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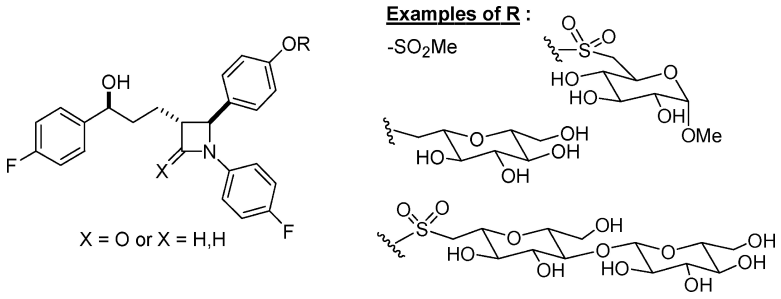

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Synthesis and in Vitro Evaluation of Inhibitors of Intestinal Cholesterol Absorption

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We have utilized our recently developed in vitro assay to address two key questions in the design of small-molecule cholesterol absorption inhibitors using ezetimibe, the only drug yet approved for the inhibition of cholesterol absorption in the small intestine, as a starting point: (1) the role of glycosylation and (2) the importance of the β-lactam scaffold of ezetimibe for inhibitory activity. A wide range of nonhydrolyzable phenolic glycosides of ezetimibe were synthesized and demonstrated to be active inhibitors of cholesterol absorption using the brush border membrane vesicle assay. The analogous azetidines provided access to a variety of inhibitors in vitro, suggesting that the β-lactam of ezetimibe merely serves as a ring scaffold to appropriately position the required substituents. Our findings highlight several promising strategies for the design of alternative small-molecule cholesterol absorption inhibitors that could ultimately be useful in preventing cardiovascular disease by lowering blood cholesterol levels.

Introduction

High blood-cholesterol levels constitute a major risk factor for cardiovascular disease,[1,2] the leading cause of death in the Western industrialized world.[3] The total blood cholesterol level is primarily regulated by two complementary mechanisms: (1) cholesterol biosynthesis in the liver and (2) absorption of dietary cholesterol in the small intestine.[4,5] Since their introduction in the late 1980s, statins have by far become the predominant class of current lipid-lowering drugs (96% of total sales in 2001).[6] Statins inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step of cholesterol biosynthesis in the liver.[2,7] However, the patient response to statins varies greatly, with half of all patients on statin therapies failing to reach their cholesterol goals.[2,8] Ezetimibe (**1**, Figure 1), which was approved in late 2002 for use either alone and in combination with a statin, is the only example to date of a drug that involves inhibition of intestinal cholesterol absorption.[9−11]

The discovery and development of ezetimibe is an interesting story, as the β-lactam scaffold was investigated within a program aimed at identifying cholesterol acylCoA:acyltransferase (ACAT) inhibitors. ACAT is the enzyme in the enterocytes that is responsible for esterifying cholesterol before its assembly into chylomicrons. However, in the initial studies no correlation between the high in vivo activity and the in vitro inhibition of ACAT was observed. Further experimentation led to the conclusion that these β-lactams inhibit intestinal cholesterol absorption by a unique mechanism that is upstream or preceding ACAT's site of action.[10,12,13] The unknown protein target nevertheless elicited consistent

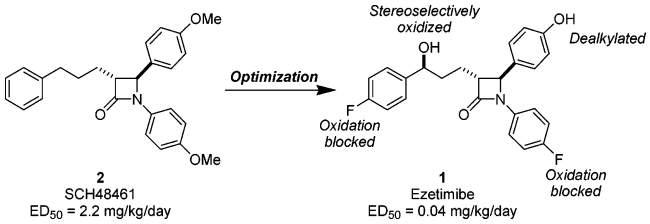

Figure 1. Development of ezetimibe (**1**) from SCH48461 (**2**).

structure−activity relationships,[11,13−15] and the optimization of the inhibitory activity was consequently accomplished by relying solely on a 7-day cholesterol-fed hamster model[14,16] as a screen for active compounds. It is important to note that in such an in vivo optimization process, the intrinsic activity of a compound is indistinguishable from differences in bioavailability and/or ease of conversion into active metabolites,[13,17] making it a very challenging medicinal chemistry effort.[10] In 1994, the β-lactam SCH48461 (**2**, Figure 1) was reported to effect remarkable reduction in liver cholesterol ester (LCE) in the 7-day cholesterol-fed hamster model (LCE ED_{50} 2.2 mg/kg/day).[14] By a combination of isolation of highly active metabolites of SCH48461 (**2**)[18] and the sites of metabolism through an extensive synthesis effort, this original lead structure was optimized as summarized in Figure 1 into SCH58235 (**1**),[11] which later came to be known as ezetimibe. Compared to SCH48461 (**2**), ezetimibe (**1**) showed a 50-fold increase in activity in hamsters (ED_{50} 0.04 mg/kg/day)[11] and as much as a 400-fold increase (ED_{50} 0.0005 mg/kg/day)[19] in the cholesterol-fed rhesus monkey.[18]

The process of cholesterol absorption in the small intestine was traditionally viewed as exclusively proceeding via passive diffusion. This paradigm has been negated by more recent evidence, such as the existence of highly efficacious small-molecule cholesterol absorption inhibitors, which strongly suggests cholesterol absorption to be protein-mediated.[5,10,20−23] The identity

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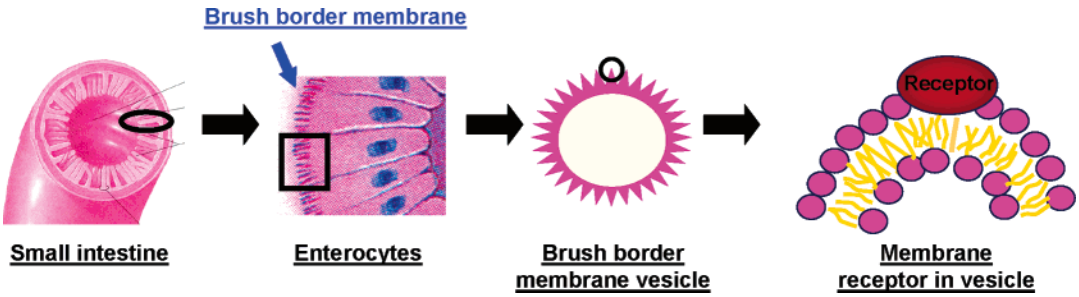


Figure 2. Schematic outline of the preparation of brush border membrane vesicles

of the intestinal proteins effecting cholesterol absorption is still a matter of active debate. A number of proteins have been suggested to be involved in cholesterol transport in the small intestine, including the scavenger receptors SR-BI[21,22,24,25] and CD36,[21,24,26] an annexin 2/caveolin 1 complex,[27] and most recently Niemann–Pick C1-like 1 (NPC1L1) protein.[28–30]

Ezetimibe (**1**) inhibits intestinal cholesterol absorption by a mechanism that is currently not fully elucidated at a molecular level.[10,28] NPC1L1 knock-out (−/−) mice showed significantly lowered cholesterol uptake compared to wild-type mice, and no further reduction of cholesterol absorption was observed when NPC1L1 knock-out (−/−) mice were treated with ezetimibe. These observations led to the suggestion of NPC1L1 as the molecular target of ezetimibe. However, reconstitution of cholesterol uptake into cells overexpressing NPC1L1 was unsuccessful, suggesting the involvement of additional proteins in intestinal cholesterol absorption.[28,29] More recently, the development of an in vitro binding assay using a number of ezetimibe analogues further strongly indicated NPC1L1 to be critically involved. Thus, these ezetimibe analogues were shown to bind to the brush border membranes of several species and to cells expressing NPC1L1 with virtually identical binding affinities. In contrast, no binding was observed to the brush border membrane of NPC1L1 knock-out mice.[30] However, the direct binding of ezetimibe analogues to NPC1L1 using radiolabeled and fluorescent analogues remains elusive.[28] In a recent intriguing finding, it was alternatively suggested that NPC1L1 is not located on the brush border membrane but inside the enterocyte.[31] This latter finding highlights the complexity of intestinal cholesterol absorption, indicating a multistep process that presumably involves a number of proteins. In independent recent investigations using photoreactive ezetimibe analogues,[32] ezetimibe was demonstrated to interact with aminopeptidase N (CD13) on the enterocyte brush border membrane. However, aminopeptidase N, which is also involved in the uptake of viruses, does not mediate cholesterol absorption, and it remains to be established whether aminopeptidase N is a vital molecular target of ezetimibe.[33]

Given our expertise with brush border membrane vesicles as an in vitro model to mimic intestinal cholesterol uptake,[22–24,34,35] we initiated a program aimed at the development of an in vitro screening assay for evaluating small-molecule inhibitors of cholesterol uptake.[36,37] An important advantage of using brush border membrane vesicles is their ready preparation from animal or human whole small intestine, leaving the relevant membrane receptors intact (Figure 2).[23,38]

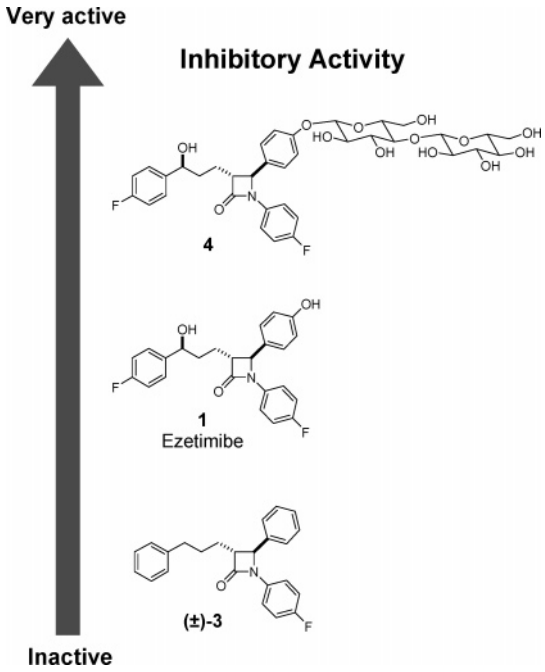


Figure 3. Relative correlation of inhibitory activities in vitro[36] and in vivo.[13,17]

Consequently, cholesterol uptake into such vesicles takes place regardless of the actual identity of the proteins involved in intestinal cholesterol uptake. We have successfully validated our brush border membrane vesicle assay by correlation of the relative inhibitory activities of a number of known ezetimibe analogues for which the corresponding in vivo data were available (Figure 3).[36] We now report a full account of our findings using this in vitro assay to evaluate a number of novel small molecules as potential inhibitors of cholesterol absorption. These new inhibitors can be divided into two general compound classes: (1) ezetimibe derivatives in which the phenol is conjugated to various carbohydrates or derivatized with simple substituents and (2) analogues of ezetimibe with the β-lactam of ezetimibe replaced by the corresponding azetidine. These structure–activity-driven investigations have resulted in a number of tangible results of immediate relevance to understanding ezetimibe's mode of action and, additionally, may lead to potentially wider application.

Results and Discussion

A number of phenolic *O*-glycosides of ezetimibe (**1**) such as the cellobioside **4** (Figure 3) display similar or increased activity profiles both in vivo[17,39] and in vitro.[36] Furthermore, ezetimibe has been shown to undergo metabolism in the intestine within 1 min into its

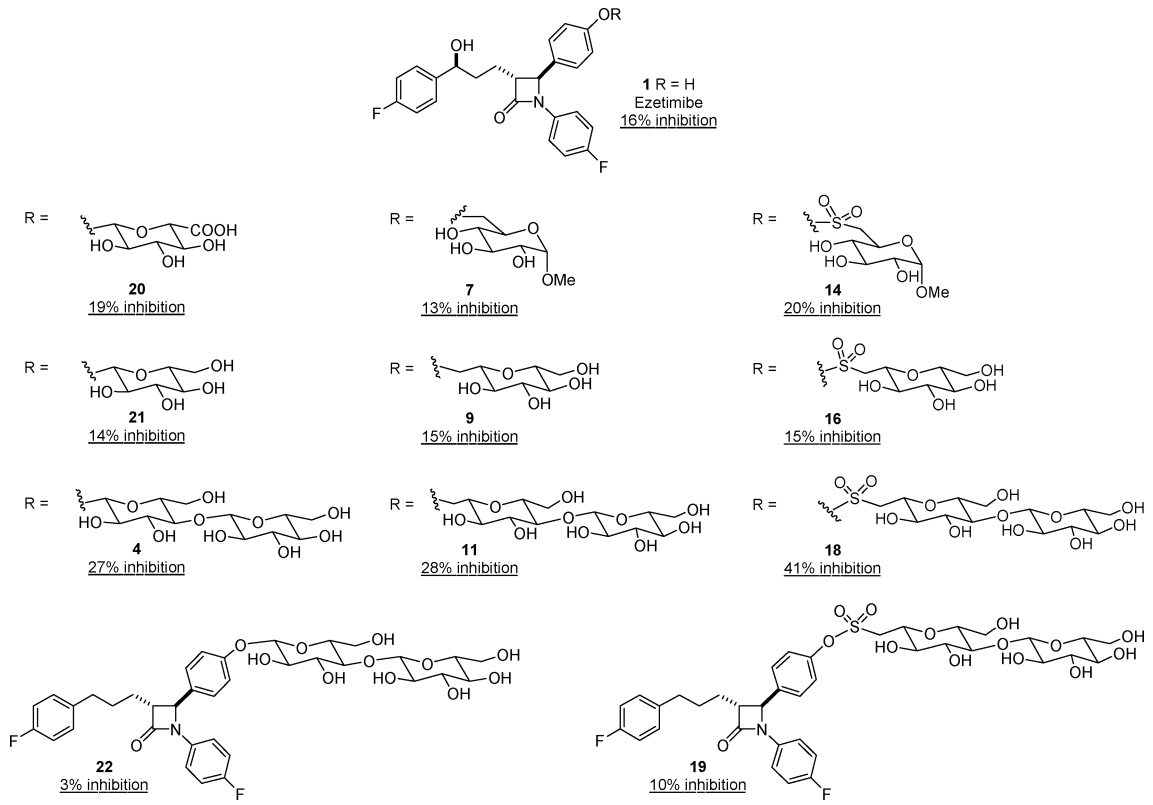


Figure 4. Inhibition in the brush border membrane vesicle assay (%) using rabbit small intestine at nominal concentrations of 6 μM. Average standard deviations were ±3% inhibition.

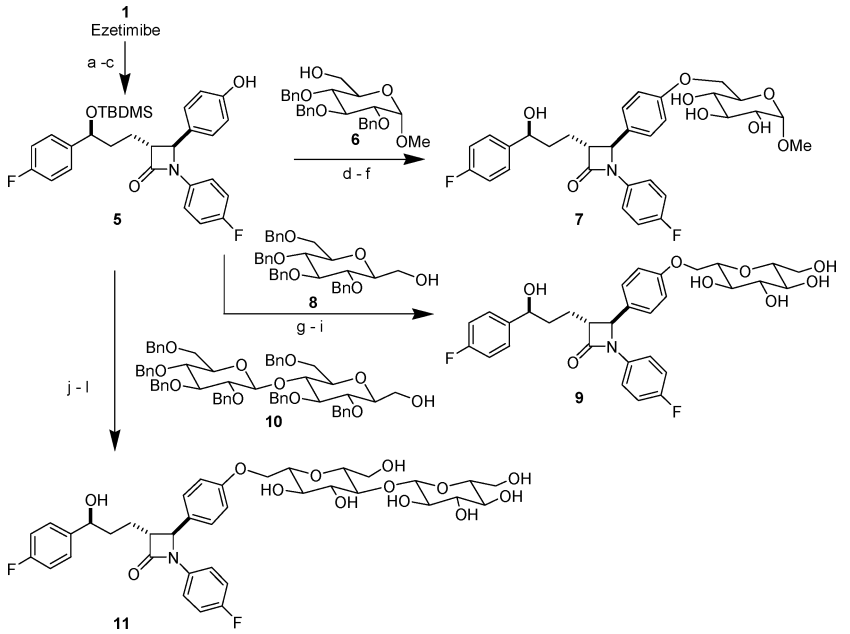
glucuronide derivative **20** (Figure 4) before entering the portal plasma.[39] Due to enterohepatic cholesterol recycling,[4,5] the glucuronide **20** is transported in bile back to the small intestine, where it repeatedly exerts its mode of action.[39] The exact nature of the active species, i.e. whether ezetimibe (**1**), its glucuronide **20**, or both are active as cholesterol absorption inhibitors, remains however elusive. We were intrigued by the role of this phenolic glycosylation with respect to inhibitory activity. To rule out rapid metabolic hydrolysis of the glycosidic bond, we synthesized the structurally closely related glycosides **7**, **9**, and **11** with nonhydrolyzable ether linkages (Scheme 1).[36,40,41] In the synthetic sequence we developed, the phenol of ezetimibe (**1**)[42] was transiently protected as the acetate ester by treatment with Ac_2O and NaOH in *i*PrOH[43] (97% yield), following silylation of the secondary alcohol (91% yield). A number of reaction conditions were investigated for the subsequent deacetylation of the phenol. Adsorption of the phenol acetate on neutral alumina and thermal heating to 70 °C[44] for 5 h gave phenol **5** in 83% yield. This protocol was shown to be superior to KCN/MeOH,[45] $NaHCO_3$/MeOH,[46] Et_3N/MeOH/H_2O,[17] and adsorption on neutral alumina and heating (3 min) under microwave irradiation.[44] In the course of these studies we observed that the secondary silyl ether was prone to elimination under a variety of different basic reaction conditions. Consequently, this base-sensitivity of the protected ezetimibe derivative governed the strategy for the subsequent introduction of the C-glycoside subunits in the desired targets.

Reaction of the free phenol with primary alcohols under the standard Mitsunobu conditions (DEAD, Ph_3P) for the construction of the ether bond did not afford any conversion. However, the use of the 1,1′-(azodicarbonyl)-dipiperidine/Bu_3P combination[41,47] effected conversion of the starting materials. Although the yields obtained were unsatisfactory (~20%), enough material could be obtained to allow testing of these compounds. The source of the modest yields was due to a predominant side reaction involving opening of the β-lactam ring by the hydrazide anion generated in the course of the reaction, highlighting the susceptibility of β-lactams with this substituent pattern to nucleophilic opening. In the subsequent deprotections, hydrogenolysis of the benzyl ethers was performed prior to the desilylation to furnish the ether-linked glycosides **7**, **9**, and **11** in good yields.

Following the synthesis of the C-glycosides, we then sought to examine an alternative, novel conjugation strategy, which would allow the use of mild conditions compatible with the base-sensitive core molecule. In developing such a conjugation strategy, it was important to identify a method for introduction of the carbohydrates that would obviate issues relating to reactivity and diastereoselectivity associated with traditional glycosylation methods.[51] We decided to examine the use of carbohydrate-derived sulfonyl chlorides, because a conjugation strategy based on sulfonate ester formation with a phenol would meet both stated requirements.[37] Related precedence for the use of a sulfonylation reaction was reported in the preparation of sulfonate-linked oligonucleotides[52,53] while, to the best of our knowledge, there have been no previous reports describing conjugation to simple carbohydrates.[54]

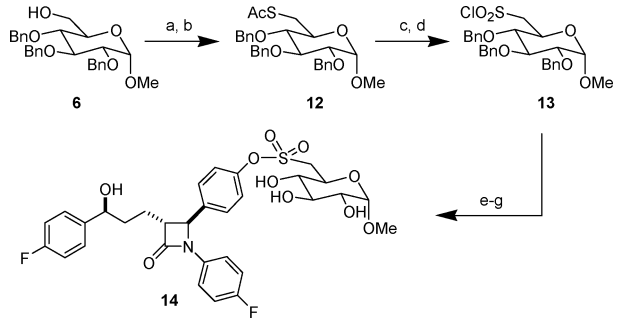
Sulfonylated carbohydrate derivatives **14**, **16**, and **18** (Schemes 2 and 3)[37] were assembled following a straightforward sequence of reactions. It is worth noting that the selection of these carbohydrates was based on our desire to introduce a minimum of structural modifications on the candidates for study, apart from the

Scheme 1[a]



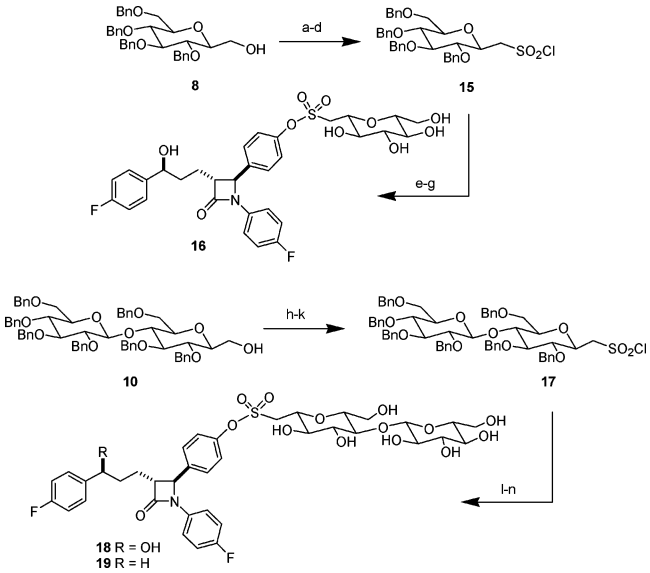
[a] (a) **1**,[42] Ac_2O, NaOH, *i*PrOH, 97%; (b) TBDMSCl, imid, DMF, 91%; (c) Al_2O_3 (neutral), 70 °C, 83%; (d) **6**,[48] 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 21%; (e) H_2, $Pd(OH)_2$/C, EtOAc/EtOH, 87%; (f) HF·pyridine, pyridine, THF, 86%; (g) **8**,[49] 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF, 21%; (h) H_2, $Pd(OH)_2$/C, EtOAc/EtOH, 59%; (i) HF·pyridine, pyridine, THF, 62%; (j) **10**,[50] 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF; (k) H_2, $Pd(OH)_2$/C, EtOAc/EtOH, 21%, two steps; (l) HF·pyridine, pyridine, THF, 65%.

Scheme 2[a]



[a] (a) MsCl, pyridine, CH_2Cl_2, 94%; (b) AcSK, EtOH, reflux, 96%; (c) Oxone, AcOK, AcOH, 90%; (d) $SOCl_2$, Ph_3P, CH_3CN, CH_2Cl_2, 95%; (e) **5**, pyridine, CH_2Cl_2, 91%; (f) H_2, $Pd(OH)_2$/C, EtOH, 81%; (g) HF·pyridine, pyridine, THF, 90%.

