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EFFICIENT SYNTHESIS OF 5-AMINO-6-DIALKYLAMINO-4-HYDROXPENTANAMIDE DERIVATIVES FOR RENIN INHIBITORS

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Abstract – We report an efficient synthetic method for 5-amino-6-dialkylamino-4-hydroxypentanamide derivatives using Shi Asymmetric Epoxidation and the ring opening of *N*-(2-nitrobenzenesulfonyl)aziridine with hindered secondary amine as key steps.

INTRODUCTION

Renin has an important role in the control of the blood pressure,¹ and its inhibitors are expected to not only treat hypertension, but also prevent disorders in organs such as the heart and kidney.² Aliskiren (**1**) is the first marketed orally active direct renin inhibitor that possesses four chiral carbons in its framework (Figure 1).³ In 2007, we reported the usefulness of a novel renin inhibitor **2**, P₁ *N*-isopropyl motif analogue of **1**.⁴ **2** had a potent renin inhibitory activity close to **1** (in-house data), and this indicates the possibility of reducing the chemical complexity of **1**. To the best of our knowledge, **2** is the first nanomolar level renin inhibitor which possesses a basic amine group at the P₁ position.

A few synthetic routes for the synthesis of 5-amino-6-dialkylamino-4-hydroxypentanamide derivatives (e.g. **2**) have been reported.^{4,5} However, there seems to be room for improvement because these synthetic approaches include several moderate-yield steps (30-63%). Thus, it is worth discovering a new efficient synthetic route to **2** for further structure-activity relationships studies. In this paper, we report the efficient synthesis of **2**, utilizing highly functionalized chiral *N*-(2-nitrobenzenesulfonyl)aziridine **3** as an intermediate.

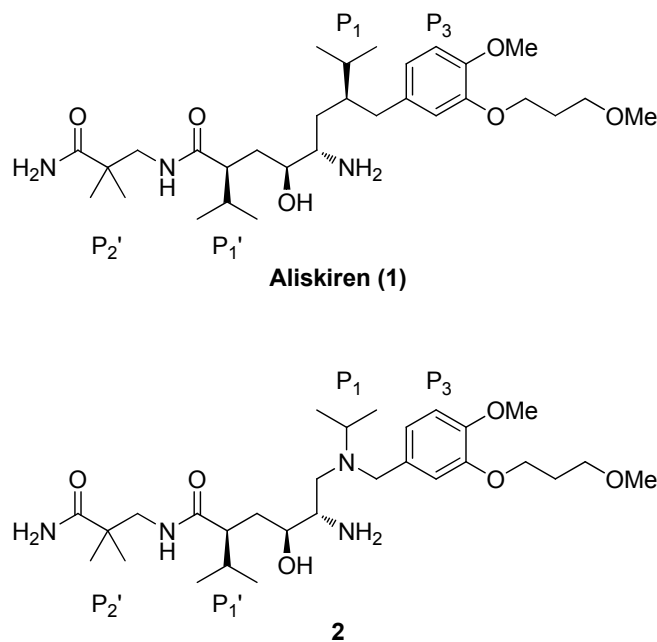
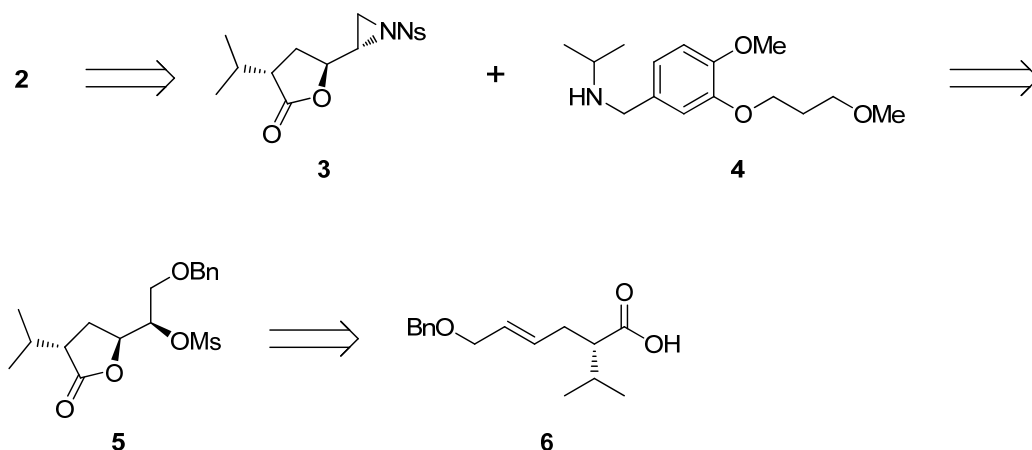


