(4-(Benzyloxy)phenyl)(4-fluorophenylamino)methyl)-6-(4-fluorophenyl)-4-hydroxytetrahydro-2*H*-pyran-2-one (26). To the mixture of the isoxazolidine **24** (13.0 g, 25.3 mmol) and KI (12.6 g, 75.9 mmol) in 200 mL of acetonitrile at room temperature were added TMSCl (10.9 mL, 75.9 mmol) and water (1 mL). After 35 min, 50 mL of saturated aq Na_2SO_4 was added, and then the product was extracted with AcOEt. After drying of resulting organic extracts ($MgSO_4$), the solvent was removed under reduced pressure to afford amino alcohol **25** as a pale yellow solid (11.46 g, 88%), which was used in the next step without further purification. Mp 69 °C; $[\alpha]^{20}_D$ −23.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.29 (9H, m), 7.09−7.03 (2H, m), 6.95−6.72 (6H, m), 5.18 (1H, dd, *J* 11.9, 4.7 Hz), 5.00 (2H, s), 4.86 (1H, d *J* 3.0 Hz), 4.80−4.73 (1H, m), 3.17 (1H, bs), 2.68−2.59 (1H, m) 2.11−2.02 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 163.8, and 161.8 (d, J_{C-F} 246.1 Hz), 158.4, 136.8, 133.7, and 133.6 (d, J_{C-F} 3.0 Hz), 128.7, 128.6, 128.3, 128.2, and 128.0 (d, J_{C-F} 23.8 Hz), 127.5, 118.1, 115.9, and 115.77 (d, *J* 22.1 Hz), 115.78 and 115.6 (d, J_{C-F} 21.6 Hz), 115.1, 115.0, 70.0, 68.9, 60.1, 50.9, 40.6; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{27}F_2NO_4Na$ $[M + Na]^+$ 538.1800, found 538.1810; IR (film) ν 3374, 1727, 1609, 1511, 1454, 1230 cm^{-1}. Anal. Calcd for $C_{31}H_{27}F_2NO_4$: C 72.22, H 5.28, F 7.37, N 2.72. Found: C 72.30, H 5.22, N 2.70, F 7.34.

(6*S*)-3-((*R*)-(4-(Benzyloxy)phenyl)(4-fluorophenylamino)-methyl)-6-(4-fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one (28). To a solution of **26** (11.46 g, 22.2 mmol) in dry PhMe (100 mL) was added Burgess reagent **27** (5.81 g, 24.4 mmol), and the mixture was kept at 90 °C for 18 h. After the mixture cooled to room temperature, water (100 mL) was added and extracted with AcOEt (2 × 200 mL). After drying over $MgSO_4$, organic solution was reduced to 20% of starting volume and filtered through silica gel pad, which was subsequently washed with Et_2O. Removal of solvent provided unsaturated lactone **28** (8.16 g, 76%) as an off-white solid. Mp 61 °C; $[\alpha]^{20}_D$ +40.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−7.27 (11H, m), 7.05−6.84 (7H, m), 6.55−6.50 (2H, m), 5.44−5.38 (1H, m), 5.30 (1H, s), 5.04 (2H, s), 2.70−2.67 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 163.5, and 161.8 (d, J_{C-F} 246 Hz), 158.4, 156.9, and 155.4 (d, J_{C-F} 235 Hz), 142.8, 139.6, 136.9, 134.2, and 134.1 (d, J_{C-F} 3.5 Hz), 133.4, 132.4, 132.4, 128.8, 128.6, 128.4, 128.0, 127.9, 129.8, 127.5, 115.8, and 115.61 (d, J_{C-F} 22.2 Hz), 115.65 and 115.5 (d, J_{C-F} 21.9 Hz), 115.2, 115.0, 114.7, 114.6, 78.1, 70.1, 58.4, 31.5, 26.9; HRMS (EI, TOF) *m*/*z* calcd for $C_{31}H_{25}F_2NO_3$ [M] 497.1803, found 497.1824; IR (film) ν 3383, 1714, 1608, 1509 cm^{-1}. Anal. Calcd for $C_{31}H_{25}F_2NO_3$: C 74.84, H 5.06, N 2.82, F 7.64. Found: C 74.93, H 5.11, N 2.78, F 7.61.

(3*S*,4*S*)-4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3′-hydroxypropyl)azetidin-2-one (20). *Method 1.* To a cooled (0 °C) solution of lactone **19** (2.0 g, 4 mmol) in 160 mL of dry diethyl ether was added 12 mL of 1 M solution of *t*-BuMgCl in diethyl ether. After 2 h, 30 mL of aq NH_4Cl was added. The aqueous layer was extracted with ether (160 mL), the organic layer was washed with satd $NaHCO_3$ (50 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Crude product **20** (1.64 g, 82%) obtained as a yellowish solid was used in the next step without further purification. An analytic sample was obtained by chromatography on silica gel (hexanes/ethyl acetate 7:3). Mp 130−133 °C [lit.[11] 132−134 °C]; $[\alpha]^{20}_D$ −42.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.20 (11H, m), 7.02−6.90 (6H, m), 5,04 (2H, s), 4.72−4.68 (1H, m), 4.55 (1H, d *J* 2.2 Hz), 3.07 (1H, dt *J* 7.1, 2.2 Hz), 2.05−1.93 (3H, m) 1.89−1.82 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 163.0, and 161.4 (d, J_{C-F} 244.2 Hz), 159.8 and 158.1 (d, J_{C-F} 241.8 Hz), 159.0, 140.0, 139.9, 136.6, 133.9, and 133.8 (d, J_{C-F} 2.9 Hz), 129.6, 128.6, 128.1, 127.5, 127.4 and 127.4, (d, J_{C-F} 8.0 Hz), 127.2, 118.4, 118.3, 115.8, 115.8, and 115.7 (d, J_{C-F} 22.0 Hz), 115.5, 115.4, and 115.3 (d, J_{C-F} 21.3 Hz), 73.3, 70.1, 61.1, 60.3, 36.5, 25.0; HRMS (ESI, TOF) *m*/*z* calcd for $C_{31}H_{27}F_2NO_3Na$ $[M + Na]^+$ 522.1851, found 522.1862; IR (KBr) ν 3441, 1743, 1609, 1510 cm^{-1}. Anal. Calcd for $C_{31}H_{27}F_2NO_3$: C 74.53, H 5.45, N 2.80, F 7.61. Found: C 74.40, H 5.53, N 2.74, F 7.56.