Scheme 3[a]



[a] (a) MsCl, pyridine, CH_2Cl_2, 99%; (b) AcSK, EtOH, reflux, 92%; (c) Oxone, AcOK, AcOH, 55%; (d) $SOCl_2$, Ph_3P, CH_3CN, CH_2Cl_2, quant.; (e) **5**, pyridine, CH_2Cl_2, 92%; (f) H_2, $Pd(OH)_2$/C, EtOH, 90%; (g) HF·pyridine, pyridine, THF, 37%; (h) MsCl, pyridine, CH_2Cl_2, 86%; (i) AcSK, EtOH, reflux, 79%; (j) Oxone, AcOK, AcOH, 96%; (k) $SOCl_2$, Ph_3P, CH_3CN, CH_2Cl_2, 66%; (l) **5**, pyridine, CH_2Cl_2; (m) H_2, $Pd(OH)_2$/C, EtOH, 52% (two steps); (n) HF·pyridine, pyridine, THF, 62% **18**.

sulfonate linkages, when compared to the ether-linked C-glycosides **7**, **9**, and **11**. The synthesis commenced with mesylation of the alcohol in **6**[48] (MsCl, pyridine, 94% yield) and conversion into its thioacetate **12**[55] in 96% yield (Scheme 2). Thioacetate **12** was oxidized with oxone[56] to give the intermediate sulfonate salt[57] (90%). Conversion into the corresponding sulfonyl chloride **13** was achieved in 95% yield using $SOCl_2$/Ph_3P[52,53] as a mild reaction protocol. It has been previously reported that the conversion rates in CH_2Cl_2 to the sulfonyl chlorides were much higher using more soluble tetraalkylammonium sulfonate salts instead of alkali-metal sulfonate salts.[53] In the present case, addition of CH_3CN as a polar cosolvent likewise facilitated a smooth transformation to **13**. This aliphatic sulfonyl chloride was only subjected to filtration through a short silica gel plug to avoid any partial hydrolysis, before it was used directly in the sulfonylation reaction.

The coupling of sulfonyl chloride **13** to the phenol of **5** proceeded in 91% yield using pyridine only as the catalyst while the yields were considerably lower when DMAP or alternatively Et_3N was used as the activating amine base. The order of the final deprotection steps (hydrogenolysis of the carbohydrate benzyl ether protecting groups followed by desilylation) proved crucial, because desilylation prior to the hydrogenolysis of the benzyl protecting groups led to concomitant hydrogenolytic removal of the benzylic hydroxyl group. Interestingly, the benzylic silyloxy group is considerably more resistant to hydrogenolysis. In this regard, protecting group debenzylation (81% yield) followed by

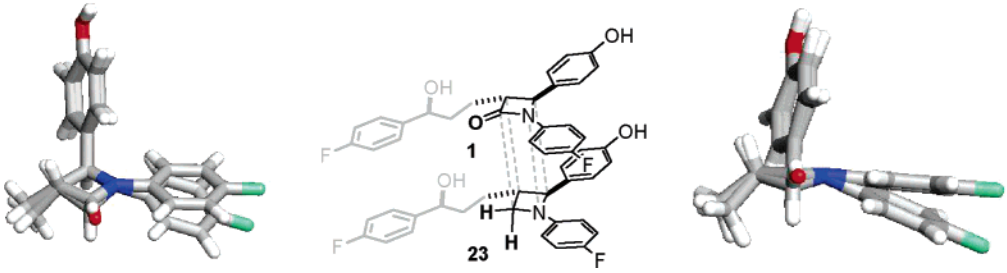


Figure 5. Geometry-optimized overlays of ezetimibe (**1**) and the azetidine **23** (right, side-view left) with the flexible C3 side chain omitted for clarity.

desilylation using HF·pyridine smoothly afforded the sulfonylated glycoside **14** in 90% yield.

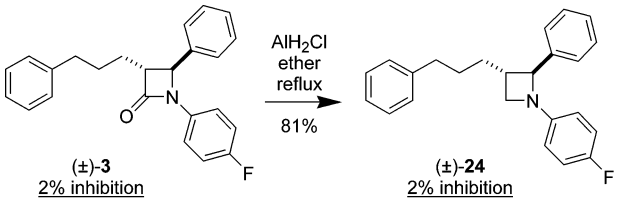
The sulfonate-linked glycoconjugates **16** and **18** were subsequently prepared by analogous reaction sequences from the alcohols **8**[49] and **10**,[50] respectively, via sulfonyl chlorides **15** and **17** (Scheme 3). However, in the disaccharide case prolonged hydrogenolysis afforded the deoxygenated disaccharide **19** as a side product, which could be separated from the major product **18** after desilylation.

The various novel glycosides of ezetimibe were subsequently evaluated in the brush border membrane vesicle assay[36,58] and shown to be efficient inhibitors of intestinal cholesterol absorption (Figure 4). The evaluation furthermore revealed that their inhibitory activities were largely independent of the nature of the linkage between the phenol and the carbohydrate domain. The *O*-monosaccharides **20**[17,36] and **21**[17,36] (19% and 14% inhibition, respectively), the ether-linked monosaccharides **7** and **9** (13% and 15% inhibition, respectively), and the sulfonate-linked monosaccharides **14** and **16** (20% and 15% inhibition, respectively) were all of comparable inhibitory activity. The highest efficacies in each series were obtained for the cellobioside derivatives **4**[17,36] (27% inhibition), **11** (28% inhibition), and **18** (41% inhibition), demonstrating a correlation between the size of the carbohydrate moiety and the inhibitory activity.

A structural feature that additionally proved vital for inhibitory activity was the benzylic hydroxyl group, as also demonstrated in the developmental work toward ezetimibe (**1**) using the animal screen (Figure 1).[11] As an additional correlation between our brush border membrane vesicle results and in vivo data, deletion of this hydroxyl group (**22**[36] vs **4**, and **19** vs **18**) likewise resulted in drastic decreases of the in vitro inhibitory activity (27% → 3% and 41% → 10% inhibition, respectively). In summary, the in vitro activities of these nonhydrolyzable glycosides **7**, **9**, **11**, **14**, **16**, and **18** suggest that a wide range of non-natural glycosides of ezetimibe are indeed capable of being potent cholesterol absorption inhibitors.

As part of the investigations of the ezetimibe precursor SCH48461 (**2**), the β-lactam ring was suggested to be an integral and essential pharmacophore for inhibition of cholesterol absorption,[13,15] with the ring-opened β-amino acid derivative of **2** being completely void of activity.[13] Beyond these observations, the β-lactam was retained in all subsequent structural modifications resulting in the development of ezetimibe (**1**).[11,59] Given our convenient in vitro brush border membrane vesicle assay, we decided to revisit the question of whether the β-lactam is indeed an essential pharmacophore or whether it serves merely as a ring scaffold to appropriately position the required substituents in the context of the optimized substituents of ezetimibe (**1**). In this regard, we chose to reduce the β-lactam to the corresponding azetidine in order to investigate whether the carbonyl oxygen plays a pivotal role in inhibitory activity. When comparing the spatial arrangement of the substituents around these two ring scaffolds, the overlays of the geometry-optimized structures (ab initio minimization, B3LYP/6-31G*)[60] of the β- lactam in **1** with azetidine **23** illustrate that the slightly puckering of the azetidine results in only minor perturbations of the positioning of the side chains compared to the more planar β-lactam (Figure 5). On the basis of this analysis, the azetidine ring could potentially serve as an efficient replacement of the β-lactam if the hydrogen-bond-accepting capabilities of the carbonyl oxygen were not essential. Such an investigation could shed further light on the important structural question of whether the β-lactam itself is important for activity or whether it potentially could be substituted by appropriate ring scaffolds that retain the required exit vectors of the substituents.

A most convenient means of examining the replacement of the β-lactam ring by an azetidine was to effect reduction of ezetimibe. The suitable reductant for the conversion of *N*-substituted β-lactams to azetidines without effecting ring cleavage has been reported to be AlH_2Cl.[61] In a simple model study with the appropriate substituent pattern of the β-lactam ring (eq 1), racemic

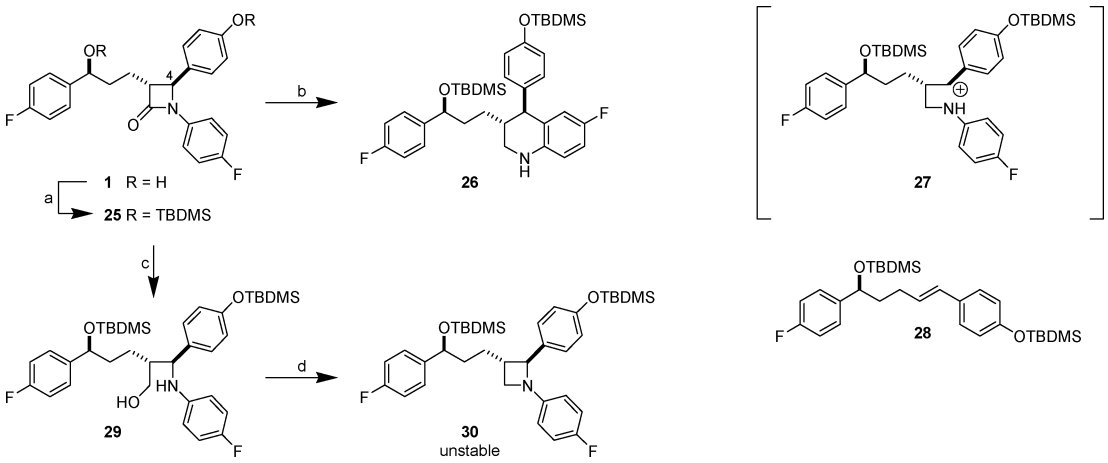


(1)

β-lactam (±)-**3**[62] was thus smoothly converted into the azetidine (±)-**24** in 81% yield, using AlH_2Cl prepared in situ from $AlCl_3$ and $LiALH_4$. As observed for the inactive β-lactam (±)-**3** when evaluated in the brush border membrane vesicle assay (2% inhibition),[36] azetidine (±)-**24** likewise proved void of activity (2% inhibition).

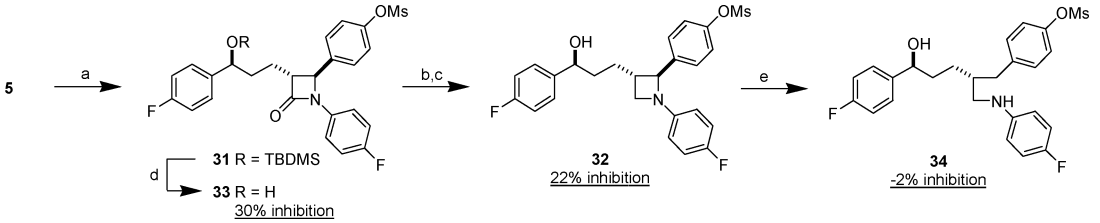
In contrast to the reduction of β-lactam (±)-**3**, treatment of ezetimibe (**1**) with AlH_2Cl afforded a complex mixture of products. In examining the reduction further, the hydroxy groups were protected as their TBDMS

Scheme 4[a]



[a] (a) TBDMSCl, imid, DMF, 97%; (b) AlH_2Cl, ether, 0 °C, 63% **26**, 16% **28**; (c) $LiAlH_4$, THF, 0 °C, 79%; (d) CBr_4, Ph_3P, Et_3N, CH_3CN, 60%.

Scheme 5[a]



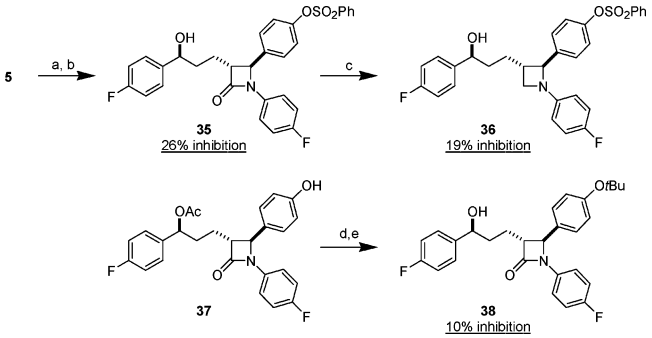
[a] (a) MsCl, pyridine, CH_2Cl_2, 92%; (b) AlH_2Cl, ether, 0 °C, 77%; (c) HF·pyridine, pyridine, THF, 85%; (d) TBAF, THF, 68%; (e) H_2, $Pd(OH)_2$/C, EtOH/EtOAc, 33%.

ethers in 97% yield (**25**, Scheme 4). Interestingly, treatment of the silyl-protected ezetimibe derivative **25** with AlH_2Cl either at reflux in ether or at 0 °C effected conversion primarily to the bicyclic aniline **26**, with no azetidine **30** isolated. As a working hypothesis, we believe that **30** is formed as an intermediate that undergoes ring opening to give an intermediate benzylic carbocation **27**, a process that is greatly facilitated by electron-donating substituents of the corresponding arene. This carbocation can subsequently undergo Friedel−Crafts reaction with the adjacent aniline to furnish the trans-substituted bicycle **26**. The intermediacy of this carbocation finds support in the formation of alkene **28**, which was isolated in 16% yield. This may be formed directly by fragmentation of the carbocation **27**, via a retro-aza-Prins fragmentation. Given the difficulties encountered and the dependency of the direct reduction strategy on subtle structural variations, an alternative strategy was pursued. Reductive ring opening of **25** with $LiAlH_4$ furnished 1,3-amino alcohol **29** in 79% yield. Subsequent reclosure of the ring by conversion into the activated phosphonium salt via the Appel reaction (CBr_4, PPh_3, and Et_3N in CH_3CN) successfully yielded azetidine **30** in 60% isolated yield. Unfortunately, azetidine **30** was observed to be rather unstable when compared to (±)-**24**. During chromatography on silica gel, azetidine **30** underwent fragmentation to give alkene **28**; moreover, it was not possible to find desilylation conditions that left the azetidine ring intact to give the desired **23**.

The stability of phenyl-substituted azetidine **24** suggested that the electron-rich nature of the arene in **30** was the cause of its observed instability. We reasoned that conversion of the electron-rich phenol to an electron-deficient phenol derivative could lead to a stable azetidine analogue. In this respect, we had previously shown that methane sulfonate esters are stable to a wide variety of chemical transformations and can be conveniently removed with LDA at −78 °C.[63] Mesylation of phenol **5** with MsCl and Et_3N afforded a dimesylate (data not shown), while MsCl and pyridine cleanly furnished mesylate **31** in 92% yield (Scheme 5). Subsequent AlH_2Cl-promoted ring reduction proceeded smoothly (77% yield) with **31**, which following deprotection with HF·pyridine furnished mesylated azetidine **32** in 85% yield. For comparison of biological activities, the corresponding mesylated β-lactam **33** was synthesized. When evaluated in the brush border membrane vesicle assay, both mesylated azetidine **32** and mesylated β-lactam **33** proved to be active inhibitors of intestinal cholesterol absorption (22% and 30% inhibition, respectively). This notable preliminary finding suggested that the azetidine ring scaffold can effectively replace the β-lactam in small-molecule cholesterol absorption inhibitor analogues of ezetimibe. As a means of examining the significance of the rigid azetidine scaffold in correctly positioning the side chains, azetidine **32** was converted into the acycle **34** by hydrogenolytic cleavage of the benzylic C−N bond. This acyclic counterpart **34** of the azetidine **32** displayed no inhibitory activity when tested in the brush border membrane vesicle assay (<2% inhibition), in excellent agreement with the reported lack of activity in animals for acyclic β-amino acids.[13]

We were intrigued by the seemingly positive effect of the mesyl substituent in enhancing the activity of ezetimibe with respect to inhibition of cholesterol absorption. In this regard, a number of additional simple

Scheme 6



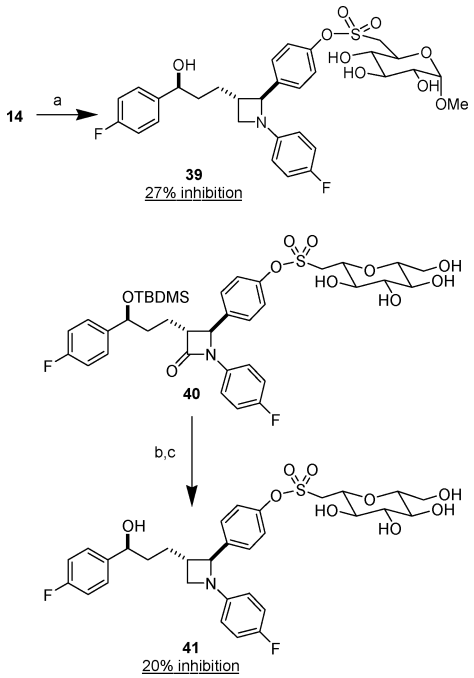
[a] (a) $PhSO_2Cl$, pyridine, CH_2Cl_2, 70%; (b) HF·pyridine, pyridine, THF, 93%; (c) AlH_2Cl, ether, 0°C, 40%; (d) $Me_2C{=}CH_2$, TfOH, 87%, (e) KCN, MeOH, 71%.

sulfonates were examined. The benzenesulfonylated β-lactam **35** and the corresponding azetidine **36** were thus synthesized through a sequence including sulfonate ester formation (70% yield), desilylation (93% yield), and ring reduction (40% yield) as outlined in Scheme 6. Both benzenesulfonylated compounds **35** and **36** were shown to be of comparable inhibitory activity (26% and 19% inhibition, respectively) as the mesylates **33** and **32** (30% and 22% inhibition, respectively) when evaluated in the brush border membrane vesicle assay. As a further test, the *tert*-butyl-substituted inhibitor **38**, as a steric analogue of the mesylate **33**, was synthesized from the monoacetate **37**[17] and subjected to evaluation as a potential cholesterol absorption inhibitor. A considerably lower inhibitory activity was obtained for **38** compared to the mesylate **33** (10% and 30% inhibition, respectively), suggesting a favorable interaction between the sulfonate linkage and the receptor at the brush border membrane.

The electron-withdrawing nature of the linkage in the sulfonyl glyconjugation approach described above (Schemes 2 and 3) made it facile to investigate azetidine glycoconjugates as cholesterol absorption inhibitors. As outlined in Scheme 7, reduction of the β-lactam ring was accomplished using AlH_2Cl to give azetidine sulfonyl conjugates **39** and **41** in 78 and 94% yield, respectively, following deprotection.[37] Interestingly, ring reduction of the corresponding sulfonylated cellobioside **18** afforded a complex mixture of products that were inseparable by standard chromatography on silica gel, suggesting a different reactivity behavior compared to the sulfonylated glycosides **14** and **40**. When evaluated in the brush border membrane vesicle assay, we were pleased to observe that both azetidine glycoconjugates **33** and **35** displayed high activities as cholesterol absorption inhibitors (27% and 20% inhibition, respectively) similar to that observed for the β-lactams counterparts **21** and **22** (20% and 15% inhibition, respectively). Thus, the use of a sulfonyl linkage to the carbohydrate moiety permitted the synthesis of stable glycosylated azetidine analogues of ezetimibe that were also active in vitro as cholesterol absorption inhibitors.

In another demonstration of the importance of the azetidine ring scaffold in optimally positioning the side chains, azetidine glycoside **43** was converted into the acyclic aniline **44** by hydrogenolytic cleavage of the benzylic C−N bond followed by desilylation (Scheme 8). This ring-opening to analogue glycoconjugate **44** resulted in a detrimental effect on the inhibitory activity (3% inhibition) compared to the azetidine counterpart **39** (27% inhibition). As observed in our earlier studies, when desilylation of the secondary ether was performed prior to the debenzylation of the carbohydrate domain, it proved possible to isolate the deoxygenated azetidine conjugate **45**. In analogy to the deoxygenated cellobiosides **22** and **19**, lack of the benzylic hydroxyl stereocenter in **45** proved detrimental for inhibitory activity (4% inhibition) compared to the azetidine glycoconjugate **39** (27% inhibition). These latter findings highlighted the importance of an appropriate ring scaffold to correctly position the ring substituents as well as the significance of the benzylic hydroxy group for inhibitory activity, as expected from in vivo data of related β-lactam derivatives.

Scheme 7[a]

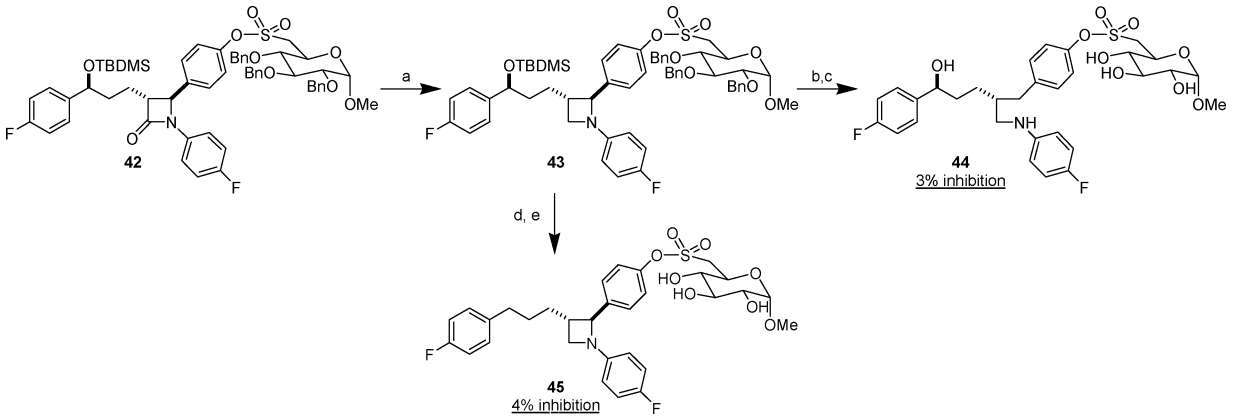


[a] (a) AlH_2Cl, ether, 0 °C, 78%; (b) AlH_2Cl, ether, 0 °C, 94%; (c) HF·pyridine, pyridine, THF, 69%.