Figure 1. Structures of Aliskiren and **2**

RESULTS AND DISCUSSION

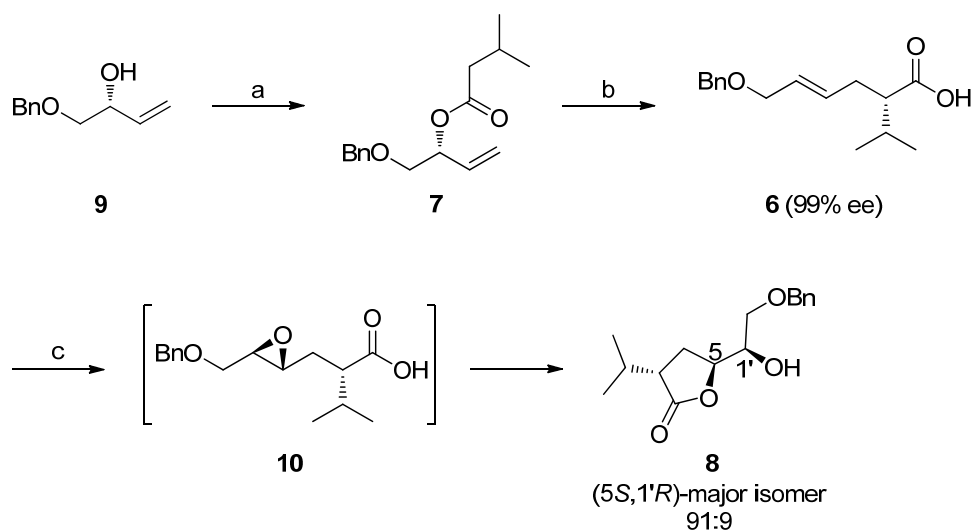
The key features of our strategy are: i) N-C bond formation through direct ring opening of aziridine **3** with secondary amine **4**; ii) S_N2 substitution of mesylate **5** with the azide group; iii) construction of two chiral centers by asymmetric epoxidation of (*E*)- γ,δ -unsaturated carboxylic acid **6**, followed by intramolecular lactonization.



Scheme 1. Synthetic strategy for the preparation of **2**

Although a number of approaches for the construction of C-2 chiral center of **6** were envisioned (e.g. Evans asymmetric alkylation), we chose the Ireland-Claisen rearrangement⁶ of ester **7** with large-scale synthesis in mind. The preparation of alcohol **8** is described in Scheme 2. The Ireland-Claisen substrate **7** was obtained by acylation of alcohol **9**, which was easily prepared from L-(+)-tartaric acid in optically