Method 2. PPh_3 (58 mg, 0.22 mmol) was added to a cooled (0 °C) solution of 2-azetidionone **21** (100 mg, 0.2 mmol) and *p*-nitrobenzoic acid (37 mg, 0.22 mmol) in 10 mL of THF. Next, DIAD (40 μL, 0.22 mmol) was added. After 3 h solvent was removed, and the residue was chromatographed (hexane to hexane/ethyl acetate 8:2) to afford 101 mg (0.16 mmol, yield 78%) of **22** as a low-melting white solid. $[\alpha]^{20}_D$ +8.6 (*c* 0.49, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29−8.17 (4H, m) 7.43−7.31 (7H, m), 7.23−7.19 (4H, m), 7.05−7.01 (2H, m), 6.98−6.88 (4H, m), 5.96 (1H, t *J* 6.9 Hz), 5.04 (2H, s), 4.54 (1H, d *J* 2.3 Hz), 3.10 (1H, dt, *J* 7.7, 2.3 Hz), 2.25−2.19 (2H, m); 1.98−1.86 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 163.6, 159.1, 150.6, 136.6, 135.3, 133.7, 130.7, 129.4, 128.6, 128.4, 128.3, 128.1, 127.4, 127.1, 123.6, 118.4, 118.3, 115.9, 115.8, 115.7, 115.7, 115.6, 76.6, 70.1, 60.9, 59.9, 33.5, 24.9; HRMS (ESI, TOF) *m*/*z* calcd for $C_{38}H_{30}F_2N_2O_6Na$ $[M + Na]^+$ 671.1964, found 671.1976; IR (KBr) ν 1747, 1725, 1608, 1528, 1509, 1270. To a solution of **22** (20 mg, 0.03 mmol) in 4 mL of MeOH was added 5 mg of K_2CO_3. After 30 min, 30 mL of EtOAc was added and 20 mL of water. Organic layer was separated and dried over $MgSO_4$. After removal of solvent the residue was chromatographed on silica gel (hexanes/AcOEt 6:4) to afford 13 mg of **20** (84%).

Ezetimibe (1). 2-Azetidinone **20** (1.64 g, 3.3 mmol) was dissolved in a mixture of AcOEt/MeOH (1:1, 100 mL), and 20 mg of 10% Pd/C was added. The mixture was saturated with hydrogen for 18 h. After filtration through Celite and silica, solvent was removed. Crude **1** was dissolved in hot MTBE (10 mL), and hexane (3 mL) was added. Collected solid was dissolved in hot methanol (10 mL), and water (1 mL) was added to provide (after drying) ezetimibe **1** (1.08 g, 80%) as a white solid. Mp 164−166 °C [lit.[11] 155−157 °C]; 99% ee; $[\alpha]^{20}_D$ −28.1 (*c* 0.15, MeOH) [lit.[11] −32.6 (*c* 0.34, MeOH)]; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.49 (1H, s), 7.28−7.24 (2H, m), 7.19−7.16 (4H, m), 7.11−7.07 (4H, m), 6.75−6.71 (2H, m), 5.25 (1H, d, *J* 4.3 Hz), 4.77 (1H, d, *J* 2.2 Hz), 4.49−4.59 (1H, m), 3.07−3.04 (1H, m) 1.84−1.66 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 162.3, and 160.7 (d, J_{C-F} 240.3 Hz), 159.3, 157.9, 157.7, 142.5, 134.4, 128.7, 128.3, 128.0, 127.9, 118.7, and 118.6 (d, J_{C-F} 8.1 Hz), 116.3, 116.2, 115.2, and 115.0 (d, J_{C-F} 20.7 Hz), 71.5, 60.0, 59.9, 36.8, 24.9; HRMS (EI, TOF) *m*/*z* calcd for $C_{24}H_{21}F_2NO_3$ [M] 409.1489 found 409.1478. Anal. Calcd for $C_{24}H_{21}F_2NO_3$: C 70.41, H 5.17, F 9.28, N 3.42. Found: C 70.46, H 5.23, F 9.24, N 3.34.

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■ ASSOCIATED CONTENT

Supporting Information

GC and/or HPLC analysis of **1**, 7, **9**, **10**, and **24**; copies of ^{1}H and ^{13}C NMR spectra; CIF files for **1**, **16**, and **24**. This material is available free of change via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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