Conclusion

We have prepared a number of derivatives of ezetimibe (**1**), the first example of a cholesterol-lowering drug that inhibits cholesterol absorption in the small intestine. Our recently established brush border membrane vesicle assay allowed us to rapidly address two key questions for derivatives of this cholesterol absorption inhibitor: (1) the role of glycosylation and (2) the importance of the β-lactam as a scaffold. In the context of our investigations, a new glycoconjugation method using sulfonate ester formation was developed and utilized in the synthesis of a number of phenolic glycoside derivatives of ezetimibe. These nonhydrolyzable glycosides proved active as inhibitors of cholesterol absorption in the brush border membrane assay, demonstrating that the phenol of ezetimibe tolerates a wide range of structural modifications in molecules that retain inhibitory activity. We furthermore investigated the reduction of the β-lactam to the corresponding azetidine to assess whether the β-lactam merely serves as a ring scaffold

Scheme 8[a]



[a] (a) AlH_2Cl, ether, 0 °C, 81%; (b) H_2, $Pd(OH)_2$/C, EtOH/EtOAc, 85%; (c) HF·pyridine, pyridine, THF, 73%; (d) TBAF, THF, 63%; (e) H_2, $Pd(OH)_2$/C, EtOH/EtOAc, 31%.

to appropriately position the required substituents. In the course of these studies the electron-withdrawing nature of sulfonate ester linkage proved crucial to achieve stability of the desired azetidine derivatives and allowed the facile synthesis of several azetidine glycoconjugates. Importantly, all the azetidines were demonstrated to be as efficacious as their β-lactam counterparts in inhibiting cholesterol absorption in vitro. This latter finding suggests that the β-lactam of ezetimibe can be easily replaced by alternative ring scaffolds. Our findings suggest that a number of structural modifications based on the ezetimibe scaffold result in effective cholesterol absorption inhibitors. The modest response of ezetimibe as an inhibitor of cholesterol absorption seems to be a general phenomenon in various in vitro systems, as it has also been observed with Caco-2 cells,[33] CHO cells,[25c] and COS-7 cells.[26] One explanation to ezetimibe's impressingly high in vivo efficacy could be its constant recycling in bile (after metabolism into its glucuronide **20**) back to the site of action, the small intestine, as previously suggested.[39] A detailed correlation between in vivo inhibitory efficacies and the in vitro inhibition results obtained in the brush border membrane vesicle assay are part of ongoing investigations and will be reported in due course.[64] The alternative strategies we thus devise for the design of new potent cholesterol absorption inhibitors could ultimately find use in the development of improved strategies for lowering blood cholesterol levels and preventing cardiovascular disease. Additionally, the use of phenol-derived sulfonate esters as a conjugation strategy may have broader applications in the design of bioactive molecules.

Experimental Section

Chemistry. Reactions in anhydrous solvents were all performed using oven-dried glassware under an atmosphere of argon. Reagent-grade solvents were all purchased from chemical companies and used without prior purification. Anhydrous THF, ether, toluene, CH_3CN and CH_2Cl_2 were dried and purified through activated alumina columns as described.[65] Diisopropylamine, triethylamine, and pyridine were distilled from KOH. For chromatographic purification, technical-grade solvents were distillated prior to use. TLC was performed using Machery-Nagel Alugram Sil G/UV_{254} TLC plates and visualized with ultraviolet light at 254 nm followed by ceric ammonium molybdate, phosphomolybdic acid, or H_2SO_4/MeOH stains. Chromatographic purification of products was accomplished by dry column vacuum chromatography[66] on either Merck silica gel 60 (15−40 μm) or Brunschwig silica 18−32, 60 Å (18−32 μM). Concentration under reduced pressure was performed by rotary evaporation at 40 °C, and the purified compounds were subsequently dried under high vacuum (<0.5 Torr). NMR spectra were recorded on a Varian Mercury 300 MHz apparatus operating at 300, 75, and 282 MHz for ^{1}H, ^{13}C/DEPT and ^{19}F, respectively, and chemical shifts (δ) were referenced to the internal solvent signals for ^{1}H and ^{13}C. Multiplicities are reported as follows: ^{1}H, s = singlet, d = dublet, t = triplet, q = quartet, m = multiplet; ^{13}C, C, CH, CH_2, CH_3 (determined by DEPT). Coupling constants are reported in hertz. IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer Spectrum RX I FT-IR apparatus (thin films on NaCl plates) and are reported as absorption maxima in cm^{-1}. Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium at the ETH, Zürich. High-resolution matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) and electrospray ionization (ESI-MS) were performed by the mass spectrometry service of the LOC at the ETH, Zürich.

Phenol 5. Ezetimibe (**1**)[42] (5.530 g, 13.5 mmol) was suspended in 2-propanol (70 mL), to which aqueous NaOH (2 M, 15 mL) followed by Ac_2O (3.0 mL, 32 mmol) was added, and the solution was stirred for 5 h followed by addition of saturated aqueous $NaHCO_3$ (200 mL). After extraction with EtOAc (4 × 50 mL), the combined organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (5.2 × 5.5 cm) on silica gel eluting with a gradient of 0−100% EtOAc in hexane (v/v) to give the intermediary phenolic acetate (5.930 g, 97%) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (2H, d, J = 8.7 Hz), 7.29−7.18 (4H, m), 7.09 (2H, d, J = 8.7 Hz), 6.99 (2H, t, J = 8.7 Hz), 6.92 (2H, t, J = 8.7 Hz), 4.67 (1H, bs), 4.61 (1H, d, J = 2.5 Hz), 3.08−3.04 (1H, m), 2.75 (1H, bs), 2.29 (3H, s), 1.97−1.85 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.16, 167.23, 163.56, 160.46, 160.32, 157.24, 150.58, 139.94, 139.90, 134.85, 133.53, 133.50 (C), 127.32, 127.21, 126.78, 122.38, 118.34, 118.23, 115.95, 115.65, 115.35, 115.07 (CH), 72.95, 60.81, 60.33 (CH), 36.61, 25.07 (CH_2), 21.19 (CH_3). IR (cm^{-1}): 3443, 3019, 2936, 2862, 1747, 1605, 1509, 1427, 1388, 1370, 1221, 1198, 1157, 1016, 835, 757, 668. MALDI-MS ($C_{26}H_{23}F_2NO_4$): $[MH - H_2O]^+$ 434.1556 (calcd 434.1568); $[MNa]^+$ 474.1485 (calcd 474.1493). This acetate (1.864 g, 4.13 mmol) was dissolved in anhydrous DMF (25 mL), imidazole (939 mg, 13.8 mmol) and TBDMSCl (1.853 g, 12.3 mmol) were added sequentially, and the solution was stirred for 3 h followed by addition of 50% saturated aqueous $NaHCO_3$ (150 mL). After extraction with EtOAc (4 × 40 mL), the combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (40 mL), evaporated on Celite, and purified by dry column vacuum chromatography

(4.2 × 5.5 cm) on silica gel eluting with a gradient of 0−30% EtOAc in hexane (v/v) to give the intermediary silylated acetate (2.137 g, 91%) as a colorless oil. R_f (1:1 EtOAc/hexane (v/v)): 0.69. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (2H, d, J = 8.7 Hz), 7.26−7.20 (4H, m), 7.10 (2H, d, J = 8.7 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 4.67 (1H, t, J = 5.3 Hz), 4.58 (1H, d, J = 1.9 Hz), 3.06−3.02 (1H, m), 2.28 (3H, s), 1.96−1.80 (4H, m), 0.88 (9H, s), 0.02 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.16, 167.06, 163.42, 160.47, 160.16, 157.23, 150.62, 140.50, 135.10, 133.74, 133.70 (C), 127.26, 127.14, 126.77, 122.37, 118.27, 118.16, 115.89, 115.58, 115.03, 114.76 (CH), 73.74, 60.67, 60.53 (CH), 37.94 (CH_2), 25.73 (CH_3), 24.55 (CH_2), 20.99 (CH_3), 18.07 (C), −4.74, −5.05 (CH_3). IR (cm^{-1}): 2953, 2930, 2857, 1752, 1606, 1510, 1472, 1426, 1385, 1370, 1252, 1219, 1197, 1166, 1140, 1102, 1086, 1015, 912, 835, 777, 736. MALDI-MS ($C_{32}H_{37}F_2NO_4Si$): [MH − TBDMSOH]$^+$ 434.1556 (calcd 434.1568); [MNa]$^+$ 588.2347 (calcd 588.2358). Anal. Calcd for $C_{32}H_{37}F_2NO_4Si$: C, 67.94; H, 6.59; N, 2.48. Found: C, 67.94; H, 6.64; N, 2.37. This silylated acetate (5.123 g, 9.06 mmol) was dissolved in CH_2Cl_2 (200 mL), neutral alumina (50 g) was added, and the suspension was evaporated to dryness. The coated alumina was dried shortly under vacuum and then heated to 70 °C for 5.5 h. After cooling, the alumina was extracted with 10% MeOH in CH_2Cl_2 (8 × 50 mL), and the combined organic extracts were evaporated on Celite and purified by dry column vacuum chromatography (5.4 × 5.5 cm) on silica gel eluting with a gradient of 0−30% EtOAc in hexane (v/v) to give phenol **5** (3.919 g, 83%) as a white foam. R_f (1:3 EtOAc/hexane (v/v)): 0.24. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26−7.14 (6H, m), 6.99−6.83 (6H, m), 6.16 (1H, bs), 4.65 (1H, t, J = 5.3 Hz), 4.52 (1H, d, J = 1.9 Hz), 3.04−2.98 (1H, m), 1.92−1.76 (4H, m), 0.86 (9H, s), 0.00 (3H, s), −0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.82, 163.28, 160.42, 156.12, 140.50, 140.45, 133.57 (C), 128.92, 127.19, 127.15, 127.08, 118.43, 118.32, 116.05, 115.85, 115.55, 115.01, 114.72 (CH), 73.82, 61.17, 60.35 (CH), 38.07 (CH_2), 25.89 (CH_3), 24.68 (CH_2), 18.25 (C), −4.54, −4.84 (CH_3). IR (cm^{-1}): 3351, 2953, 2938, 2857, 1722, 1615, 1604, 1510, 1450, 1391, 1361, 1252, 1223, 1156, 1103, 1087, 863, 834, 776, 760. MALDI-MS ($C_{30}H_{35}F_2NO_3Si$): [MH − TBDMSOH]$^+$ 392.1451 (calcd 392.1462); [MH]$^+$ 524.2409 (calcd 524.2433); [MNa]$^+$ 546.2242 (calcd 546.2252). Anal. Calcd for $C_{30}H_{35}F_2NO_3Si$: C, 68.81; H, 6.74; N, 2.67. Found: C, 68.61; H, 6.82; N, 2.66.

Glycoside 7. Phenol **5** (257.5 mg, 0.492 mmol) and alcohol **6**[48,67] (333 mg, 0.717 mmol) were dissolved in anhydrous THF (15 mL) at 0 °C, Bu_3P (0.40 mL, 1.3 mmol) and 1,1′-(azodicarbonyl)dipiperidine (248 mg, 0.98 mmol) were added sequentially, and the suspension was allowed to warm to ambient temperature over several hours. After stirring at room temperature for 14 h, EtOAc/hexane (1:4 (v/v), 30 mL) was added and the suspension was filtered through Celite (2 × 15 mL EtOAc/hexane (1:4 (v/v)) washings). The filtrate was evaporated on Celite and purified by dry column vacuum chromatography (3.8 × 3.3 cm) on silica gel eluting with a gradient of 0−30% EtOAc in hexane (v/v) to give the intermediary fully protected glycoside (98.5 mg, 21%) as a colorless oil. R_f (1:1 EtOAc/hexane (v/v)): 0.74. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.16 (21H, m), 7.02−6.86 (6H, m), 5.03 (1H, d, J = 10.6 Hz), 4.88 (1H, d, J = 10.6 Hz), 4.86 (1H, d, J = 11.2 Hz), 4.84 (1H, d, J = 11.8 Hz), 4.70 (1H, d, J = 12.5 Hz), 4.66 (1H, t, J = 3.7 Hz), 4.68−4.65 (1H, m), 4.54 (1H, d, J = 5.6 Hz), 4.52 (1H, d, J = 3.1 Hz), 4.11 (2H, d, J = 2.5 Hz), 4.06 (1H, t, J = 9.0 Hz), 3.92 (1H, dt, J = 2.5, 10.0 Hz), 3.73 (1H, t, J = 9.3 Hz), 3.62 (1H, dt, J = 3.4, 9.7 Hz), 3.40 (3H, s), 3.07−3.00 (1H, m), 1.96−1.78 (4H, m), 0.90 (9H, s), 0.03 (3H, s), −0.15 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.20, 163.24, 160.24, 160.00, 158.53, 157.03, 140.50, 140.47, 138.42, 137.85, 137.80, 133.74, 129.70 (C), 128.26, 128.20, 127.97, 127.84, 127.62, 127.52, 127.16, 127.05, 126.91, 118.19, 118.09, 115.72, 115.43, 115.17, 114.97, 114.68, 98.14, 82.01, 79.77, 77.22 (CH), 75.76, 75.04 (CH_2), 73.79 (CH), 73.37 (CH_2), 69.06 (CH), 66.63 (CH_2), 60.97, 60.44 (CH), 55.25 (CH_3), 38.08 (CH_2), 25.87 (CH_3), 24.69 (CH_2), 18.22 (C), −4.56, −4.87 (CH_3). IR (cm^{-1}): 3031, 2929, 2857, 1749, 1608, 1510, 1454, 1386, 1361, 1250, 1220, 1156, 1139, 1087, 1028, 835, 775, 750, 698. MALDI-MS ($C_{58}H_{65}F_2NO_8Si$): [MNa]$^+$ 992.4350 (calcd 992.4345). This fully protected glycoside (134 mg, 0.138 mmol) was dissolved in EtOH (10 mL), $Pd(OH)_2$/C (20% (w/w), 36 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 15 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (3.5 × 2.0 cm) on silica gel eluting with a gradient of 0−100% EtOAc in hexane followed by 10% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated glycoside (84 mg, 87%) as a light yellow oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.39. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26−7.14 (6H, m), 6.96 (2H, t, J = 8.7 Hz), 6.91−6.83 (4H, m), 5.02 (1H, bs), 4.70−4.64 (2H, m), 4.49 (1H, s), 4.24−4.10 (3H, m), 3.92 (1H, d, J = 5.6 Hz), 3.84−3.74 (2H, m), 3.61−3.50 (2H, m), 3.34 (3H, s), 2.97 (1H, dd, J = 5.6, 6.8 Hz), 1.92−1.76 (4H, m), 0.86 (9H, s), 0.00 (3H, s), −0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.18, 158.64, 157.00, 156.00, 140.52, 133.71, 129.87 (C), 127.17, 127.06, 126.96, 118.20, 118.11, 115.76, 115.45, 115.23, 115.15, 114.98, 114.69, 99.30, 74.49, 73.81, 71.91, 69.91 (CH), 67.15 CH_2), 60.89, 60.47 (CH), 55.23 (CH_3), 38.10 (CH_2), 25.86 (CH_3), 24.73 (CH_2), 18.23 (C), −4.55, −4.84 (CH_3). IR (cm^{-1}): 3390, 2931, 2858, 1748, 1609, 1510, 1472, 1428, 1387, 1362, 1250, 1223, 1155, 1143, 1104, 1079, 1059, 1042, 835, 776, 757. MALDI-MS ($C_{37}H_{47}F_2NO_8Si$): [MNa]$^+$ 722.2940 (calcd 722.2937). This silylated glycoside (84 mg, 0.12 mmol) was dissolved in THF (2.5 mL), TBAF (0.5 mL, 1 M in THF) was added, and the solution was stirred for 20 h. After dilution with EtOAc (25 mL), the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.0 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give glycoside **7** (60 mg, 86%) as a white solid after coevaporation with hexane (10 mL). Glycoside **7** could be further purified by chromatotron eluting with 10% MeOH in CH_2Cl_2 (v/v). R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.26. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.32−7.22 (6H, m), 7.04−6.93 (6H, m), 4.75 (1H, d, J = 1.9 Hz), 4.66 (1H, d, J = 3.7 Hz), 4.59 (1H, dd, J = 4.4, 5.6 Hz), 4.25 (1H, dd, J = 1.2, 10.6 Hz), 4.13 (1H, dd, J = 5.6, 10.6 Hz), 3.84−3.78 (1H, m), 3.64 (1H, t, J = 9.3 Hz), 3.45−3.34 (2H, m), 3.37 (3H, s), 3.08−3.03 (1H, m), 1.96−1.78 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.14, 164.49, 160.11, 153.40, 141.76, 141.71, 134.74, 130.60 (C), 128.35, 128.24, 128.11, 119.49, 119.38, 116.37, 116.06, 115.98, 115.63, 115.35, 100.88, 74.80, 73.35, 73.10, 71.29 (CH), 68.35 (CH_2), 61.72, 60.85 (CH), 55.29 (CH_3), 37.21, 25.84 (CH_2). MALDI-MS ($C_{31}H_{33}F_2NO_8$): [MNa]$^+$ 608.2074 (calcd 608.2072).

***C*-Glycoside 9.** Phenol **5** (143 mg, 0.273 mmol) and alcohol **8**[49,68] (180 mg, 0.325 mmol) were dissolved in anhydrous THF (10 mL) at 0 °C, Bu_3P (0.20 mL, 0.80 mmol) and 1,1′-(azodicarbonyl)dipiperidine (206 mg, 0.82 mmol) were added sequentially, and the suspension was allowed to warm to ambient temperature over several hours and stirred for 24 h. EtOAc/hexane (1:4 (v/v), 20 mL) was added, the suspension was filtered through Celite (2 × 10 mL EtOAc/hexane (1:4 (v/v)) washings) and the filtrate was evaporated on Celite and purified by dry column vacuum chromatography (4.1 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary fully protected glycoside (60.1 mg, 21%) as a colorless oil. R_f (1:1 EtOAc/hexane (v/v)): 0.79. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.17 (26H, m), 7.04−6.89 (6H, m), 4.96 (2H, bs), 4.89 (1H, d, J = 9.3 Hz), 4.86 (1H, d, J = 8.7 Hz), 4.69 (1H, t, J = 5.3 Hz), 4.63−4.53 (5H, m), 4.21 (1H, d, J = 10.6 Hz), 4.10 (1H, dd, J = 5.0, 10.6 Hz), 3.85−3.52 (7H, m), 3.07−3.02 (1H, m), 2.01−1.78 (4H, m), 0.91 (9H, s), 0.05 (3H, s), −0.13 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.25, 158.74, 140.53, 140.49, 138.29, 137.85, 137.79, 137.65, 133.81 (C), 129.53, 128.32, 128.28, 128.18, 127.96, 127.81, 127.78, 127.74, 127.66, 127.54, 127.48, 127.18, 127.08, 126.90, 118.22, 118.12, 115.77, 115.47, 115.30, 114.98, 114.70 (CH), 87.12, 79.14, 78.25, 77.87, 77.71 (CH), 75.56, 75.11, 75.03 (CH_2), 73.82 (CH), 73.44, 68.93, 67.23 (CH_2), 61.02, 60.47 (CH), 38.10 (CH_2), 25.89 (CH_3), 24.71 (CH_2), 18.24 (C), −4.54, −4.83

(CH_3). IR (cm^{-1}): 2951, 2929, 2858, 1749, 1608, 1510, 1454, 1386, 1361, 1250, 1223, 1156, 1141, 1101, 1028, 911, 835, 777, 735, 699. MALDI-MS ($C_{65}H_{71}F_2NO_8Si$): $[MNa]^+$ 1082.4831 (calcd 1082.4815). This fully protected glycoside (72 mg, 0.068 mmol) was dissolved in EtOH (5 mL), $Pd(OH)_2$/C (20% (w/w), 40 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 17 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (3.8 × 2.0 cm) on silica gel eluting with a gradient of 0−100% EtOAc in hexane followed by 10% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated glycoside (28 mg, 59%) as a colorless oil. R_f (20% MeOH in CH_2Cl_2 (v/v)): 0.64. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24−7.11 (6H, m), 6.95 (2H, t, J = 8.7 Hz), 6.85−6.79 (4H, m), 5.22 (1H, bs), 4.93 (1H, bs), 4.65 (1H, t, J = 5.3 Hz), 4.45 (1H, bs), 4.36 (1H, bs), 4.14 (1H, d, J = 10.0 Hz), 3.97 (1H, d, J = 8.1 Hz), 3.69 (2H, bs), 3.51 (3H, bs), 3.22 (1H, d, J = 6.2 Hz), 2.94 (1H, dd, J = 5.6, 6.8 Hz), 2.76 (1H, bs), 1.88−1.68 (4H, m), 0.86 (9H, s), 0.00 (3H, s), −0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.22, 163.28, 160.05, 158.36, 157.03, 140.57, 133.75, 130.30, 129.52, 127.22, 127.11, 118.23, 115.83, 115.54, 116.35, 115.05, 114.91, 114.76, 79.16, 78.33, 77.70, 73.88, 70.18, 69.52, 67.75, 61.54, 60.79, 60.57, 38.14, 25.91, 24.81, 18.27, −4.51, −4.80. IR (cm^{-1}): 3391, 2930, 2858, 1747, 1609, 1510, 1387, 1362, 1223, 1140, 1086, 1043, 1014, 835, 758. MALDI-MS ($C_{37}H_{47}F_2NO_8Si$): $[MH - TBDMSOH]^+$ 568.2132 (calcd 568.2147); $[MNa]^+$ 722.2939 (calcd 722.2937). This silylated glycoside (27.0 mg, 0.039 mmol) was dissolved in THF (1.0 mL), TBAF (0.2 mL, 1 M in THF) was added, and the solution was stirred for 15 h, diluted with CH_2Cl_2, evaporated on Celite, and purified by dry column vacuum chromatography (3.5 × 2.0 cm) on silica gel eluting with a gradient of 0−18% MeOH in CH_2Cl_2 (v/v) to give *C*-glycoside **9** (14.0 mg, 62%) as a white solid after coevaporation with hexane (10 mL). R_f (20% MeOH in CH_2Cl_2 (v/v)): 0.56. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.33−7.23 (6H, m), 7.05−6.94 (6H, m), 4.78 (1H, d, J = 1.9 Hz), 4.59 (1H, t, J = 5.3 Hz), 4.29 (1H, dd, J = 1.5, 10.3 Hz), 4.13 (1H, dd, J = 5.6, 10.6 Hz), 3.85 (1H, d, J = 11.2 Hz), 3.67−3.61 (1H, m), 3.57−3.51 (1H, m), 3.44−3.37 (2H, m), 3.31−3.28 (2H, m), 3.11−3.06 (1H, m), 1.97−1.81 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.20, 160.12, 130.69, 128.36, 128.25, 128.14, 119.52, 119.41, 116.35, 116.04, 115.93, 115.63, 115.35, 81.55, 79.49, 79.39, 73.35, 71.30, 71.23, 68.77, 62.66, 61.74, 60.86, 37.22, 25.84. MALDI-MS ($C_{31}H_{33}F_2NO_8$): $[MH - TBDMSOH]^+$ 568.2143 (calcd 568.2147); $[MNa]^+$ 608.2073 (calcd 608.2072).

***C*-Glycoside 11.** Phenol **5** (80.3 mg, 0.153 mmol) and alcohol **10**[50] (101.5 mg, 0.103 mmol) were dissolved in anhydrous THF (10 mL) at 0 °C, Bu_3P (50 mg, 0.20 mmol) and 1,1′-(azodicarbonyl)dipiperidine (39.5 mg, 0.17 mmol) were added sequentially, and the suspension was allowed to warm to ambient temperature over several hours. After stirring at room temperature for 26 h, EtOAc/hexane (1:4 (v/v), 30 mL) was added, and the suspension was filtered through Celite (2 × 10 mL EtOAc/hexane (1:4 (v/v)) washings). The filtrate was evaporated on Celite and purified by dry column vacuum chromatography (4.5 × 2.0 cm) on silica gel eluting with a gradient of 0−25% EtOAc in hexane (v/v) to give a 1:1 mixture of the intermediary fully protected glycoside and unreacted phenol **5** (49.7 mg) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.64; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.39, 163.27, 160.31, 158.82, 157.09, 140.54, 140.49, 139.05, 138.37, 138.29, 138.19, 137.85, 133.78, 133.73, 129.40, 128.96, 128.23, 128.12, 128.04, 127.94, 127.86, 127.73, 127.63, 127.57, 127.49, 127.41, 127.20, 127.10, 126.87, 118.30, 118.19, 116.01, 115.78, 115.49, 115.30, 114.99, 114.71, 102.41, 85.35, 84.84, 82.70, 79.29, 78.01, 77.82, 77.19, 75.64, 75.25, 75.10, 75.02, 74.96, 74.81, 73.84, 73.26, 68.99, 68.15, 67.49, 61.07, 60.44, 38.09, 25.90, 24.72, 18.25, −4.53, −4.83. MALDI-MS ($C_{92}H_{99}F_2NO_{13}Si$): $[MNa]^+$ 1514.6763 (calcd 1514.6751). This mixture (49.7 mg) was dissolved in EtOH/EtOAc (10 mL, 1:1 (v/v)), $Pd(OH)_2$/C (20% (w/w), 31 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 3 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.6 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated glycoside (18.7 mg, 21% from **5**) as a colorless oil. R_f (20% MeOH in CH_2Cl_2 (v/v)): 0.44. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.31−7.23 (6H, m), 7.04−6.94 (6H, m), 4.71 (1H, d, J = 1.9 Hz), 4.41 (1H, d, J = 7.5 Hz), 4.12 (1H, dd, J = 5.3, 10.9 Hz), 3.91−3.81 (3H, m), 3.66 (1H, d, J = 5.6, 11.8 Hz), 3.57−3.47 (3H, m), 3.40−3.20 (7H, m), 3.07 (1H, t, J = 5.9 Hz), 1.92−1.78 (4H, m), 0.87 (9H, s), 0.02 (3H, s), −0.18 (3H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.71, 160.66, 145.96, 142.43, 131.16, 131.05, 128.89, 128.80, 128.62, 120.00, 119.89, 116.83, 116.54, 116.41, 116.02, 115.74, 115.58, 104.65, 80.78, 80.43, 79.64, 78.16, 77.90, 75.13, 74.99, 71.43, 62.50, 62.08, 61.29, 38.96, 26.38, 25.75, 19.06, −4.40. MALDI-MS ($C_{43}H_{57}F_2NO_{13}Si$): $[MNa]^+$ 884.3668 (calcd 884.3465). This silylated glycoside (18.3 mg, 0.021 mmol) was dissolved in anhydrous THF (2.5 mL, Teflon bottle) at 0 °C, anhydrous pyridine (0.50 mL) followed by HF·pyridine complex (0.50 mL) was added, and the solution was stirred for 17 h. $NaHCO_3$(s) was added and the suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.6 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give *C*-glycoside **11** (10.3 mg, 65%) as a white solid. R_f (20% MeOH in CH_2Cl_2 (v/v)): 0.31. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.33−7.24 (6H, m), 7.05−6.94 (6H, m), 4.78 (1H, d, J = 1.9 Hz), 4.60 (1H, t, J = 4.4 Hz), 4.41 (1H, d, J = 7.5 Hz), 4.30 (1H, d, J = 10.0 Hz), 4.12 (1H, dd, J = 5.0, 10.6 Hz), 3.91−3.84 (3H, m), 3.66 (1H, d, J = 5.6, 11.8 Hz), 3.57−3.49 (3H, m), 3.40−3.20 (6H, m), 3.10−3.06 (1H, m), 1.97−1.82 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.52, 164.87, 160.42, 142.07, 133.18 (C), 131.03, 130.87, 128.68, 128.59, 128.47, 123.36, 119.86, 119.74, 116.69, 116.38, 116.25, 116.22, 115.96, 115.88, 115.68, 104.54, 80.71, 80.36, 79.58, 78.11, 77.85, 74.94, 73.70, 71.38 (CH), 69.02, 62.47 (CH_2), 62.09 (CH_2+CH), 61.20 (CH), 37.54, 26.18 (CH_2). MALDI-MS ($C_{37}H_{43}F_2NO_{13}$): $[MNa]^+$ 770.2589 (calcd 770.2600).

Thioacetate 12.[55,68] Alcohol **6**[48,67] (1.181 g, 2.54 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL) at 0 °C, anhydrous pyridine (3.0 mL) followed by MsCl (0.50 mL, 6.4 mmol) was added, and the solution was stirred at 0 °C for 1 h and at room temperature for 7 h followed by addition of saturated aqueous $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (25 mL) and H_2O (25 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.1 × 3.3 cm) on silica gel eluting with a gradient of 0−100% CH_2Cl_2 in hexane (v/v) followed by 0.25−1.0% MeOH in CH_2Cl_2 (v/v) to give the intermediary mesylate (1.303 g, 94%) as a colorless oil after coevaporation with acetonitrile (3 × 10 mL). R_f (1% MeOH in CH_2Cl_2 (v/v)): 0.60. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.26 (15H, m), 5.02 (1H, d, J = 10.6 Hz), 4.92 (1H, d, J = 10.6 Hz), 4.84 (1H, d, J = 10.6 Hz), 4.80 (1H, d, J = 12.5 Hz), 4.66 (1H, d, J = 11.8 Hz), 4.63 (1H, d, J = 10.6 Hz), 4.60 (1H, d, J = 3.7 Hz), 4.41−4.32 (2H, m), 4.02 (1H, t, J = 9.3 Hz), 3.85 (1H, dt, J = 3.7, 10.0 Hz), 3.52 (1H, dt, J = 3.7, 6.2 Hz), 3.50 (1H, bs), 3.39 (3H, s), 2.98 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.30, 137.75, 137.56 (C), 128.36, 128.30, 127.94, 127.84, 127.76, 127.57 (CH), 98.06, 81.73, 79.69, 76.86 (CH), 75.73, 75.09, 73.44 (CH_2), 68.59 (CH), 68.36 (CH_2), 55.46, 37.54 (CH_3). IR (cm^{-1}): 3031, 2913, 1497, 1454, 1359, 1177, 1089, 1074, 1046, 1003, 965, 931, 813, 739, 699. MALDI-MS ($C_{29}H_{34}O_8S$): $[MNa]^+$ 565.1873 (calcd 565.1872). Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32. Found: C, 63.99; H, 6.27. This mesylate (1.290 g, 2.38 mmol) was dissolved in EtOH (25 mL), KOSCMe (869 mg, 7.61 mmol) was added, and the unclear solution was stirred at reflux for 4 h (orange precipitate). After cooling, 50% saturated aqueous $NaHCO_3$ (100 mL) was added and the suspension was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.1 × 3.3 cm) on silica gel eluting with a gradient of 0−30% EtOAc in hexane (v/v) to give thioacetate

12 (1.189 g, 96%) as a light orange solid. R_f (1:1 EtOAc/hexane (v/v)): 0.64. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41−7.32 (15H, m), 5.03 (1H, d, J = 10.6 Hz), 4.94 (1H, d, J = 10.6 Hz), 4.86 (1H, d, J = 10.6 Hz), 4.82 (1H, d, J = 11.8 Hz), 4.69 (1H, d, J = 11.8 Hz), 4.66 (1H, d, J = 10.6 Hz), 4.58 (1H, d, J = 3.1 Hz), 4.02 (1H, t, J = 9.0 Hz), 3.81 (1H, dt, J = 2.5, 7.5 Hz), 3.55 (1H, dd, J = 3.7, 9.3 Hz), 3.48 (1H, dd, J = 3.1, 13.7 Hz), 3.40 (3H, s), 3.35 (1H, t, J = 9.5 Hz), 3.08 (1H, dd, J = 7.5, 13.7 Hz), 2.36 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.67, 138.46, 137.90, 137.78 (C), 128.33, 128.29, 128.03, 127.94, 127.85, 127.81, 127.74, 127.53 (CH), 97.72, 81.69, 80.36, 79.78 (CH), 75.64, 75.04, 73.22 (CH_2), 69.23 (CH), 55.02 (CH_3), 30.73 (CH_2), 30.39 (CH_3). IR (cm^{-1}): 3063, 3031, 2908, 1694, 1497, 1454, 1358, 1201, 1156, 1136, 1092, 1072, 1050, 1029, 999, 955, 737, 698, 630. MALDI-MS ($C_{30}H_{34}O_6S$): $[MNa]^+$ 545.1974 (calcd 545.1974). Anal. Calcd for $C_{30}H_{34}O_6S$: C, 68.94; H, 6.56. Found: C, 68.77; H, 6.63.

Sulfonyl Chloride 13. Thioacetate **12**[55,68] (1.180 g, 2.26 mmol) was dissolved in AcOH (25 mL) to which KOAc (4.082 g, 41.6 mmol) followed by Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, 4.019 g, 8.69 mmol) was added, and after stirring for 15 h, saturated aqueous $NaHCO_3$ (100 mL), H_2O (50 mL), and saturated aqueous Na_2CO_3 (50 mL) were carefully added. After extraction with EtOAc (4 × 40 mL), the combined organic layer was washed with saturated aqueous Na_2CO_3 (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.0 × 3.3 cm) on silica gel eluting with a gradient of 0−90% EtOAc in hexane (v/v) followed by 0−50% MeOH in EtOAc (v/v) to give the intermediary sulfonate salt[57] (1.116 g, 90%) as a white solid. R_f (1:3 MeOH/EtOAc (v/v)): 0.40. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.37−7.21 (15H, m), 4.90 (1H, d, J = 11.2 Hz), 4.86 (1H, d, J = 10.6 Hz), 4.84 (1H, d, J = 11.2 Hz), 4.73 (1H, d, J = 3.1 Hz), 4.72 (1H, d, J = 11.2 Hz), 4.64 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 11.2 Hz), 4.16 (1H, t, J = 9.2 Hz), 3.90 (1H, t, J = 9.3 Hz), 3.55 (1H, dd, J = 3.4, 9.3 Hz), 3.48 (3H, s), 3.30−3.22 (2H, m), 2.92 (1H, dd, J = 10.0, 14.3 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 140.03, 139.57, 139.55 (C), 129.42, 129.31, 129.15, 128.93, 128.89, 128.84, 128.67, 128.59 (CH), 98.53, 83.03, 81.65, 81.52 (CH), 76.44, 75.83, 73.85 (CH_2), 68.52 (CH), 55.95 (CH_3), 53.65 (CH_2). IR (cm^{-1}): 3484, 3030, 2922, 1497, 1454, 1360, 1230, 1198, 1177, 1156, 1093, 1058, 1028, 736, 696. MALDI-MS ($C_{28}H_{31}NaO_8S$): $[MNa]^+$ 573.1536 (calcd 573.1535). This sulfonate salt (696 mg, 1.26 mmol) was suspended in anhydrous acetonitrile/CH_2Cl_2 (10 mL, 1:1 (v/v)) at 0 °C, Ph_3P (1.002 g, 3.8 mmol) and thionyl chloride (0.40 mL, 5.5 mmol) were added sequentially, and the suspension was stirred at room temperature for 13 h. EtOAc/hexane (1:4 (v/v), 100 mL) was added, the suspension was filtered through Celite (4 × 15 mL EtOAc/hexane (1:3 (v/v)) washings), and the filtrate was evaporated and dried shortly under vacuum to give sulfonyl chloride **13** (657 mg, 95%) as a yellowish oil. R_f (1:1 EtOAc/hexane (v/v)): 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42−7.28 (15H, m), 5.05 (1H, d, J = 10.6 Hz), 4.96 (1H, d, J = 11.8 Hz), 4.85 (1H, d, J = 10.6 Hz), 4.83 (1H, d, J = 11.8 Hz), 4.67 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 11.2 Hz), 4.60 (1H, d, J = 3.1 Hz), 4.33 (1H, t, J = 9.6 Hz), 4.07 (1H, t, J = 9.0 Hz), 3.85 (1H, dd, J = 1.2, 13.7 Hz), 3.55 (1H, d, J = 9.3 Hz), 3.52 (1H, t, J = 10.0 Hz), 3.46 (3H, s), 3.26 (1H, t, J = 9.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.02, 137.57, 137.06 (C), 128.58, 128.36, 128.30, 128.23, 128.12, 127.92, 127.66 (CH), 98.00, 81.56, 79.41, 78.49 (CH), 75.85, 74.76, 73.38, 66.75 (CH_2), 65.93 (CH), 55.90 (CH_3). MALDI-MS ($C_{28}H_{31}ClO_7S$): $[MNa]^+$ 569.1378 (calcd 569.1377).

Sulfonate 42. Sulfonyl chloride **13** (197 mg, 0.36 mmol) was suspended in anhydrous CH_2Cl_2 (5 mL), anhydrous pyridine (0.5 mL) followed by phenol **5** (70.0 mg, 0.13 mmol) was added, and the solution was stirred for 22 h, diluted with EtOAc (25 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.3 × 2.0 cm) on silica gel eluting with a gradient of 0−35% EtOAc in hexane (v/v) to give sulfonate **42** (125.5 mg, 91%) as a colorless oil/glass. R_f (1% MeOH in CH_2Cl_2 (v/v)): 0.77. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.14 (23H, m), 7.00 (2H, t, J = 8.7 Hz), 6.95 (2H, t, J = 8.7 Hz), 5.05 (1H, d, J = 11.2 Hz), 4.97 (1H, d, J = 11.2 Hz), 4.84 (1H, d, J = 11.8 Hz), 4.82 (1H, d, J = 10.6 Hz), 4.69 (1H, t, J = 6.8 Hz), 4.67 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 3.7 Hz), 4.56 (1H, d, J = 12.5 Hz), 4.54 (1H, d, J = 10.6 Hz), 4.29 (1H, t, J = 9.5 Hz), 4.06 (1H, t, J = 9.0 Hz), 3.57 (1H, t, J = 3.1 Hz), 3.53 (1H, d, J = 3.1 Hz), 3.46 (3H, s), 3.26 (1H, t, J = 9.3 Hz), 3.14 (1H, dd, J = 10.0, 14.3 Hz), 2.96 (1H, dt, J = 1.9, 6.8 Hz), 1.97−1.78 (4H, m), 0.90 (9H, s), 0.04 (3H, s), −0.13 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.62, 163.27, 160.37, 160.03, 157.14, 148.91, 140.33, 138.05, 137.63, 137.29, 136.67, 133.45, 133.42 (C), 128.44, 128.31, 128.18, 128.04, 127.96, 127.86, 127.65, 127.15, 127.03, 126.97, 123.15, 118.13, 118.03, 115.93, 115.64, 115.02, 114.75 (CH), 97.92, 81.67, 79.60, 79.23 (CH), 75.78, 74.86 (CH_2), 73.78 (CH), 73.37 (CH_2), 65.64, 60.66, 60.48 (CH), 55.73 (CH_3), 51.63, 38.06 (CH_2), 25.85 (CH_3), 24.69 (CH_2), 18.22 (C), −4.54, −4.87 (CH_3). IR (cm^{-1}): 3032, 2930, 2858, 1750, 1605, 1510, 1455, 1386, 1252, 1220, 1153, 1086, 1073, 1048, 870, 836, 755, 699. MALDI-MS ($C_{58}H_{65}F_2NO_{10}SiS$): $[MNa]^+$ 1056.3969 (calcd 1056.3964). Anal. Calcd for $C_{58}H_{65}F_2NO_{10}SiS$: C, 67.35; H, 6.33; N, 1.35. Found: C, 67.43; H, 6.44; N, 1.33.

***β*-Lactam 14.** Sulfonate **42** (105.1 mg, 0.102 mmol) was dissolved in EtOH (5 mL), $Pd(OH)_2$/C (20% (w/w), 33 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 6 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 2.0 cm) on silica gel eluting with a gradient of 0−10% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated *β*-lactam (63.2 mg, 81%) as a colorless oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.36. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, d, J = 8.7 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.37 (2H, dd, J = 5.9, 8.4 Hz), 7.28 (2H, dd, J = 5.0, 9.3 Hz), 7.11−7.01 (4H, m), 4.96 (1H, d, J = 1.9 Hz), 4.84 (1H, t, J = 5.3 Hz), 4.69 (1H, d, J = 3.7 Hz), 4.61 (1H, d, J = 5.0 Hz), 4.35 (1H, d, J = 3.1 Hz), 4.16 (1H, dt, J = 1.2, 10.0 Hz), 3.87 (1H, dd, J = 1.2, 14.9 Hz), 3.79 (1H, d, J = 7.5 Hz), 3.65 (1H, t, J = 9.0 Hz), 3.56 (1H, dd, J = 10.0, 14.9 Hz), 3.45−3.40 (1H, m), 3.38 (3H, s), 3.27−3.14 (2H, m), 2.00−1.88 (4H, m), 0.87 (9H, s), 0.05 (3H, s), −0.15 (3H, s). ^{13}C NMR (75 MHz, acetone-d_6) δ: 167.25, 163.96, 160.84, 160.75, 157.65, 150.14, 141.91, 141.87, 138.13, 134.95, 134.91 (C), 128.32, 128.23, 123.84, 118.98, 118.88, 116.43, 116.12, 115.49, 115.21 (CH), 100.74, 74.77, 74.42, 73.55, 73.04, 68.01, 61.25, 60.50 (CH), 55.56 (CH_3), 52.83, 38.50 (CH_2), 26.16 (CH_3), 25.34 (CH_2), 18.65 (C), −4.47, −4.71 (CH_3). IR (cm^{-1}): 3396, 2951, 2931, 2857, 1754, 1701, 1605, 1510, 1426, 1385, 1250, 1220, 1151, 1103, 1088, 1053, 1015, 988, 872, 836, 778. MALDI-MS ($C_{37}H_{47}F_2NO_{10}SSi$): $[MNa]^+$ 786.2559 (calcd 786.2556). This silylated *β*-lactam (58.9 mg, 0.077 mmol) was dissolved in anhydrous THF (2.5 mL, Teflon bottle), anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) was added, and the solution was stirred for 14.5 h, diluted with ether (20 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 2.0 cm) on silica gel eluting with a gradient of 0−10% MeOH in CH_2Cl_2 (v/v) to give *β*-lactam **14** (44.9 mg, 90%) as a white solid. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.26. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.56 (2H, d, J = 8.7 Hz), 7.43 (2H, d, J = 8.7 Hz), 7.37 (2H, dd, J = 5.6, 8.7 Hz), 7.30 (2H, dd, J = 4.7, 9.0 Hz), 7.06 (2H, d, J = 9.3 Hz), 7.03 (2H, d, J = 8.7 Hz), 4.99 (1H, d, J = 2.5 Hz), 4.69 (1H, d, J = 3.7 Hz), 4.61 (1H, d, J = 5.0 Hz), 4.42 (1H, d, J = 3.7 Hz), 4.34 (1H, bs), 4.15 (1H, dt, J = 1.2, 8.7 Hz), 3.86 (1H, dd, J = 1.2, 14.9 Hz), 3.79 (1H, d, J = 8.1 Hz), 3.65 (1H, t, J = 8.7 Hz), 3.57 (1H, dd, J = 10.0, 14.9 Hz), 3.44−3.38 (1H, m), 3.38 (3H, s), 3.32−3.14 (2H, m), 2.08−1.86 (4H, m). ^{13}C NMR (75 MHz, acetone-d_6) δ: 167.42, 163.87, 160.85, 157.67, 150.13, 142.52, 138.18, 134.93 (C), 128.35, 128.22, 128.13, 123.83, 119.01, 118.89, 116.44, 116.13, 115.40, 115.11 (CH), 100.74, 74.77, 73.56, 73.04, 72.77, 68.01, 61.27, 60.56 (CH), 55.56 (CH_3), 52.83, 37.54, 25.70 (CH_2). IR (cm^{-1}): 3395, 2925, 1732, 1604, 1509, 1365, 1219, 1148, 1103, 1051, 1014, 871, 834, 752. MALDI-MS ($C_{31}H_{33}F_2NO_{10}S$): $[MNa]^+$ 672.1693

(calcd 672.1691). Anal. Calcd for $C_{31}H_{33}F_2NO_{10}S$: C, 57.31; H, 5.12; N, 2.16. Found: C, 57.34; H, 5.26; N, 2.21.

Sulfonyl Chloride 15. Alcohol **8**[49] (1.069 g, 1.93 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL), anhydrous pyridine (3.0 mL) followed by MsCl (0.50 mL, 6.4 mmol) was added, and after stirring for 2.5 h, saturated aqueous $NaHCO_3$ (50 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (25 mL) and H_2O (25 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.2 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary mesylate[55] (1.202 g, 99%) as a colorless oil after coevaporation with acetonitrile (3 × 15 mL). R_f (1:1 EtOAc/hexane (v/v)): 0.52. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.18 (20H, m), 4.94−4.83 (4H, m), 4.66 (1H, d, J = 10.9 Hz), 4.60 (1H, d, J = 10.9 Hz), 4.56−4.50 (3H, m), 4.37 (1H, dd, J = 3.7, 11.5 Hz), 3.77−3.45 (7H, m), 2.98 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.10, 137.70, 137.59, 137.34 (C), 128.44, 128.36, 128.33, 128.29, 127.95, 127.79, 127.75, 127.67, 127.62, 127.51 (CH), 86.76, 78.62, 77.86, 77.32, 76.86 (CH), 75.60, 75.21, 75.10, 73.36, 69.20, 68.68 (CH_2), 37.92 (CH_3). IR (cm^{-1}): 3031, 2866, 1497, 1454, 1356, 1219, 1175, 1096, 964, 914, 772, 748, 698. MALDI-MS ($C_{36}H_{40}O_8S$): $[MNa]^+$ 655.2344 (calcd 655.2342). Anal. Calcd for $C_{36}H_{40}O_8S$: C, 68.33; H, 6.37. Found: C, 68.33; H, 6.46. This mesylate (1.190 g, 1.88 mmol) was dissolved in EtOH (25 mL), KOSCMe (888 mg, 7.78 mmol) was added, and the unclear solution was stirred at reflux for 16 h (orange precipitate). After cooling, 50% saturated aqueous $NaHCO_3$ (100 mL) was added and the suspension was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.0 × 3.3 cm) on silica gel eluting with a gradient of 0−40% EtOAc in hexane (v/v) to give the intermediary thioacetate[69] (1.064 g, 92%) as a light orange solid. R_f (1:1 EtOAc/hexane (v/v)): 0.69. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43−7.18 (20H, m), 4.93 (2H, s), 4.91 (1H, d, J = 11.8 Hz), 4.85 (1H, d, J = 10.6 Hz), 4.68 (1H, d, J = 10.6 Hz), 4.66 (1H, d, J = 11.8 Hz), 4.62 (1H, d, J = 10.0 Hz), 4.58 (1H, d, J = 11.8 Hz), 3.78−3.40 (8H, m), 3.10 (1H, dd, J = 6.2, 13.7 Hz), 2.36 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.82, 138.28, 138.10, 137.85, 137.60 (C), 128.35, 128.30, 128.26, 128.19, 128.13, 127.77, 127.72, 127.68, 127.62, 127.58, 127.53, 127.41 (CH), 86.85, 80.56, 79.12, 78.22, 77.86 (CH), 75.52, 75.18, 74.99, 73.42, 68.66, 31.10 (CH_2), 30.57 (CH_3). IR (cm^{-1}): 3064, 3031, 2902, 2865, 1693, 1497, 1454, 1360, 1210, 1134, 1099, 1069, 1028, 737, 698, 629. MALDI-MS ($C_{37}H_{40}O_6S$): $[MH]^+$ 613.2617 (calcd 613.2524); $[MNa]^+$ 635.2445 (calcd 635.2443). This thioacetate (2.190 g, 3.57 mmol) was suspended in AcOH (25 mL), KOAc (4.216 g, 43 mmol) followed by Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, 8.076 g, 17.5 mmol) was added, and after stirring for 11 h, saturated aqueous Na_2CO_3 (100 mL) and H_2O (100 mL) were carefully added. After extraction with EtOAc (5 × 100 mL), the combined organic layer was washed with saturated aqueous Na_2CO_3 (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.3 × 3.3 cm) on silica gel eluting with a gradient of 0−90% EtOAc in hexane (v/v) followed by 0−50% MeOH in EtOAc (v/v) to give the intermediary sulfonate salt (467 mg, 20%) as a white solid. Further extractions of the aqueous layer with CH_2Cl_2 (100 + 3 × 50 mL), evaporation on Celite and purification by dry column vacuum chromatography (4.3 × 3.3 cm) on silica gel eluting with a gradient of 0−100% MeOH in EtOAc (v/v) followed by 20% MeOH in CH_2Cl_2 (v/v) gave additional sulfonate salt (810 mg, 35%) as a white solid. R_f (1:3 MeOH/EtOAc (v/v)): 0.49. ^{1}H NMR (300 MHz, suspension in CD_2Cl_2/CD_3OD) δ: 7.37−7.18 (20H, m), 4.86−4.35 (8H, m), 3.86−3.21 (8H, m), 2.97 (1H, dd, J = 8.7, 14.3 Hz). MALDI-MS ($C_{35}H_{37}NaO_8S$): $[MH]^+$ 641.1467 (calcd 641.2185); $[MNa]^+$ 663.1206 (calcd 663.2005). This sulfonate salt (810 mg, 1.26 mmol) was suspended in anhydrous acetonitrile/CH_2Cl_2 (30 mL, 2:1 (v/v)) at 0 °C, Ph_3P (2.087 g, 7.96 mmol) and thionyl chloride (1.50 mL, 21 mmol) were added sequentially at 0 °C, and the suspension was stirred at room temperature for 2.5 h. EtOAc/hexane (1:4 (v/v), 100 mL) was added, the suspension was filtered through Celite (2 × 12.5 mL EtOAc/hexane (1:4 (v/v)) washings), and the filtrate was evaporated and dried shortly under vacuum to give sulfonyl chloride **15** (871 mg, quant.) as a light yellow oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.84. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48−7.21 (20H, m), 5.02−4.85 (4H, m), 4.68−4.55 (4H, m), 3.98−3.35 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.86, 137.72, 137.68, 136.96 (C), 128.64, 128.34, 128.32, 128.27, 128.24, 128.20, 127.99, 127.79, 127.67, 127.61, 127.49 (CH), 86.83, 79.20, 78.46, 77.59 (CH), 75.68, 74.96, 74.82 (CH_2), 74.20 (CH), 73.46, 68.04, 66.69 (CH_2). MALDI-MS ($C_{35}H_{37}ClO_7S$): $[MNa]^+$ 659.1849 (calcd 659.1846).

***β*-Lactam 40.** Sulfonyl chloride **15** (871 mg, 1.26 mmol) was suspended in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (1.0 mL) followed by phenol **5** (334 mg, 0.634 mmol) was added, and the solution was stirred for 13 h, diluted with EtOAc (50 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.3 × 3.3 cm) on silica gel eluting with a gradient of 0−100% CH_2Cl_2 in hexane (v/v) to give the intermediary fully protected sulfonate (657 mg, 92%) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.76. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.15 (28H, m), 7.01 (2H, t, J = 8.7 Hz), 6.96 (2H, t, J = 8.7 Hz), 5.03−4.81 (4H, m), 4.73−4.51 (6H, m), 3.95 (1H, t, J = 8.4 Hz), 3.78 (4H, bs), 3.57−3.53 (1H, m), 3.48 (1H, d, J = 1.2 Hz), 3.40 (1H, t, J = 9.0 Hz), 3.24 (1H, dd, J = 9.3, 14.9 Hz), 3.02−2.95 (1H, m), 1.97−1.80 (4H, m), 0.92 (9H, s), 0.06 (3H, s), −0.11 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.72, 163.24, 160.35, 160.01, 157.13, 149.25, 140.37, 140.33, 137.90, 137.65, 137.58, 137.12, 136.97, 136.52, 133.52, 133.48 (C), 128.46, 128.32, 128.28, 128.17, 128.02, 127.97, 127.81, 127.76, 127.67, 127.63, 127.52, 127.13, 127.02, 123.32, 118.13, 118.02, 115.90, 115.60, 115.01, 114.72 (CH), 86.83, 79.13, 78.83, 77.73 (CH), 75.56, 75.00, 74.85 (CH_2), 74.19, 73.77 (CH), 73.31 (CH_2), 68.36, 60.57, 60.53 (CH), 51.31, 38.03 (CH_2), 25.85 (CH_3), 24.67 (CH_2), 18.20 (C), −4.57, −4.87 (CH_3). IR (cm^{-1}): 2951, 2929, 2858, 1751, 1605, 1510, 1454, 1386, 1362, 1251, 1220, 1151, 1102, 871, 835, 776, 754, 699. MALDI-MS ($C_{65}H_{71}F_2NO_{10}SiS$): $[MNa]^+$ 1146.4440 (calcd 1146.4434). Anal. Calcd for $C_{65}H_{71}F_2NO_{10}SiS$: C, 69.43; H, 6.36; N, 1.25. Found: C, 69.27; H, 6.47; N, 1.28. This sulfonate (236 mg, 0.210 mmol) was dissolved in EtOH/EtOAc (10 mL, 1:1 (v/v)), $Pd(OH)_2/C$ (20% (w/w), 73 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 3.5 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.6 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give *β*-lactam **40** (145 mg, 90%) as a white foam. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.25. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, dd, J = 6.5, 8.7 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.40−7.20 (4H, m), 7.11−6.98 (4H, m), 4.97 (1H, dd, J = 2.3, 10.5 Hz), 4.83 (1H, bs), 4.61 (1H, bs), 4.48 (1H, bs), 4.30 (1H, bs), 3.90−3.81 (3H, m), 3.71−3.64 (1H, m), 3.56−3.38 (5H, m), 3.25−3.14 (2H, m), 2.66 (1H, t, J = 7.2 Hz), 1.98−1.81 (4H, m), 0.88 (9H, s), 0.05 (3H, s), −0.15 (3H, s). ^{13}C NMR (75 MHz, acetone-d_6) δ: 168.30, 161.88, 158.69, 151.25, 142.96, 139.63, 139.16, 139.13, 135.98 (C), 131.66, 131.56, 129.36, 129.28, 124.92, 120.00, 119.90, 117.46, 117.16, 116.62, 116.52 (CH), 82.13, 80.16, 76.75, 75.44, 74.46, 72.35 (CH), 63.64 (CH_2), 61.60, 61.55 (CH), 54.03, 39.52 (CH_2), 27.20 (CH_3), 26.35 (CH_2), 19.68 (C), −3.44, −3.69 (CH_3). IR (cm^{-1}): 3380, 2930, 2858, 1749, 1604, 1510, 1385, 1363, 1220, 1172, 1149, 1088, 1032, 1016, 872, 835, 757. MALDI-MS ($C_{37}H_{47}F_2NO_{10}SiS$): $[MNa]^+$ 786.2563 (calcd 786.2556). Anal. Calcd for $C_{37}H_{47}F_2NO_{10}SiS$: C, 58.17; H, 6.20; N, 1.83. Found: C, 58.02; H, 6.26; N, 1.85.

***β*-Lactam 16.** *β*-Lactam **40** (31.5 mg, 0.041 mmol) was dissolved in anhydrous THF (2.5 mL, Teflon bottle), anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) was added, and the solution was stirred for 24 h, diluted with ether (20 mL), and washed with saturated aqueous $NaHCO_3$

(3 × 5 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.3 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give β-lactam **16** (9.8 mg, 37%) as a white solid. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.22 (run twice). ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz), 7.36 (2H, dd, J = 5.6, 8.7 Hz), 7.29 (2H, dd, J = 4.8, 9.2 Hz), 7.06 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 9.0 Hz), 4.98 (1H, d, J = 2.5 Hz), 4.68 (1H, bs), 4.58 (1H, bs), 4.38 (1H, bs), 4.27 (1H, bs), 3.89−3.80 (3H, m), 3.66 (1H, d, J = 10.6 Hz), 3.54−3.36 (5H, m), 3.24−3.14 (2H, m), 2.00−1.86 (4H, m). ^{13}C NMR (75 MHz, acetone-d_6) δ: 168.48, 151.29, 143.63, 139.23, 136.09 (C), 129.37, 129.29, 129.19, 124.97, 120.05, 119.94, 117.49, 117.18, 116.46, 116.18 (CH), 82.17, 80.18, 76.78, 74.49, 73.79, 72.42 (CH), 63.67 (CH_2), 62.35, 61.63 (CH), 54.06, 38.62, 26.75 (CH_2). IR (cm^{-1}): 3364, 2924, 1734, 1509, 1388, 1220, 1148, 1102, 872, 835, 769. MALDI-MS ($C_{31}H_{33}F_2NO_{10}S$): $[MNa]^+$ 672.1744 (calcd 672.1691).

Sulfonyl Chloride 17. Alcohol **10**[50] (895.3 mg, 0.907 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (1.0 mL) followed by MsCl (0.20 mL, 2.6 mmol) was added, and after stirring for 1 h, saturated aqueous $NaHCO_3$ (40 mL) was added. The layers were separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.2 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary mesylate (830.7 mg, 86%) as a white solid. R_f (1:1 EtOAc/hexane (v/v)): 0.67. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49−7.24 (35H, m), 5.31 (1H, d, J = 11.2 Hz), 5.00 (1H, d, J = 11.2 Hz), 4.98−4.79 (6H, m), 4.66−4.36 (9H, m), 4.09 (1H, t, J = 9.3 Hz), 3.90 (1H, dd, J = 2.8, 10.9 Hz), 3.83 (1H, d, J = 10.0 Hz), 3.75−3.62 (5H, m), 3.55−3.39 (5H, m), 2.97 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.97, 138.37, 138.21, 138.04, 137.61 (C), 128.37, 128.29, 128.18, 128.08, 127.93, 127.84, 127.76, 127.38, 127.34, 127.24, 102.51, 84.86, 82.64, 78.70, 77.94, 76.84, 76.53, 76.38, 75.57 (CH), 75.22, 75.09 (CH_2), 74.96, 74.78 (CH_2, CH), 73.21, 73.02, 69.22, 68.89, 67.76 (CH_2), 37.74 (CH_3). IR (cm^{-1}): 3063, 3030, 2867, 1497, 1454, 1358, 1277, 1209, 1174, 1150, 1092, 1071, 1028, 984, 922, 812, 737, 698, 527. MALDI-MS ($C_{63}H_{68}O_{13}S$): $[MNa]^+$ 1087.4284 (calcd 1087.4278). Anal. Calcd for $C_{63}H_{68}O_{13}S$: C, 71.03; H, 6.43. Found: C, 70.94; H, 6.62. This mesylate (825 mg, 0.774 mmol) was dissolved in EtOH (20 mL), KOSCMe (278 mg, 2.43 mmol), *i*PrOH (10 mL) and THF (10 mL) were added, and the orange solution was stirred at reflux for 3 h (orange precipitate). Additional KOSCMe (512 mg, 4.48 mmol) was added and the suspension was stirred at reflux for 16 h. After cooling, 50% saturated aqueous $NaHCO_3$ (100 mL) was added and the suspension was extracted with ether (4 × 30 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.2 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary thioacetate (637 mg, 79%) as a light orange solid. R_f (1:3 EtOAc/hexane (v/v)): 0.45. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43−7.19 (35H, m), 5.22 (1H, d, J = 11.2 Hz), 4.92 (1H, d, J = 11.2 Hz), 4.88 (1H, d, J = 11.2 Hz), 4.87−4.71 (5H, m), 4.62 (1H, d, J = 12.5 Hz), 4.60−4.43 (5H, m), 4.41 (1H, d, J = 11.8 Hz), 4.06 (1H, t, J = 9.3 Hz), 3.86 (1H, dd, J = 3.7, 11.2 Hz), 3.75 (1H, dd, J = 1.6, 10.9 Hz), 3.69−3.55 (5H, m), 3.51−3.31 (6H, m), 3.05 (1H, dd, J = 6.8, 13.7 Hz), 2.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.04, 139.19, 138.53, 138.30, 138.24, 138.17, 137.96 (C), 128.33, 128.26, 128.20, 128.04, 127.79, 127.71, 127.63, 127.55, 127.47, 127.29, 127.19, 102.40, 85.12, 84.88, 82.71, 79.85, 79.30, 78.05, 77.87 (CH), 75.62, 75.18 (CH_2), 75.09 (CH), 74.94, 74.81, 73.26, 73.21, 68.96, 67.86, 31.12 (CH_2), 30.49 (CH_3). IR (cm^{-1}): 3030, 2868, 1692, 1496, 1454, 1358, 1210, 1067, 1028, 773, 735, 698, 626. MALDI-MS ($C_{64}H_{68}O_{11}S$): $[MNa]^+$ 1067.4365 (calcd 1067.4380). Anal. Calcd for $C_{64}H_{68}O_{11}S$: C, 73.54; H, 6.56. Found: C, 73.50; H, 6.60. This thioacetate (631 mg, 0.604 mmol) was suspended in AcOH (10 mL), KOAc (933 mg, 9.5 mmol) followed by Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, 1.179 g, 2.55 mmol) was added, and after stirring for 18 h, saturated aqueous Na_2CO_3 (50 mL) and H_2O (50 mL) were carefully added. After extraction with $CHCl_3$ (4 × 25 mL), the combined organic layer was washed with saturated aqueous Na_2CO_3 (25 mL), evaporated on Celite, and purified by dry column vacuum chromatography (4.1 × 3.3 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give the intermediary sulfonate salt (622 mg, 96%) as a colorless oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.29. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.14 (35H, m), 5.19−4.34 (15H, m), 4.17−3.22 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.97, 138.32, 138.21, 138.06, 137.88, 137.84, 128.70, 128.36, 128.18, 128.05, 127.86, 127.76, 127.63, 127.57, 127.44, 127.29, 127.20, 126.94, 84.53, 84.45, 82.01, 79.48, 77.96, 77.75, 76.06, 76.01, 75.46, 74.94, 74.79, 74.67, 74.57, 73.28, 73.08, 73.02, 53.42. IR (cm^{-1}): 3478, 3063, 3030, 2870, 1497, 1454, 1361, 1315, 1210, 1174, 1069, 1048, 1028, 736, 698, 621. MALDI-MS ($C_{62}H_{65}NaO_{13}S$): $[MH]^+$ 1073.4098 (calcd 1073.4122); $[MNa]^+$ 1095.3926 (calcd 1095.3941). This sulfonate salt (334 mg, 0.311 mmol) was dissolved in anhydrous acetonitrile/CH_2Cl_2 (4 mL, 1:1 (v/v)) at 0 °C, Ph_3P (264 mg, 1.01 mmol) and thionyl chloride (0.10 mL, 1.37 mmol) were added sequentially at 0 °C, and the suspension was stirred at room temperature for 6 h. EtOAc/hexane (1:4 (v/v), 30 mL) was added, the suspension was filtered through a short pad of silica gel (4 × 5 mL EtOAc/hexane (1:3 (v/v)) washings), and the filtrate was evaporated and dried shortly under vacuum to give sulfonyl chloride **17** (220 mg, 66%) as a light yellow foam. R_f (1:3 EtOAc/hexane (v/v)): 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50−7.26 (35H, m), 5.30 (1H, d, J = 11.2 Hz), 4.98 (1H, d, J = 10.6 Hz), 4.96−4.81 (5H, m), 4.79 (1H, d, J = 10.6 Hz), 4.67−4.50 (6H, m), 4.48 (1H, d, J = 11.8 Hz), 4.23−4.15 (1H, m), 3.98−3.91 (2H, m), 3.85−3.57 (8H, m), 3.51−3.38 (3H, m), 3.30 (1H, t J = 9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.77, 138.45, 138.17, 138.11, 137.78, 137.27 (C), 128.63, 128.38, 128.31, 128.18, 128.12, 127.94, 127.78, 127.70, 127.63, 127.55, 127.42, 127.29, 102.32, 84.98, 84.80, 82.66, 79.23, 77.95, 77.82, 75.78 (CH), 75.60, 75.38 (CH_2), 75.12 (CH), 74.99, 74.78, 74.70 (CH_2), 74.21 (CH), 73.24, 68.95, 67.35, 66.79 (CH_2). IR (cm^{-1}): 3089, 3063, 3030, 2868, 1496, 1454, 1362, 1313, 1280, 1209, 1167, 1091, 1067, 1028, 913, 771, 736, 698, 601. MALDI-MS ($C_{62}H_{65}ClO_{12}S$): $[MNa]^+$ 1091.3767 (calcd 1091.3783).

***β*-Lactam 18.** Sulfonyl chloride **17** (271 mg, 0.253 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL), anhydrous pyridine (0.5 mL) followed by phenol **5** (75.7 mg, 0.145 mmol) was added, and the solution was stirred for 38 h, diluted with EtOAc (50 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.5 × 3.3 cm) on silica gel eluting with a gradient of 0−20% EtOAc in toluene (v/v) to give a 4:1 mixture of the intermediary fully protected sulfonate and unreacted phenol **5** (166 mg) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.73. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49−7.17 (41H, m), 7.06 (2H, d, J = 8.7 Hz), 7.02 (2H, t, J = 8.1 Hz), 6.96 (2H, d, J = 8.7 Hz), 5.31 (1H, d, J = 11.2 Hz), 5.01−4.74 (7H, m), 4.65−4.45 (8H, m), 4.21 (1H, t, J = 9.3 Hz), 4.02−3.96 (2H, m), 3.86−3.60 (6H, m), 3.53−3.47 (4H, m), 3.33 (1H, d, J = 9.3 Hz), 3.26 (1H, t, J = 9.0 Hz), 3.19 (1H, d, J = 9.3 Hz), 3.06−3.00 (1H, m), 2.06−1.84 (4H, m), 0.96 (9H, s), 0.10 (3H, s), −0.07 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.70, 160.35, 160.00, 156.27, 149.33, 140.35, 140.31, 138.63, 138.26, 138.00, 137.90, 137.59, 137.45, 137.29, 136.51, 133.47 (C), 128.82, 128.73, 128.34, 128.19, 128.08, 127.98, 127.85, 127.66, 127.56, 127.45, 127.30, 127.25, 127.12, 127.01, 125.10, 123.32, 118.11, 118.01, 115.91, 115.60, 115.00, 114.93, 114.72, 102.39, 84.93, 84.80, 82.56, 78.82, 78.55, 77.95, 75.99 (CH), 75.60, 75.31 (CH_2), 75.15 (CH), 74.96, 74.76 (CH_2), 74.23, 73.77 (CH), 73.21, 73.08, 68.97, 67.62 (CH_2), 61.02, 60.57, 60.39 (CH), 51.26, 38.02 (CH_2), 25.85 (CH_3), 24.67 (CH_2), 18.19 (C), −4.56, −4.87 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.94 (1F, septet, J = 4.3 Hz), −117.10 (1F, septet, J = 4.3 Hz). MALDI-MS ($C_{92}H_{99}F_2NO_{15}SiS$): $[MNa]^+$ 1578.6365 (calcd 1578.6370). This fully

protected sulfonate (166 mg 4:1 mixture) was dissolved in EtOH (5 mL), $Pd(OH)_2/C$ (20% (w/w), 94 mg) was added, and the suspension was evacuated four times with H_2 and stirred under an H_2 atmosphere for 11.5 h. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.3 × 2.0 cm) on silica gel eluting with a gradient of 0−10% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated β-lactam (69.5 mg, 52% from **5**) as a colorless oil. R_f (20% MeOH in CH_2Cl_2 (v/v)): 0.46. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.46−7.38 (4H, m), 7.31−7.23 (4H, m), 7.04−6.95 (4H, m), 4.75−4.68 (1H, m), 4.44 (1H, d, J = 8.1 Hz), 3.92−3.80 (5H, m), 3.69−3.18 (11H, m), 3.10−3.05 (1H, m), 1.95−1.75 (4H, m), 0.86 (9H, s), 0.01 (3H, s), −0.19 (3H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.31, 169.21, 161.76, 158.91, 150.96, 142.28, 138.45, 135.01, 134.98, 131.06, 130.95 (C), 128.83, 124.50, 119.92, 119.83, 116.99, 116.68, 116.10, 116.04, 115.81, 115.74, 104.54, 80.33, 80.10, 78.11, 77.81, 77.72, 76.30, 75.13, 74.89, 73.61, 71.38 (CH), 62.47, 61.63 (CH_2), 61.56, 61.47 (CH), 53.26, 38.83 (CH_2), 26.38 (CH_3), 25.75 (CH_2), 19.04 (C), −4.40, −4.70 (CH_3). ^{19}F NMR (282 MHz, CD_3OD) δ: −117.94 (1F, septet, J = 4.3 Hz), −120.10 (1F, septet, J = 4.3 Hz). MALDI-MS ($C_{43}H_{57}F_2NO_{15}SiS$): $[MNa]^+$ 948.3088 (calcd 948.3084). This silylated β-lactam (59.5 mg, 0.073 mmol) was dissolved in anhydrous THF (2.0 mL, Teflon bottle), anhydrous pyridine (0.40 mL) followed by HF·pyridine complex (0.40 mL) was added, and the solution was stirred for 14 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.4 × 2.0 cm) on silica gel eluting with a gradient of 10−20% MeOH in CH_2Cl_2 (v/v) to give β-lactam **18** (38.1 mg, 64%) as a white solid. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.17 (eluted three times). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.45 (2H, t, J = 9.3 Hz), 7.40 (2H, d, J = 8.7 Hz), 7.33−7.24 (4H, m), 7.02 (2H, t, J = 8.1 Hz), 6.98 (2H, d, J = 8.7 Hz), 4.90 (1H, d, J = 1.9 Hz), 4.60 (1H, dd, J = 5.0, 6.2 Hz), 4.43 (1H, d, J = 7.5 Hz), 3.92−3.79 (5H, m), 3.69−3.49 (4H, m), 3.44−3.18 (6H, m), 3.12−3.06 (1H, m), 1.99−1.82 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ: 169.31, 165.08, 162.17, 161.85, 158.96, 150.98, 142.15, 138.51, 135.01 (C), 128.88, 128.76, 124.46, 119.97, 119.86, 116.99, 116.68, 116.13, 115.84, 104.54, 80.35, 80.06, 78.11, 77.81, 77.71, 76.31, 74.91, 73.77, 73.63, 71.39 (CH), 62.45, 61.50 (CH_2), 61.42 (CH), 53.26, 37.45, 26.12 (CH_2). ^{19}F NMR (282 MHz, CD_3OD) δ: −118.08 (1F, septet, J = 4.3 Hz), −120.21 (1F, septet, J = 4.3 Hz). MALDI-MS ($C_{37}H_{43}F_2NO_{15}S$): $[MNa]^+$ 834.2223 (calcd 834.2219).

Azetidine (±)-24. $LiAlH_4$ (114 mg, 3.0 mmol) and $AlCl_3$ (390 mg, 2.9 mmol) were suspended in anhydrous ether (15 mL) and refluxed for 30 min. Azetidinone (±)-**3**[62] (361 mg, 1.00 mmol) dissolved in anhydrous ether (15 mL) was added, and after stirring at reflux for 30 min, the suspension was cooled, and H_2O (5 mL) was added dropwise followed by addition of 50% saturated aqueous $NaHCO_3$ (30 mL). The layers were separated, the aqueous layer was extracted with EtOAc/hexane and ether, and the combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL), evaporated on Celite, and purified by dry column vacuum chromatography (3.7 × 3.3 cm) on silica gel eluting with a gradient of 0−10% EtOAc in hexane (v/v) to give azetidine (±)-**24** (281 mg, 81%) as a colorless oil. R_f (1:9 EtOAc/hexane (v/v)): 0.53. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.14 (10H, m), 6.87 (2H, t, J = 8.7 Hz), 6.38 (2H, dd, J = 4.7, 9.0 Hz), 4.46 (1H, d, J = 6.8 Hz), 4.17 (1H, t, J = 6.8 Hz), 3.35 (1H, dd, J = 6.8, 7.5 Hz), 2.69−2.58 (3H, m), 1.85−1.56 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.64, 154.52, 148.53, 142.69, 141.95 (C), 128.66, 128.25, 127.47, 125.99, 125.73, 115.41, 115.12, 113.04, 112.94 (CH), 74.37 (CH), 56.05 (CH_2), 42.09 (CH), 35.85, 33.52, 28.92 (CH_2). IR (cm^{-1}): 3026, 2933, 2852, 1603, 1508, 1473, 1453, 1321, 1222, 1120, 823, 773, 747, 699. MALDI-MS ($C_{24}H_{24}FN$): $[MH]^+$ 346.1982 (calcd 346.1971). Anal. Calcd for $C_{24}H_{24}FN$: C, 83.44; H, 7.00; N, 4.05. Found: C, 83.45; H, 7.06; N, 4.27.

Silyl Ether 25. Ezetimibe **1**[42] (279 mg, 0.681 mmol) was dissolved in anhydrous DMF (5 mL), imidazole (262 mg, 3.84 mmol) and TBDMSCl (500 mg, 3.32 mmol) were added sequentially, and the solution was stirred for 5 h followed by addition of 50% saturated aqueous $NaHCO_3$ (50 mL). After extraction with EtOAc (4 × 20 mL), the combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL), evaporated on Celite, and purified by dry column vacuum chromatography (3.8 × 3.3 cm) on silica gel eluting with a gradient of 0−10% EtOAc in hexane (v/v) to give silyl ether **25** (424 mg, 97%) as a colorless oil. R_f (1:3 EtOAc/hexane (v/v)): 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25−7.21 (4H, m), 7.17 (2H, d, J = 8.1 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 6.83 (2H, d, J = 8.1 Hz), 4.66 (1H, t, J = 5.6 Hz), 4.51 (1H, d, J = 2.5 Hz), 3.08−3.02 (1H, m), 1.96−1.78 (4H, m), 0.98 (9H, s), 0.88 (9H, s), 0.20 (6H, s), 0.02 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.27, 163.28, 160.27, 160.04, 157.06, 155.71, 140.58, 140.54, 133.89, 133.86 (C), 129.99, 127.22, 127.11, 126.94, 120.56, 118.24, 118.15, 115.74, 115.44, 114.99, 114.72 (CH), 73.84, 61.08, 60.44 (CH), 38.08 (CH_2), 25.90, 25.68 (CH_3), 24.75 (CH_2), 18.26, 18.24 (C), −4.28, −4.52, −4.83 (CH_3). IR (cm^{-1}): 2954, 2930, 2858, 1752, 1607, 1510, 1385, 1259, 1223, 1101, 1085, 914, 834, 778. MALDI-MS ($C_{36}H_{49}F_2NO_3Si_2$): $[MH - TBDMSOH]^+$ 506.2329 (calcd 506.2327); $[MH]^+$ 638.3289 (calcd 638.3297); $[MNa]^+$ 660.3117 (calcd 660.3117). Anal. Calcd for $C_{36}H_{49}F_2NO_3Si_2$: C, 67.78; H, 7.74; N, 2.20. Found: C, 67.70; H, 7.60; N, 2.02.

Bicycle 26. $LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 40 min, and cooled to 0 °C. Azetidinone **25** (180.8 mg, 0.283 mmol) dissolved in anhydrous ether (5 mL) was added, and after stirring at 0 °C for 30 min, H_2O (1 mL) was added dropwise. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (3.5 × 3.3 cm) on silica gel eluting with a gradient of 0−50% CH_2Cl_2 in hexane (v/v) to give bicycle **26** (110.8 mg, 63%) and olefin **28** (24.1 mg, 16%) as colorless oils. **26:** R_f (1:9 EtOAc/hexane (v/v)): 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18−7.14 (2H, m), 6.95 (2H, t, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.74 (2H, d, J = 8.1 Hz), 6.68 (1H, dd, J = 2.8, 8.4 Hz), 6.44 (1H, dd, J = 6.5, 8.7 Hz), 6.38 (1H, dd, J = 2.8, 9.6 Hz), 4.48 (1H, dd, J = 5.0, 6.8 Hz), 3.78 (1H, bs), 3.61 (1H, d, J = 7.5 Hz), 3.26 (1H, dd, J = 3.1, 11.2 Hz), 2.91 (1H, dd, J = 7.8, 11.5 Hz), 1.91−1.85 (1H, m), 1.68−1.44 (3H, m), 1.16−1.04 (1H, m), 0.99 (9H, s), 0.80 (9H, s), 0.20 (6H, s), 0.06 (3H, s), −0.21 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.60, 160.36, 157.37, 154.27, 141.53, 141.01, 138.13 (C), 130.07, 127.56, 127.46, 125.58, 125.50, 120.01, 117.27, 116.98, 115.17, 114.89, 114.78, 114.08, 113.79 (CH), 74.64, 48.97 (CH), 44.52 (CH_2), 39.89 (CH), 38.67, 28.28 (CH_2), 26.00, 25.90 (CH_3), 18.38, 18.32 (C), −4.16, −4.43, −4.77 (CH_3). IR (cm^{-1}): 2955, 2930, 2858, 1607, 1506, 1472, 1408, 1361, 1258, 1222, 1170, 1144, 1085, 1006, 915, 837, 808, 779, 735, 667. MALDI-MS ($C_{36}H_{51}F_2NO_2Si_2$): $[MH - TBDMSOH]^+$ 492.2517 (calcd 492.2534); $[M]^+$ 623.3414 (calcd 623.3426). Anal. Calcd for $C_{36}H_{51}F_2NO_2Si_2$: C, 69.30; H, 8.24; N, 2.24. Found: C, 69.47; H, 8.32; N, 2.15. **28:** R_f (1:9 EtOAc/hexane (v/v)): 0.70. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29−7.25 (2H, m), 7.18 (2H, t, J = 8.7 Hz), 6.19 (2H, t, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 6.30 (1H, d, J = 15.6 Hz), 6.04 (1H, dd, J = 6.8, 15.6 Hz), 4.68 (1H, dd, J = 5.0, 7.5 Hz), 2.26−2.13 (2H, m), 1.91−1.66 (2H, m), 0.98 (9H, s), 0.89 (9H, s), 0.19 (6H, s), 0.04 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.42, 160.18, 154.72, 141.28, 131.10, 129.49 (C), 128.25, 127.42, 127.32, 126.87, 120.10, 114.97, 114.69, 73.85 (CH), 40.64, 28.94 (CH_2), 25.84, 25.68 (CH_3), 18.22, 18.18 (C), −4.42, −4.60, −4.91 (CH_3). IR (cm^{-1}): 3030, 2956, 2930, 2887, 2858, 1605, 1509, 1472, 1362, 1258, 1223, 1169, 1155, 1088, 1006, 965, 915, 837, 804, 779, 701, 665.

Amino Alcohol 29. Azetidinone **25** (1.880 g, 2.95 mmol) was dissolved in anhydrous THF (50 mL) at 0 °C, $LiAlH_4$ (534 mg, 14.1 mmol) was added, and the mixture was stirred at 0 °C for 23 h. Saturated aqueous $NHCO_3$ (2 mL) was carefully added, and the suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 5.5 cm) on silica gel eluting with a gradient of 0−20% EtOAc in hexane (v/v) to give amino alcohol **29** (1.496 g, 79%) as a colorless oil.

R_f (1:3 EtOAc/hexane (v/v)): 0.47. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19 (2H, dd, J = 5.6, 8.7 Hz), 7.10 (2H, d, J = 8.7 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.78 (2H, t, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 6.42 (2H, dd, J = 4.4, 9.3 Hz), 4.54 (1H, dd, J = 5.0, 6.8 Hz), 4.28 (1H, d, J = 6.2 Hz), 3.73 (1H, dd, J = 2.8, 10.9 Hz), 3.60 (1H, dd, J = 5.3, 10.9 Hz), 1.84−1.76 (1H, m), 1.72−1.50 (3H, m), 1.37−1.20 (1H, m), 0.99 (9H, s), 0.85 (9H, s), 0.20 (6H, s), −0.03 (3H, s), −0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.17, 159.94, 157.12, 154.33, 154.02, 143.62, 140.94, 140.91, 134.52 (C), 127.62, 127.16, 127.05, 119.84, 115.43, 115.13, 114.88, 114.73, 114.60, 74.41 (CH), 63.62 (CH_2), 61.91, 46.19 (CH), 38.51 (CH_2), 25.85, 25.69 (CH_3), 24.71 (CH_2), 18.22 (C), −4.30, −4.56, −4.88 (CH_3). IR (cm^{-1}): 3400, 2957, 2938, 2859, 1607, 1510, 1472, 1362, 1257, 1222, 1102, 1086, 914, 837, 779, 736, 668. MALDI-MS ($C_{36}H_{53}F_2NO_3Si_2$): [MH − TBDMSOH]$^+$ 510.2624 (calcd 510.2640); [MNa]$^+$ 664.3420 (calcd 664.3430). Anal. Calcd for $C_{36}H_{53}F_2NO_3Si_2$: C, 67.35; H, 8.32; N, 2.18. Found: C, 67.40; H, 8.23; N, 2.21.

Azetidine 30. Amino alcohol **29** was dissolved in anhydrous acetonitrile (5 mL), Ph_3P (99 mg, 0.38 mmol), CBr_4 (133 mg, 0.40 mmol), and anhydrous Et_3N (0.10 mL, 0.71 mmol) were added sequentially, and the mixture was stirred at room temperature for 12 h. After dilution with EtOAc/hexane (20 mL, 1:4 (v/v)), the suspension was filtered through a short pad of silica gel and the filter cake was washed with EtOAc/hexane (2 × 25 mL, 1:4 (v/v)). The filtrates were evaporated on Celite and purified by dry column vacuum chromatography (4.0 × 3.3 cm) on silica gel eluting with a gradient of 0−7% EtOAc in hexane (v/v) to give azetidine **30** (85 mg, 60%) and the acyclic amino bromide (52.8 mg, 33%) as colorless oils. **30:** R_f (1:19 EtOAc/hexane (v/v)): 0.57. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (2H, d, J = 8.1 Hz), 7.18−7.14 (2H, m), 6.98 (2H, t, J = 8.7 Hz), 6.87−6.81 (4H, m), 6.34 (2H, dd, J = 4.4, 8.7 Hz), 6.42 (2H, dd, J = 4.4, 9.3 Hz), 4.55 (1H, dd, J = 5.0, 6.2 Hz), 4.31 (1H, d, J = 6.8 Hz), 4.08 (1H, dd, J = 6.2, 7.5 Hz), 3.23 (1H, dd, J = 6.8, 7.4 Hz), 2.57 (1H, dd, J = 6.8, 7.5 Hz), 1.78−1.50 (4H, m), 1.02 (9H, s), 0.89 (9H, s), 0.24 (6H, s), 0.02 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.24, 160.00, 158.64, 157.58, 154.97, 154.47, 148.67, 148.64, 140.89, 140.86, 135.39 (C), 127.18, 127.07, 126.78, 120.07, 120.02, 115.33, 115.04, 114.92, 114.63, 113.05, 112.95, 74.07, 73.87 (CH), 55.78 (CH_2), 41.91 (CH), 37.96, 29.52 (CH_2), 25.90, 25.77 (CH_3), 18.29 (C), −4.23, −4.48, −4.83 (CH_3). MALDI-MS ($C_{36}H_{51}F_2NO_2Si_2$): [MH − TBDMSOH]$^+$ 492.2518 (calcd 492.2534); [M]$^+$ 623.3405 (calcd 623.3426); [MNa]$^+$ 646.3314 (calcd 646.3324).

Acyclic Amino Bromide: R_f (1:19 EtOAc/hexane (v/v)): 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19 (2H, dd, J = 5.6, 8.7 Hz), 7.09 (2H, d, J = 8.7 Hz), 6.97 (2H, t, J = 8.7 Hz), 6.79 (2H, t, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 6.47 (2H, dd, J = 4.4, 8.7 Hz), 4.51 (1H, dd, J = 3.7, 7.5 Hz), 4.37 (1H, d, J = 6.8 Hz), 3.94 (1H, bs), 3.72 (1H, dd, J = 3.7, 10.0 Hz), 3.40 (1H, dd, J = 5.0, 10.6 Hz), 2.00−1.91 (1H, m), 1.74−1.47 (3H, m), 1.32−1.15 (1H, m), 0.99 (9H, s), 0.83 (9H, s), 0.20 (6H, s), −0.06 (3H, s), −0.20 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.36, 160.12, 157.44, 154.80, 154.32, 143.37, 141.15, 141.12, 133.11 (C), 127.93, 127.29, 127.19, 127.09, 126.87, 120.43, 120.01, 115.56, 115.27, 114.98, 114.86, 114.69, 114.64, 74.26, 60.13, 45.62 (CH), 38.34, 35.91, 25.83 (CH_2), 25.75, 25.59 (CH_3), 18.05 (C), −4.44, −4.72, −5.06 (CH_3). IR (cm^{-1}): 2956, 2930, 2858, 1607, 1509, 1472, 1362, 1257, 1222, 1100, 1086, 916, 837, 776. MALDI-MS ($C_{36}H_{52}BrF_2NO_2Si_2$): [MH − $H_2NC_6H_4F$]$^+$ 593.2283 (calcd 593.2282).

Mesylate 31. Phenol **5** (176 mg, 0.336 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (0.5 mL) followed by MsCl (0.1 mL, 1.29 mmol) was added, and the solution was stirred for 22 h, diluted with EtOAc (50 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give mesylate **31** (195.5 mg, 92%) as a colorless oil. R_f (1% MeOH in CH_2Cl_2 (v/v)): 0.74. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.26−7.18 (4H, m), 6.98 (2H, t, J = 8.7 Hz), 6.93 (2H, t, J = 8.7 Hz), 4.67 (1H, dd, J = 4.4, 6.2 Hz), 4.59 (1H, d, J = 1.9 Hz), 3.16 (3H, s), 3.04−3.00 (1H, m), 1.93−1.79 (4H, m), 0.87 (9H, s), 0.01 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.83, 163.46, 160.57, 160.21, 157.34, 148.88, 140.53, 140.49, 137.07, 133.59, 133.56 (C), 127.36, 127.28, 127.18, 122.94, 118.26, 118.16, 116.04, 115.73, 115.10, 114.81 (CH), 73.79, 60.67, 60.41 (CH), 37.97 (CH_2), 37.59, 25.76 (CH_3), 24.60 (CH_2), 18.11 (C), −4.71, −5.02 (CH_3). IR (cm^{-1}): 2952, 2931, 2857, 1752, 1605, 1509, 1371, 1252, 1220, 1176, 1153, 1102, 1086, 971, 871, 835, 777. MALDI-MS ($C_{31}H_{37}F_2NO_5SiS$): [MH − TBDMSOH]$^+$ 470.1228 (calcd 470.12376); [MNa]$^+$ 624.2029 (calcd 624.2027). Anal. Calcd for $C_{31}H_{37}F_2NO_5SiS$: C, 61.87; H, 6.20; N, 2.33. Found: C, 61.69; H, 6.19; N, 2.15.

Azetidine 32. $LiAlH_4$ (58 mg, 1.5 mmol) and $AlCl_3$ (202 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min, and cooled to 0 °C. Mesylate **31** (195.5 mg, 0.325 mmol) dissolved in anhydrous ether (5 mL) was added, and after stirring at 0 °C for 15 min, saturated aqueous $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.6 × 3.3 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary silylated azetidine (146.4 mg, 77%) as a colorless oil. R_f (1:3 EtOAc/hexane (v/v)): 0.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (2H, d, J = 8.7 Hz), 7.30 (2H, d, J = 8.7 Hz), 7.18 (2H, dd, J = 5.0, 8.7 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.85 (2H, t, J = 8.7 Hz), 6.31 (2H, dd, J = 4.4, 9.3 Hz), 4.58 (1H, t, J = 5.3 Hz), 4.40 (1H, d, J = 6.8 Hz), 4.11 (1H, t, J = 7.2 Hz), 3.28 (1H, t, J = 7.2 Hz), 3.17 (3H, s), 2.56−2.49 (1H, m), 1.77−1.50 (4H, m), 0.88 (9H, s), 0.01 (3H, s), −0.15 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.22, 159.99, 157.69, 154.57, 148.23, 148.07, 141.97, 140.62 (C), 127.41, 127.13, 127.03, 122.25, 115.43, 115.13, 114.96, 114.68, 113.00, 112.90 (CH), 73.86, 73.29 (CH), 55.88 (CH_2), 41.88 (CH), 37.90 (CH_2), 37.43 (CH_3), 29.43 (CH_2), 25.85 (CH_3), 18.24 (C), −4.53, −4.88 (CH_3). IR (cm^{-1}): 2932, 2856, 1605, 1509, 1473, 1372, 1331, 1252, 1222, 1198, 1171, 1151, 1090, 970, 870, 836, 776. MALDI-MS ($C_{31}H_{39}F_2NO_4SiS$): [MH − TBDMSOH]$^+$ 456.1442 (calcd 456.14449); [MNa]$^+$ 610.2236 (calcd 610.22348). Anal. Calcd for $C_{31}H_{39}F_2NO_4SiS$: C, 63.34; H, 6.69; N, 2.38. Found: C, 63.49; H, 6.87; N, 2.33. This silylated azetidine (146.3 mg, 0.249 mmol) was dissolved in anhydrous THF (5.0 mL, Teflon bottle) at 0 °C, anhydrous pyridine (1.0 mL) followed by HF·pyridine complex (1.0 mL) was added, and the solution was stirred at 0 °C for 1 h and at room temperature for 7 h, diluted with ether (30 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 2.0 cm) on silica gel eluting with a gradient of 0−90% EtOAc in hexane (v/v) to give azetidine **32** (100.0 mg, 85%) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.22 (2H, dd, J = 5.6, 8.7 Hz), 7.01 (2H, t, J = 8.7 Hz), 6.84 (2H, t, J = 8.7 Hz), 6.30 (2H, dd, J = 4.3, 9.3 Hz), 4.57 (1H, t, J = 5.6 Hz), 4.41 (1H, d, J = 6.8 Hz), 4.12 (1H, t, J = 6.8 Hz), 3.30 (1H, dd, J = 6.8, 7.5 Hz), 3.16 (3H, s), 2.55 (1H, dt, J = 6.8, 7.5 Hz), 1.93 (1H, bs), 1.88−1.53 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.62, 160.37, 157.74, 154.61, 148.22, 148.01, 141.89, 139.95, 139.91 (C), 127.46, 127.28, 127.17, 122.29, 115.46, 115.42, 115.13, 113.02, 112.92 (CH), 73.43, 73.28 (CH), 55.92 (CH_2), 41.81 (CH), 37.49 (CH_3), 36.28, 29.85 (CH_2). IR (cm^{-1}): 3416, 2938, 2853, 1508, 1367, 1221, 1196, 1171, 1149, 970, 871, 823. MALDI-MS ($C_{25}H_{25}F_2NO_4S$): [MH − H_2O]$^+$ 456.1447 (calcd 456.1445); [M]$^+$ 473.1481 (calcd 473.1472); [MNa]$^+$ 496.1380 (calcd 496.1370).

***β*-Lactam 33.** *β*-Lactam **31** (67.7 mg, 0.112 mmol) was dissolved in THF (2 mL), TBAF (0.2 mL, 1 M in THF) was added, and the solution was stirred for 1.5 h, diluted with EtOAc (20 mL), and washed successively with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 2.0 cm) on silica gel eluting with a gradient of 0−90% EtOAc in hexane (v/v) to give *β*-lactam **33** (37.0 mg, 68%) as a white solid. R_f (1:1 EtOAc/hexane (v/v)):

0.17. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37−7.17 (8H, m), 7.03−6.91 (4H, m), 4.69 (1H, t, J = 5.9 Hz), 4.65 (1H, d, J = 1.9 Hz), 3.16 (3H, s), 3.07−3.01 (1H, m), 2.63 (1H, bs), 2.03−1.84 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.11, 163.76, 160.68, 160.50, 157.44, 148.89, 139.92, 136.86, 133.41 (C), 127.40, 127.27, 122.98, 118.35, 118.24, 116.10, 115.79, 115.45, 115.18, 115.11 (CH), 73.03, 60.48, 60.41 (CH), 37.63 (CH_3), 36.48, 25.00 (CH_2). IR (cm^{-1}): 3428, 2937, 1744, 1604, 1510, 1426, 1369, 1221, 1176, 1152, 1103, 1016, 971, 912, 872, 835, 788, 734. MALDI-MS ($C_{25}H_{23}F_2NO_5S$): $[MH - H_2O]^+$ 470.1239 (calcd 470.1238); $[MNa]^+$ 510.1164 (calcd 510.1163). Anal. Calcd for $C_{25}H_{23}F_2NO_5S$: C, 61.59; H, 4.75; N, 2.87. Found: C, 61.79; H, 4.89; N, 2.76.

***β*-Lactam 35.** Phenol **5** (104.0 mg, 0.199 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (0.5 mL) followed by $PhSO_2Cl$ (0.10 mL, 0.78 mmol) was added, and the solution was stirred for 19 h. Additional $PhSO_2Cl$ (0.10 mL, 0.78 mmol) was added, and the solution was stirred for a further 69 h, diluted with EtOAc (50 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 3.3 cm) on silica gel eluting with a gradient of 0−100% CH_2Cl_2 in hexane (v/v) followed by 0.5−1.0% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated benzene sulfonate (92.0 mg, 70%) as a colorless oil. R_f (1% MeOH in CH_2Cl_2 (v/v)): 0.72. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (2H, d, J = 7.5 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.51 (2H, t, J = 7.5 Hz), 7.25−7.14 (6H, m), 7.00 (2H, d, J = 8.7 Hz), 6.97 (2H, d, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 4.66 (1H, dd, J = 4.4, 6.2 Hz), 4.55 (1H, d, J = 1.9 Hz), 3.02−2.96 (1H, m), 1.94−1.75 (4H, m), 0.87 (9H, s), 0.00 (3H, s), −0.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.82, 163.44, 160.51, 157.29, 149.35, 140.54 (C), 136.77 (CH), 135.26, 134.32, 133.56, 129.13 (C), 128.31, 127.27, 127.17, 127.08, 123.15, 118.23, 118.12, 115.93, 115.63, 115.09, 114.82, 73.76, 60.53, 60.40 (CH), 37.92 (CH_2), 25.75 (CH_3), 24.59 (CH_2), 18.10 (C), −4.71, −5.03 (CH_3). IR (cm^{-1}): 2953, 2930, 2857, 1752, 1605, 1510, 1450, 1382, 1252, 1221, 1202, 1181, 1155, 1093, 1016, 868, 835, 776, 753, 700, 687. MALDI-MS ($C_{36}H_{39}F_2NO_5SSi$): $[MH - TBDMSOH]^+$ 532.1395 (calcd 532.1394); $[MNa]^+$ 686.2185 (calcd 686.2184). This silylated benzene sulfonate (90.0 mg, 0.136 mmol) was dissolved in anhydrous THF (2.5 mL, Teflon bottle) at 0 °C, anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) was added, and the solution was allowed to warm slowly to room temperature. After 14 h, the mixture was diluted with ether (20 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (5.0 × 2.0 cm) on silica gel eluting with a gradient of 0−100% CH_2Cl_2 in hexane (v/v) followed by 1−7% MeOH in CH_2Cl_2 (v/v) to give *β*-lactam **35** (69.2 mg, 93%) as a white foam. R_f (3% MeOH in CH_2Cl_2 (v/v)): 0.33. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (2H, dd, J = 1.2, 7.5 Hz), 7.67 (1H, tt, J = 1.2, 7.5 Hz), 7.51 (2H, t, J = 7.5 Hz), 7.29−7.22 (4H, m), 7.15 (2H, dd, J = 4.4, 8.7 Hz), 6.99 (2H, t, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 6.92 (2H, t, J = 8.7 Hz), 4.68 (1H, dd, J = 5.6, 6.2 Hz), 4.60 (1H, d, J = 1.9 Hz), 3.06−2.98 (1H, m), 2.55 (1H, bs), 2.04−1.84 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.87, 163.56, 160.44, 160.31, 157.22, 149.23, 139.84, 139.79 (C), 136.46 (CH), 135.10, 134.26, 133.37 (C), 129.07, 128.22, 127.26, 127.16, 127.02, 123.07, 118.21, 118.11, 115.93, 115.62, 115.36, 115.07, 72.98, 60.50, 60.32 (CH), 36.54, 25.09 (CH_2). IR (cm^{-1}): 3440, 3069, 3017, 2927, 2862, 1747, 1604, 1510, 1450, 1426, 1378, 1221, 1201, 1180, 1154, 1094, 1016, 868, 835, 753, 700, 687, 668. MALDI-MS ($C_{30}H_{25}F_2NO_5S$): $[MH - H_2O]^+$ 532.1388 (calcd 532.1394); $[MNa]^+$ 572.1302 (calcd 572.1319).

Azetidine 36. $LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (202 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min, and cooled to 0 °C. *β*-Lactam **35** (62.8 mg, 0.114 mmol) dissolved in anhydrous ether (5 mL) was added, and after stirring at 0 °C for 20 min, saturated aqueous $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.8 × 2.0 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give azetidine **36** (24.5 mg, 40%) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.46. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88−7.82 (2H, m), 7.70−7.63 (1H, m), 7.55−7.47 (2H, m), 7.38−7.30 (2H, m), 7.24−7.19 (2H, m), 7.05−6.98 (4H, m), 6.83 (2H, t, J = 8.7 Hz), 6.26 (2H, dd, J = 4.4, 9.3 Hz), 4.56 (1H, dd, J = 5.0, 7.5 Hz), 4.36 (1H, d, J = 6.8 Hz), 4.09 (1H, dd, J = 6.8, 7.5 Hz), 3.27 (1H, dd, J = 6.8, 7.5 Hz), 2.79 (1H, d, J = 5.6 Hz), 2.52 (1H, dd, J = 6.8, 7.5 Hz), 1.89−1.52 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.65, 160.40, 157.73, 154.61, 148.65, 148.07, 141.59, 139.94, 135.36 (C), 134.11, 129.24, 129.03, 128.30, 127.28, 127.17, 122.54, 115.45, 115.15, 112.99, 112.90, 73.47, 73.32 (CH), 55.89 (CH_2), 41.74 (CH), 36.30, 29.93 (CH_2). IR (cm^{-1}): 3411, 2937, 2853, 1604, 1508, 1474, 1450, 1374, 1221, 1198, 1175, 1151, 1093, 1016, 867, 823, 752, 700, 686. MALDI-MS ($C_{30}H_{27}F_2NO_4S$): $[MH - H_2O]^+$ 518.1596 (calcd 518.1601); $[M]^+$ 535.1619 (calcd 535.1629); $[MNa]^+$ 558.1512 (calcd 558.1527).

***tert*-Butyl Ether 38.** 2-Methylpropene (10 mL) was condensed in a dried flask at −78 °C, and anhydrous CH_2Cl_2 (5 mL), followed by phenol **37**[17,36] (83.7 mg, 0.185 mmol) and 5 drops of triflic acid, was added sequentially. After 5 min, the suspension was transferred to a −20 °C cooling bath. After 40 min, Et_3N (0.5 mL) was added and the solution was stirred at room temperature until all 2-methylpropene had evaporated. The solution was evaporated on Celite and purified by dry column vacuum chromatography (4.7 × 2.0 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give the intermediary acetylated *tert*-butyl ether (81.8 mg, 87%) as a white foam. R_f (1:1 EtOAc/hexane (v/v)): 0.47. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29−7.19 (6H, m), 7.01 (2H, t, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 5.70 (1H, t, J = 6.8 Hz), 4.55 (1H, d, J = 1.9 Hz), 3.08 (1H, dt, J = 1.9, 7.5 Hz), 2.10−1.98 (2H, m), 2.05 (3H, s), 1.90−1.81 (2H, m), 1.35 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.11, 166.95, 163.97, 160.71, 160.50, 157.26, 155.84, 135.70, 133.81 (C), 131.72, 128.23, 128.11, 126.41, 124.46, 118.33, 118.23, 115.85, 115.58, 115.29 (CH), 78.79 (C), 74.75, 60.85, 59.90 (CH), 33.53 (CH_2), 28.78 (CH_3), 24.83 (CH_2), 21.13 (CH_3). IR (cm^{-1}): 2979, 2935, 1747, 1608, 1510, 1389, 1368, 1234, 1159, 1102, 1015, 896, 835, 757. MALDI-MS ($C_{30}H_{31}F_2NO_4$): $[MNa]^+$ 530.2111 (calcd 530.2119). This acetylated *tert*-butyl ether (78.2 mg, 0.154 mmol) was dissolved in anhydrous MeOH (5 mL), KCN (48 mg, 0.74 mmol) was added, and the solution was stirred at room temperature for 4 h, evaporated on Celite, and purified by dry column vacuum chromatography (4.6 × 2.0 cm) on silica gel eluting with a gradient of 0−50% EtOAc in hexane (v/v) to give *tert*-butyl ether **38** (51.1 mg, 71%) as a colorless oil. R_f (1:3 EtOAc/hexane (v/v)): 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30−7.18 (6H, m), 7.02−6.87 (6H, m), 4.70 (1H, t, J = 5.6 Hz), 4.57 (1H, d, J = 1.9 Hz), 3.10−3.04 (1H, m), 2.61 (1H, bs), 2.03−1.87 (4H, m), 1.34 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.65, 163.72, 160.46, 157.31, 155.76, 140.05, 133.81, 131.83 (C), 127.40, 127.29, 126.88, 126.45, 124.47, 124.13, 118.39, 118.29, 115.88, 115.58, 115.40, 115.29, 115.11, 114.30, 114.20 (CH), 78.84 (C), 72.95, 61.06, 60.13 (CH), 36.54 (CH_2), 28.79 (CH_3), 24.96 (CH_2). IR (cm^{-1}): 3424, 2979, 2934, 1737, 1606, 1510, 1390, 1367, 1222, 1158, 895, 835, 757. MALDI-MS ($C_{28}H_{29}F_2NO_3$): $[MH - H_2O]^+$ 448.2082 (calcd 448.2088); $[MNa]^+$ 488.2001 (calcd 488.2013). Anal. Calcd for $C_{28}H_{29}F_2NO_3$: C, 72.24; H, 6.28; N, 3.01. Found: C, 72.39; H, 6.51; N, 2.95.

Azetidine 39. $LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min, and cooled to 0 °C. *β*-Lactam **14** (26.8 mg, 0.041 mmol) dissolved in anhydrous THF (1 mL, 2 × 0.5 mL rinse) was added, and after stirring at 0 °C for 10 min, saturated aqueous $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.7 × 2.0 cm) on silica gel eluting with a gradient of 0−12% MeOH in CH_2Cl_2 (v/v) to give azetidine **39** (20.4 mg, 78%) as a colorless oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.20. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.63−7.59 (2H, m), 7.49−7.42 (2H, m), 7.36−7.29 (2H, m),

7.10−7.01 (2H, m), 6.92−6.77 (2H, m), 6.40−6.35 (2H, m), 4.72 (1H, d, J = 3.7 Hz), 4.62 (1H, d, J = 5.0 Hz), 4.61 (1H, bs), 4.52 (1H, d, J = 6.9 Hz), 4.31 (2H, t, J = 4.4 Hz), 4.21−4.15 (2H, m), 3.90 (1H, dd, J = 1.2, 14.9 Hz), 3.76 (1H, d, J = 8.1 Hz), 3.68 (1H, dd, J = 3.7, 9.3 Hz), 3.66−3.57 (2H, m), 3.41 (3H, s, OMe), 3.38−3.31 (1H, m), 3.25 (1H, dt, J = 5.0, 13.7 Hz), 2.62 (1H, dd, J = 6.8, 14.3 Hz), 1.92−1.84 (1H, m), 1.74−1.57 (3H, m). ^{13}C NMR (75 MHz, acetone-d_6) δ: 163.90, 160.69, 158.31, 155.22, 149.93, 149.72, 149.52, 142.90, 142.84 (C), 129.60, 129.44, 128.30, 128.24, 128.13, 123.51, 122.99, 115.95, 115.91, 115.66, 115.40, 115.11, 113.87, 113.77, 113.67, 113.57 (CH), 100.84, 74.86, 74.03, 73.68, 73.14, 72.87, 68.09 (CH), 56.67 (CH_2), 55.63 (CH_3), 52.83 (CH_2), 42.78 (CH), 37.60, 29.83 (CH_2). IR (cm^{-1}): 3390, 2935, 2850, 1605, 1508, 1474, 1366, 1221, 1147, 1052, 1015, 874, 824, 755. MALDI-MS ($C_{31}H_{35}F_2NO_9S$): [MH − H_2O]$^+$ 618.1968 (calcd 618.1973); [MH]$^+$ 636.2045 (calcd 636.2079); [MNa]$^+$ 658.1901 (calcd 658.1898).

Azetidine 41. $LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min, and cooled to 0 °C. β-Lactam **40** (41.3 mg, 0.054 mmol) dissolved in anhydrous ether (5 mL) was added, and after stirring at 0 °C for 10 min, saturated aqueous $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on Celite and purified by dry column vacuum chromatography (4.2 × 2.0 cm) on silica gel eluting with a gradient of 0−20% MeOH in CH_2Cl_2 (v/v) to give the intermediary silylated azetidine (38.2 mg, 94%) as a white foam. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.31. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.58 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz), 7.29 (2H, dd, J = 5.6, 8.7 Hz), 7.05 (2H, t, J = 8.7 Hz), 6.88 (2H, t, J = 9.0 Hz), 6.37 (2H, dd, J 4.7, 9.0 Hz), 4.71 (1H, t, J = 5.5 Hz), 4.61 (1H, d, J = 5.0 Hz), 4.49 (2H, d, J = 6.8 Hz), 4.30 (1H, bs), 4.17 (1H, t, J = 7.2 Hz), 3.92−3.83 (3H, m), 3.74−3.66 (1H, m), 3.57−3.40 (5H, m), 3.32−3.15 (2H, m), 2.63−2.56 (1H, m), 1.82−1.56 (4H, m), 0.87 (9H, s), 0.04 (3H, s), −0.17 (3H, s). ^{13}C NMR (75 MHz, acetone-d_6) δ: 164.97, 161.76, 159.31, 156.21, 150.76, 150.47, 150.45, 143.77, 143.11, 143.07 (C), 129.35, 129.22, 124.60, 116.95, 116.65, 116.48, 116.19, 114.86, 114.75 (CH), 82.15, 80.21, 76.81, 75.43, 74.99, 74.52, 72.41 (CH), 63.70, 57.54, 53.95 (CH_2), 43.62 (CH), 39.47, 31.22 (CH_2), 27.20 (CH_3), 19.70 (C), −3.40, −3.68 (CH_3). IR (cm^{-1}): 3377, 2930, 2856, 1605, 1508, 1472, 1361, 1252, 1222, 1147, 1090, 1015, 871, 836, 776, 760. MALDI-MS ($C_{37}H_{49}F_2NO_9SSi$): [MNa]$^+$ 772.2767 (calcd 772.2763). This silylated azetidine (34.3 mg, 0.046 mmol) was dissolved in anhydrous THF (2.5 mL, Teflon bottle), anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) was added, and the solution was stirred for 14 h, diluted with ether (20 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 5 mL). The organic layer was evaporated on Celite and purified by dry column vacuum chromatography (4.9 × 2.0 cm) on silica gel eluting with a gradient of 0−18% MeOH in CH_2Cl_2 (v/v) to give azetidine **41** (20.2 mg, 69%) as a colorless oil. R_f (10% MeOH in CH_2Cl_2 (v/v)): 0.24. ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.61 (2H, d, J = 8.1 Hz), 7.48 (2H, d, J = 8.7 Hz), 7.30 (2H, dd, J = 5.6, 8.7 Hz), 7.04 (2H, t, J = 8.7 Hz), 6.89 (2H, m), 6.38 (2H, dd, J = 4.4, 8.7 Hz), 4.60 (2H, d, J = 4.4 Hz), 4.52 (1H, d, J = 6.8 Hz), 4.45 (1H, d, J = 2.5 Hz), 4.29 (2H, d, J = 4.4 Hz), 4.19 (1H, t, J = 6.8 Hz), 4.03−3.83 (3H, m), 3.80−3.67 (1H, m), 3.60−3.31 (6H, m), 3.25 (1H, p, J = 4.4 Hz), 2.62 (1H, dd, J = 7.5, 14.3 Hz), 1.92−1.82 (1H, m), 1.78−1.61 (3H, m). ^{13}C NMR (75 MHz, acetone-d_6) δ: 164.04, 155.14, 149.92, 149.71, 149.47, 142.77, 129.48 (C), 128.19, 128.16, 128.05, 123.52, 123.03, 115.87, 115.58, 115.39, 115.32, 115.05, 113.78, 113.69, 113.61, 113.51 (CH), 81.09, 79.15, 75.76, 73.98, 73.46, 72.75, 71.36 (CH), 62.63, 56.60, 52.88 (CH_2), 42.68 (CH), 37.52, 29.61 (CH_2). IR (cm^{-1}): 3370, 2933, 1605, 1508, 1474, 1360, 1220, 1146, 1087, 1015, 873, 823, 771. MALDI-MS ($C_{31}H_{35}F_2NO_9S$): [MH − H_2O]$^+$ 618.1973 (calcd 618.1973); [M]$^+$ 635.1996 (calcd 635.2001); [MNa]$^+$ 658.1900 (calcd 658.1898).

Brush Border Membrane Vesicle Assay. Materials. Egg phosphatidylcholine was purchased from Avanti Polar Lipids, cholesterol oleate and cholesterol were from Sigma, phosphate-buffered saline (PBS) was from Invitrogen Corp., [1α,2α(N)-^{3}H]cholesterol oleyl ether (37 Ci/mmol), [4-^{14}C-cholesterol], and Sepharose CL-4B were from Amersham Biosciences, the BCA protein assay kit was from Pierce, and the glucose dehydrogenase kit was from Diagnostic Systems.

Preparation of Brush Border Membrane Vesicles. Brush border membrane vesicles were prepared and characterized [total protein content by the BCA method, sucrase activity and lipid uptake (4.2 mg of protein/mL, 0.20 mg SUV/mL; see below)] essentially as previously described.[23,38] The source was small intestine (stored at −78 °C) from freshly killed farm rabbits. The isolation buffer was 2 mM Tris-HCl plus HCl to pH 7.1, 50 mM D-mannitol, and 0.83 mM EGTA; 10 mM $MgCl_2$ was used in the precipitation step. The brush border pellet was redispersed in 12 mM Tris-HCl plus HCl to pH 7.1, 0.30 M D-mannitol, and 5 mM EGTA.

Preparation of Small Unilamellar Vesicles (SUV). A total of 2 mg of egg phosphatidylcholine and cholesteryl oleate (99:1 molar ratio) for control measurements and egg phosphatidylcholine, cholesteryl oleate, and inhibitor (90:1:9 molar ratio) for inhibition experiments and in either case a trace amount ^{3}H-labeled cholesteryl oleyl ether (or ^{14}C-labeled cholesterol) were dried from a chloroform−methanol solution (2:l v/v) by rotary evaporation. The lipid film was dried under high vacuum for at least 1 h and then dispersed in PBS buffer (2 mL). The suspension was sonicated with a microtip sonicator (Branson 250) for 1−1.5 h (output 2.2, 60% duty cycle).[70] After sonication, the vesicles were centrifuged (pressure 3.0, 3 min) in a Beckman airfuge and characterized by gel filtration (Sepharose CL-4B, 45 × 1 cm) as previously reported.[35,71]

Inhibition of Cholesterol Absorption by Brush Border Membrane Vesicles. Brush border membrane vesicles (5.0 mg of protein/mL) were incubated at room temperature for 20 min with either control SUV (99:1 molar ratio egg phosphatidylcholine and cholesteryl oleate) or SUV containing inhibitors (90:1:9 molar ratio egg phosphatidylcholine, cholesteryl oleate, and inhibitor). The experiment was terminated by centrifugation (pressure 3.0, 3 min) in a Beckman airfuge. The donor SUV remained in the supernatant under these conditions and the brush border membrane vesicles precipitated. The radioactivity present in both donor SUV and brush border membrane vesicles was counted in triplicate in a Beckman LS 7500 liquid scintillation counter.

Percent inhibition was calculated from relative radioactivities in the supernatants and pellets according to the formula: % inhibition = [(% supernatant inhibitor SUV − % supernatant control SUV) × 100%]/% pellet control SUV.

The following are the obtained inhibitions: **1**, 16 ± 4%; (±)-**3**, 2 ± 2%; **4**,[36]27 ± 4%; **7**, 13 ± 4%; **9**, 15 ± 3%; **11**, 28 ± 4%; **14**, 20 ± 5%; **16**, 15 ± 3%; **18**, 41 ± 4%; **19**, 10 ± 3%; **20**,[36]19 ± 4%; **21**,[36]14 ± 2%; **22**,[36]3 ± 4%; (±)-24, 2 ± 3%; **32**, 22 ± 2%; **33**, 30 ± 4%; **34**, <2 ± 2%; **35**, 26 ± 3%; **36**, 19 ± 3%, **38**, 10 ± 4%; **39**, 27 ± 4%; **41**, 20 ± 5%; **44**, 3 ± 3%; **45**, 4 ± 3%.

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Supporting Information Available: Experimental procedures and spectral data for all described compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Sudhop, T.; von Bergmann, K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* **2002**, *62*, 2333−2347, and references therein.
(2) Bruckert, E. New advances in lipid-modifying therapies for reducing cardiovascular risk. *Cardiology* **2002**, *97*, 59−66, and references therein.
(3) American Heart Association. Heart Disease and Stroke. Statistics−2003 Update. Available from The American Heart Association at http://www.americanheart.org/downloadable/heart/1059-0179711482003HDSStatsBookREV10590179711482007−105-90179 711482003.pdf.

(4) Bays, H. Ezetimibe. *Expert Opin. Investig. Drugs* **2002**, *11*, 1587−1604.
(5) Turley, S. D.; Dietschy, J. M. Sterol absorption by the small intestine. *Curr. Opin. Lipidol.* **2003**, *14*, 233−240.
(6) Earl, J.; Kirkpatrick, P. Ezetimibe. *Nat. Rev. Drug Discovery* **2003**, *2*, 97−98.
(7) Maron, D. J.; Fazio, S.; Linton, M. F. Current perspectives on statins. *Circulation* **2000**, *101*, 207−213.
(8) Euroaspire Principal results from Euroaspire II. *Eur. Heart J.* **2001**, *22*, 554−572.
(9) (a) Zetia (Ezetimibe). FDA Drug Approvals List [online] http://www.fda.gov/cder/foi/label/2002/21445lbl.pdf. (b) 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. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur. Heart J.* **2003**, *24*, 729−741. (c) 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. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin. Ther.* **2001**, *23*, 1209−1230. (d) Gagne, C.; Bays, H. E.; Weiss, S. R.; Mata, P.; Quinto, K.; Melino, M.; Cho, M.; Musliner, T. A.; Gumbiner, B. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am. J. Cardiol.* **2002**, *90*, 1084−1091.
(10) Clader, J. W. The discovery of ezetimibe: A view from outside the receptor. *J. Med. Chem.* **2004**, *47*, 1−9.
(11) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R.; Yumibe, N.; Clader, J. W.; Burnett, D. A. Discovery of 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A designed, potent, orally active inhibitor of cholesterol absorption. *J. Med. Chem.* **1998**, *41*, 973−980.
(12) Salisbury, B. G.; Davis, H. R.; Burrier, R. E.; Burnett, D. A.; Boykow, G.; Caplen, M. A.; Clemmons, A. L.; Compton, D. S.; Hoos, L. M.; McGregor, D. G.; Schnitzerpolokoff, R.; Smith, A. A.; Weig, B. C.; Zilli, D. L.; Clader, J. W.; Sybertz, E. J. Hypocholesterolemic activity of a novel inhibitor of cholesterol absorption, SCH-48461. *Atherosclerosis* **1995**, *115*, 45−63.
(13) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H. R.; Burrier, R. E.; Salisbury, B.; Davis, H. R. 2-Azetidinone cholesterol absorption inhibitors: Structure−activity relationships on the heterocyclic nucleus. *J. Med. Chem.* **1996**, *39*, 3684−3693.
(14) Burnett, D. A.; Caplen, M. A.; Davis, H. R.; Burrier, R. E.; Clader, J. W. 2-Azetidinones as inhibitors of cholesterol absorption. *J. Med. Chem.* **1994**, *37*, 1733−1736.
(15) Dugar, S.; Kirkup, M. P.; Clader, J. W.; Lin, S. I.; Rizvi, R.; Snow, M. E.; Davis, H. R.; McCombie, S. W. γ-Lactams and related compounds as cholesterol absorption inhibitors: Homologs of the β-lactam cholesterol absorption inhibitor SCH 48461. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2947−2952.
(16) Schnitzerpolokoff, R.; Compton, D.; Boykow, G.; Davis, H.; Burrier, R. Effects of acyl-CoA−cholesterol O-acyltransferase inhibition on cholesterol absorption and plasma-lipoprotein composition in hamsters. *Comp. Biochem. Physiol. A* **1991**, *99*, 665−670.
(17) Vaccaro, W. D.; Davis, H. R. Sugar-substituted 2-azetidinone cholesterol absorption inhibitors: Enhanced potency by modification of the sugar. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313−318.
(18) van Heek, M.; France, C. F.; Compton, D. S.; McLeod, R. L.; Yumibe, N. P.; Alton, K. B.; Sybertz, E. J.; Davis, H. R. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 157−163.
(19) van Heek, M.; Compton, D. S.; Davis, H. R. The cholesterol absorption inhibitor, ezetimibe, decreases diet-induced hypercholesterolemia in monkeys. *Eur. J. Pharmacol.* **2001**, *415*, 79−84.
(20) (a) Hernandez, M.; Montenegro, J.; Steiner, M.; Kim, D.; Sparrow, C.; Detmers, P. A.; Wright, S. D.; Chao, Y. S. Intestinal absorption of cholesterol is mediated by a saturable, inhibitable transporter. *Biochim. Biophys. Acta Mol. Cell. Biol. Lipids* **2000**, *1486*, 232−242. (b) Detmers, P. A.; Patel, S.; Hernandez, M.; Montenegro, J.; Lisnock, J.; Pikounis, B.; Steiner, M.; Kim, D.; Sparrow, C.; Chao, Y. S.; Wright, S. D. A target for cholesterol absorption inhibitors in the enterocyte brush border membrane. *Biochim. Biophys. Acta* **2000**, *1486*, 243−252.
(21) Jourdheuil-Rahmani, D.; Charbonnier, M.; Domingo, N.; Luccioni, F.; Lafont, H.; Lairon, D. Biliary anionic peptide fraction and ApoA-I regulate intestinal cholesterol uptake. *Biochem. Biophys. Res. Commun.* **2002**, *292*, 390−395.
(22) Hauser, H.; Dyer, J. H.; Nandy, A.; Vega, M. A.; Werder, M.; Bieliauskaite, E.; Weber, F. E.; Compassi, S.; Gemperli, A.; Boffelli, D.; Wehrli, E.; Schulthess, G.; Phillips, M. C. Identification of a receptor mediating absorption of dietary cholesterol in the intestine. *Biochemistry* **1998**, *37*, 17843−17850.
(23) Thurnhofer, H.; Hauser, H. Uptake of cholesterol by small intestinal brush-border membrane is protein-mediated. *Biochemistry* **1990**, *29*, 2142−2148.
(24) Werder, M.; Han, C. H.; Wehrli, E.; Bimmler, D.; Schulthess, G.; Hauser, H. Role of scavenger receptors SR-BI and CD36 in selective sterol uptake in the small intestine. *Biochemistry* **2001**, *40*, 11643−11650.
(25) (a) Cai, S. F.; Kirby, R. J.; Howles, P. N.; Hui, D. Y. Differentiation-dependent expression and localization of the class B type I scavenger receptor in intestine. *J. Lipid Res.* **2001**, *42*, 902−909. (b) Cai, L.; Eckhardt, E. R. M.; Shi, W.; Zhao, Z.; Nasser, M.; de Villiers, W. J. S.; van der Westhuyzen, D. R. Scavenger receptor class B type I reduces cholesterol absorption in cultured enterocyte CaCo-2 cells. *J. Lipid Res.* **2004**, *45*, 253−262. (c) Altmann, S. W.; Davis, H. R.; Yao, X. R.; Laverty, M.; Compton, D. S.; Zhu, L. J.; Crona, J. H.; Caplen, M. A.; Hoos, L. M.; Tetzloff, G.; Priestley, T.; Burnett, D. A.; Strader, C. D.; Graziano, M. P. The identification of intestinal scavenger receptor class B, type I (SR-BI) by expression cloning and its role in cholesterol absorption. *Biochim. Biophys. Acta* **2002**, *1580*, 77−93. (d) Levy, E.; Menard, D.; Suc, I.; Delvin, E.; Marcil, V.; Brissette, L.; Thibault, L.; Bendayan, M. Ontogeny, immunolocalisation, distribution and function of SR-BI in the human intestine. *J. Cell Sci.* **2004**, *117*, 327−337. (e) Play, B.; Salvini, S.; Haikal, Z.; Charbonnier, M.; Harbis, A.; Roussel, M.; Lairon, D.; Jourdheuil-Rahmani, D. Glucose and galactose regulate intestinal absorption of cholesterol. *Biochem. Biophys. Res. Commun.* **2003**, *310*, 446−451.
(26) van Bennekum, A.; Werder, M.; Thuahnai, S. T.; Han, C.-H.; Williams, D. L.; Wettstein, P.; Schulthess, G.; Phillips, M. C.; Hauser, H. Two class B scavenger receptors, SR-BI and CD36, mediate intestinal absorption of dietary cholesterol and beta-carotene. *Biochemistry* **2005**, *44*, 4517−4525.
(27) Smart, E. J.; De Rose, R. A.; Farber, S. A. Annexin 2−caveolin 1 complex is a target of ezetimibe and regulates intestinal cholesterol transport. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 3450−3455.
(28) Altmann, S. W.; Davis, H. R.; Zhu, L. J.; Yao, X. R.; Hoos, L. M.; Tetzloff, G.; Iyer, S. P. N.; Maguire, M.; Golovko, A.; Zeng, M.; Wang, L. Q.; Murgolo, N.; Graziano, M. P. Niemann−Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* **2004**, *303*, 1201−1204.
(29) Davis, H. R.; Zhu, L.-j.; Hoos, L. M.; Tetzloff, G.; Maguire, M.; Liu, J.; Yao, X.; Iyer, S. P. N.; Lam, M.-H.; Lund, E. G.; Detmers, P. A.; Graziano, M. P.; Altmann, S. W. Niemann−Pick C1 like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole body cholesterol homeostasis. *J. Biol. Chem.* **2004**, *279*, 33586−33592.
(30) Garcia-Calvo, M.; Lisnock, J. M.; Bull, H. G.; Hawes, B. E.; Burnett, D. A.; Braun, M. P.; Crona, J. H.; Davis, H. R.; Dean, D. C.; Detmers, P. A.; Graziano, M. P.; Hughes, M.; MacIntyre, D. E.; Ogawa, A.; O'Neill, K. A.; Iyer, S. P. N.; Shevell, D. E.; Smith, M. M.; Tang, Y. S.; Makarewicz, A. M.; Ujjainwalla, F.; Altmann, S. W.; Chapman, K. T.; Thornberry, N. A. The target of ezetimibe is Niemann−Pick Cl-like 1 (NPC1L1). *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8132−8137.
(31) Davies, J. P.; Scott, C.; Oishi, K.; Liapis, A.; Ioannou, Y. A. Inactivation of NPC1L1 causes multiple lipid transport defects and protects against diet-induced hypercholesterolemia. *J. Biol. Chem.* **2005**, *280*, 12710−12720.
(32) (a) Kramer, W.; Glombik, H.; Petry, S.; Heuer, H.; Schafer, H. L.; Wendler, W.; Corsiero, D.; Girbig, F.; Weyland, C. Identification of binding proteins for cholesterol absorption inhibitors as components of the intestinal cholesterol transporter. *FEBS Lett.* **2000**, *487*, 293−297. (b) Frick, W.; Bauer-Schafer, A.; Bauer, J.; Girbig, F.; Corsiero, D.; Heuer, H.; Kramer, W. Synthesis of a biotin-tagged photoaffinity probe of 2-azetidinone cholesterol absorption inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 1639−1642. (c) Kramer, W.; Girbig, F.; Corsiero, D.; Burger, K.; Fahrenholz, F.; Jung, C.; Muller, G. Intestinal cholesterol absorption: identification of different binding proteins for cholesterol and cholesterol absorption inhibitors in the enterocyte brush border membrane. *Biochim. Biophys. Acta* **2003**, *1633*, 13−26.
(33) Kramer, W.; Girbig, F.; Corsiero, D.; Pfenninger, A.; Frick, W.; Jahne, G.; Rhein, M.; Wendler, W.; Lottspeich, F.; Hochleitner, E. O.; Orso, E.; Schmitz, G. Aminopeptidase N (CD13) is a molecular target of the cholesterol absorption inhibitor ezetimibe in the enterocyte brush border membrane. *J. Biol. Chem.* **2005**, *280*, 1306−1320.
(34) (a) Compassi, S.; Werder, M.; Boffelli, D.; Weber, F. E.; Hauser, H.; Schulthess, G. Cholesteryl ester absorption by small intestinal brush border membrane is protein-mediated. *Biochemistry* **1995**, *34*, 16473−16482. (b) Compassi, S.; Werder, M.; Weber,

F. E.; Boffeli, D.; Hauser, H. Comparison of cholesterol and sitosterol uptake in different brush border membrane models. *Biochemistry* **1997**, *36*, 6643−6652. (c) Schulthess, G.; Compassi, S.; Boffelli, D.; Werder, M.; Weber, F. E.; Hauser, H. A comparative study of sterol absorption in different small-intestinal brush border membrane models. *J. Lipid Res.* **1996**, *37*, 2405−2419. (d) Werder, M.; Hauser, H.; Abele, S.; Seebach, D. β-Peptides as inhibitors of small-intestinal cholesterol and fat absorption. *Helv. Chim. Acta* **1999**, *82*, 1774−1783.

(35) Schulthess, G.; Compassi, S.; Werder, M.; Han, C. H.; Phillips, M. C.; Hauser, H. Intestinal sterol absorption mediated by scavenger receptors is competitively inhibited by amphipathic peptides and proteins. *Biochemistry* **2000**, *39*, 12623−12631.

(36) Kværnø, L.; Ritter, T.; Werder, M.; Hauser, H.; Carreira, E. M. An in vitro assay for evaluation of small-molecule inhibitors of cholesterol absorption. *Angew. Chem., Int. Ed.* **2004**, *43*, 4653−4656.

(37) Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. Carbohydrate sulfonyl chlorides for the simple, convenient access to glycoconjugates. *Org. Lett.* **2005**, *7*, 1145−1148.

(38) Hauser, H.; Howell, K.; Dawson, R. M. C.; Bowyer, D. E. Rabbit small intestinal brush-border membrane preparation and lipid-composition. *Biochim. Biophys. Acta* **1980**, *602*, 567−577.

(39) van Heek, M.; Farley, C.; Compton, D. S.; Hoos, L.; Alton, K. B.; Sybertz, E. J.; Davis, H. R. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. *Br. J. Pharmacol.* **2000**, *129*, 1748−1754.

(40) Similar *C*-linked glycosides of ezetimibe have been previously reported, see: Tomiyama, H.; Yokota, M.; Noda, A.; Ohno, A. Preparation of β-lactam compounds as serum cholesterol-lowering agents. WO2002066464, 113 pp.

(41) For a synthesis of a related *C*-linked glycoside of SCH48461, see: Vaccaro, W. D.; Sher, R.; Davis, H. R. Sugar-substituted 2-azetidinones as cholesterol absorption inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 35−40.

(42) Wu, G. Z.; Wong, Y. S.; Chen, X.; Ding, Z. X. A novel one-step diastereo- and enantioselective formation of *trans*-azetidinones and its application to the total synthesis of cholesterol absorption inhibitors. *J. Org. Chem.* **1999**, *64*, 3714−3718.

(43) Srivastava, V.; Tandon, A.; Ray, S. Convenient and selective acetylations of phenols, amines and alcohols. *Synth. Commun.* **1992**, *22*, 2703−2710.

(44) Varma, R. S.; Varma, M.; Chatterjee, A. K. Microwave-assisted deacetylation on alumina—A simple deprotection methodology. *J. Chem. Soc., Perkin Trans. 1* **1993**, 999−1000.

(45) Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. Studies in sugar chemistry. 2. A simple method For O-deacylation of polyacylated sugars. *J. Org. Chem.* **1986**, *51*, 727−730.

(46) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons Inc.: New York, 1999.

(47) Tsunoda, T.; Yamamiya, Y.; Ito, S. 1,1′-(Azodicarbonyl)dipiperidine-tributylphosphine, a new reagent system for Mitsunobu reaction. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.

(48) Jaramillo, C.; Chiara, J. L.; Martinlomas, M. An effective strategy for the synthesis of 6-*O*-(2-amino-2-deoxy-alpha-D-glucopyranosyl)-D-chiro and D-myo-inositol 1-phosphate related to putative insulin mimetics. *J. Org. Chem.* **1994**, *59*, 3135−3141.

(49) RajanBabu, T. V.; Reddy, G. S. 1-Methylene sugars as *C*-glycoside precursors. *J. Org. Chem.* **1986**, *51*, 5458−5461.

(50) Spak, S. J.; Martin, O. R. The synthesis of an *O*,*C*-trisaccharide: The *O*,*C*-analog of methyl 4′-*O*-β-D-glucopyranosylgentiobioside. *Tetrahedron* **2000**, *56*, 217−224.

(51) (a) *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, Heidelberg, New York, 2001. (b) *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: New York, Oxford, 1999.

(52) (a) Johnson, D. C.; Widlanski, T. S. Multiple routes for the synthesis of *N*-acyl sulfonamide-bridged nucleosides. *Synthesis* **2002**, 809−815. (b) Huang, J. X.; McElroy, E. B.; Widlanski, T. S. Synthesis of Sulfonate-Linked DNA. *J. Org. Chem.* **1994**, *59*, 3520−3521.

(53) Huang, J. X.; Widlanski, T. S. Facile synthesis of sulfonyl chlorides. *Tetrahedron Lett.* **1992**, *33*, 2657−2660.

(54) Although there is literature precedence for the synthesis of a sugar sulfonyl chloride, its use was limited to the preparation of simple esters (from 2-propanol, tert-butyl alcohol, methanol) and amides (from N-butylamine, and an amino sugar); see: Ulgar, V.; Maya, I.; Fuentes, J.; Fernandez-Bolanos, J. G. *Tetrahedron* **2002**, *20*58, 7967−7973.

(55) Paterson, D. E.; Griffin, F. K.; Alcaraz, M. L.; Taylor, R. J. K. A Ramberg-Bäcklund approach to the synthesis of *C*-glycosides, *C*-linked disaccharides, and *C*-glycosyl amino acids. *Eur. J. Org. Chem.* **2002**, 1323−1336.

(56) Reddie, R. N. Peroxomonosulfate oxidation of acetylthio compounds to sulfonates. *Synth. Commun.* **1987**, *17*, 1129−1139.

(57) Liptak, A.; Balla, E.; Janossy, L.; Sajtos, F.; Szilagyi, L. The first synthesis of secondary sugar sulfonic acids by nucleophilic displacement reactions. *Tetrahedron Lett.* **2004**, *45*, 839−842.

(58) Refer to ref 36 for a detailed description of the development of the brush border membrane vesicle assay. Most importantly, brush border membrane vesicles can inherently only mimic the first uptake step, namely that of cholesterol into the brush border membrane, of the overall multistep process of cholesterol absorption. In summary, the small-molecule inhibitors were incorporated into phospholipid unilamellar donor vesicles together with cholesteryl oleyl ester and trace amounts of radiolabeled cholesteryl oleyl ether. The latter was used as a nonhydrolyzable analogue of cholesteryl oleyl ester since both have been shown to exhibit identical brush border membrane uptake kinetics (ref 34a). Cholesteryl ester instead of free cholesterol was chosen for standard inhibition experiments, since passive diffusion is negligible for cholesteryl ester (ref 22). Cholesteryl ester is absorbed into brush border membrane vesicles with essentially the same uptake kinetics as free cholesterol (ref 34a) and into both SR-BI and CD36 transfected COS-7 cells (ref 26).

(59) Ezetimibe has been shown to be extensively metabolized into its glucuronide **20** while hydrolytic opening of the β-lactam ring is not a major metabolic pathway; see ref 39 and the following: Kosoglou, T.; Statkevich, P.; Johnson-Levonas, A. O.; Paolini, J. F.; Bergman, A. J.; Alton, K. B. Ezetimibe—A review of its metabolism, pharmacokinetics and drug interactions. *Clin. Pharmacokinet.* **2005**, *44*, 467−494.

(60) Ab initio calculations: Initial energy-minimization by molecular mechanics using MacroModel v. 7.0 [pseudosystematical Monte Carlo conformational search (100 steps, limit 30 kJ/mol) with $CHCl_3$ as solvent, MMFFs force field] was followed by a quantum-mechanical geometry optimization using Jaguar v. 4.2 (B3LYP/6-31G*) in Maestro v. 4.1.

(61) (a) Yamashita, M.; Ojima, I. Effective Route to Azetidines From Azetidin-2-Ones Using Hydroalanes As Specific Reducing Agents. *J. Am. Chem. Soc.* **1983**, *105*, 6339−6342. (b) Ojima, I.; Zhao, M. Z.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. Azetidines and bisazetidines—Their synthesis and use as the key intermediates to enantiomerically pure diamines, amino-alcohols, and polyamines. *J. Org. Chem.* **1991**, *56*, 5263−5277. (c) Ojima, I.; Yamato, T.; Nakahashi, K. Synthesis of novel chiral disazetidines by the hydroalane reduction of bis-beta-lactams. *Tetrahedron Lett.* **1985**, *26*, 2035−2038.

(62) Browne, M.; Burnett, D. A.; Caplen, M. A.; Chen, L. Y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; Vaccaro, W.; Viziano, M.; Zhao, H. R. *trans*-Diastereoselective synthesis of 3-alkyl substituted β-lactams via the acid chloride-imine reaction of nonactivated acid-chlorides. *Tetrahedron Lett.* **1995**, *36*, 2555−2558.

(63) Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. Mild cleavage of aryl mesylates: Methanesulfonate as potent protecting group for phenols. *Org. Lett.* **2004**, *6*, 1513−1514.

(64) In preliminary animal experiments using ezetimibe (**1**) as a reference compound, essentially carried out as described in ref 26, we have established that inhibitor **18** is indeed an inhibitor of cholesterol absorption in C57BL/6 mice at a dose of 10 mg/kg/day (70% of the inhibition obtained for ezetimibe).

(65) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and convenient procedure for solvent purification. *Organometallics* **1996**, *15*, 1518−1520.

(66) Pedersen, D. S.; Rosenbohm, C. Dry column vacuum chromatography. *Synthesis* **2001**, 2431−2434.

(67) Bernet, B.; Vasella, A. Carbocyclic compounds from monosaccharides. 1. Transformations in the glucose series. *Helv. Chim. Acta* **1979**, *62*, 1990−2016.

(68) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. Ramberg-Bäcklund approaches to the synthesis of *C*-linked disaccharides. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939−2942.

(69) Gervay, J.; Flaherty, T. M.; Holmes, D. Studies on the synthesis of *C*-glycoside sulfones as potential glycosyl transferase inhibitors. *Tetrahedron* **1997**, *53*, 16355−16364.

(70) (a) Mütsch, B.; Gains, N.; Hauser, H. Interaction of intestinal brush-border membrane-vesicles with small unilamellar phospholipid-vesicles—Exchange of lipids between membranes is mediated by collisional contact. *Biochemistry* **1986**, *25*, 2134−2140. (b) Brunner, J.; Hauser, H.; Semenza, G. Single bilayer lipid−protein vesicles formed from phosphatidylcholine and small intestinal sucrase-isomaltase. *J. Biol. Chem.* **1978**, *253*, 7538−7546.

(71) Schurtenberger, P.; Hauser, H. Characterization of the size distribution of unilamellar vesicles by gel-filtration, quasi-elastic light-scattering and electron-microscopy. *Biochim. Biophys. Acta* **1984**, 778, 470−480.

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