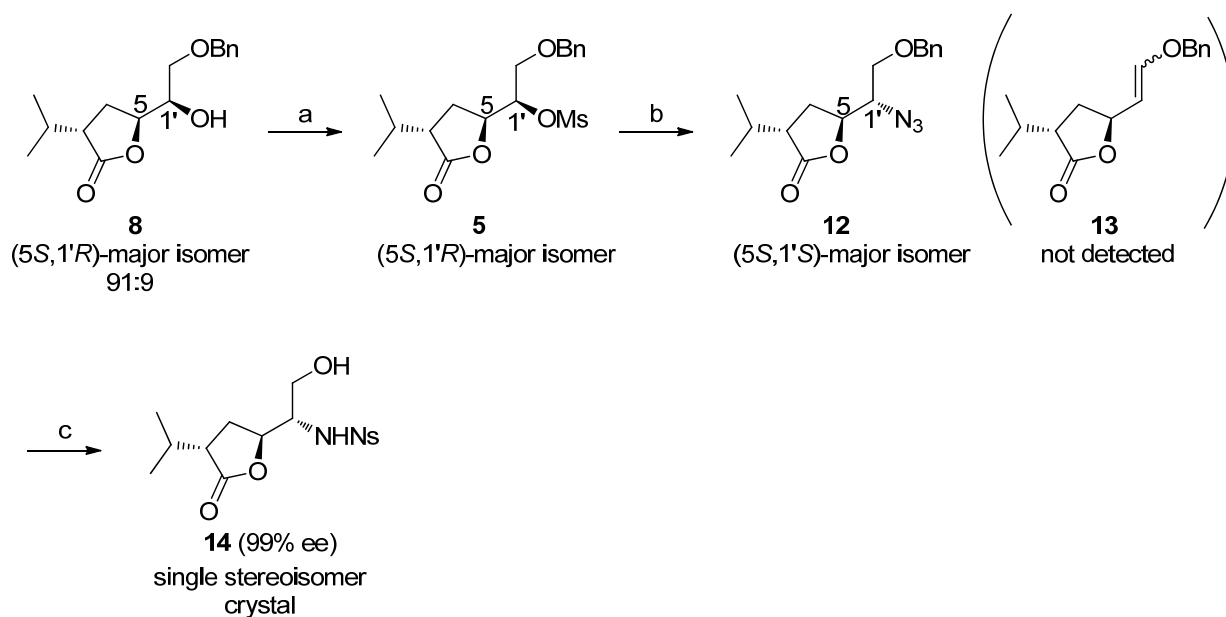
pure form.⁷ Ireland-Claisen rearrangement proceeded under the standard condition. After TMSCl was added to the enolate formed by **7** and LDA at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was warmed up to room temperature to afford (*E*)- γ,δ -unsaturated carboxylic acid **6** (54% yield and 91% ee). The ee value of **6** was enhanced after crystallization with (+)-dehydroabietylamine in *n*-hexane- CHCl_3 (10:1).⁸ Overall, enantiomerically pure (*S*)-**6** (99% ee) was obtained in 47% yield from **9** without chromatographic purification. The first key reaction, asymmetric epoxidation of (*E*)- γ,δ -unsaturated carboxylic acid **6** was achieved by applying Shi's method.⁹ Formation of (3*S*,4*S*)-epoxide **10** from **6** followed by one-pot intramolecular lactonization produced a ratio of 91:9 mixture of alcohol (71% yield) in which the (5*S*,1'*R*)-isomer **8** was predominant as determined by HPLC analysis. In this reaction, a slow addition of Oxone[®] and K_2CO_3 in the aq $\text{Na}_2(\text{EDTA})$ solution over a period of 6 hours to the reaction mixture of **6** and 1,2:4,5-di-*O*-isopropylidene- β -D-*erythro*-2,3-hexodiulo-2,6-pyranose (**11**) (1 equiv) was necessary to complete the reaction. Furthermore, the challenge of reducing the loading amount of **11** was not successful due to lowering the yield. With the difficulty of isolating a single diastereomer, this mixture was used for the next step.



Scheme 2. Reagents and conditions: (a) isovaleryl chloride, Et_3N , DMAP, CH_2Cl_2 , rt, 95%. (b) (i) LDA, TMSCl, THF, $-78\text{ }^{\circ}\text{C}$ to rt (ii) crystallization with (+)-dehydroabietylamine in *n*-hexane- CHCl_3 (10:1), 47%. (c) **11**, Oxone[®], K_2CO_3 , aq $\text{Na}_2(\text{EDTA})$, $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$, dimethoxymethane-MeCN (2:1), $0\text{ }^{\circ}\text{C}$, 71%.

Mesylation of **8** with MsCl and Et_3N created a diastereomeric mixture of mesylate containing (5*S*,1'*R*)-isomer **5** as a major product (Scheme 3). The second key reaction, $\text{S}_{\text{N}}2$ substitution of the methanesulfonyloxy group with the azide group, was accomplished by treating **5** with sodium azide (NaN_3) in DMPU to obtain (5*S*,1'*S*)-azide **12** as a major isomer. Under this conditions, the production of olefin **13**, which was observed when the bromo group was employed instead of the methanesulfonyloxy

group, was not detected.¹⁰ Hydrogenation of the diastereomeric mixture of azide in the presence of HCl, and the subsequent reaction with 2-nitrobenzenesulfonyl chloride (NsCl)¹¹ under the Schotten-Baumann condition, followed by crystallization gave *N*-Ns alcohol **14** as a single stereoisomer in 70% yield from **12** (42% yield from **6**). The ee value of **14** was determined to be 99% by chiral HPLC analysis. The structure and absolute configuration of **14** was confirmed by single crystal X-ray analysis as shown in Figure 2.



Scheme 3. Reagents and conditions: (a) MsCl, Et₃N, CH₂Cl₂, 0 °C, 97%. (b) NaN₃, DMPU, 60 °C, 87%. (c) (i) cat. Pd-C, H₂, HCl, EtOH, rt (ii) NsCl, Et₃N, THF-H₂O (10:1), rt (iii) crystallization in diisopropyl ether-AcOEt (10:1), 70% (3 steps from **12**).

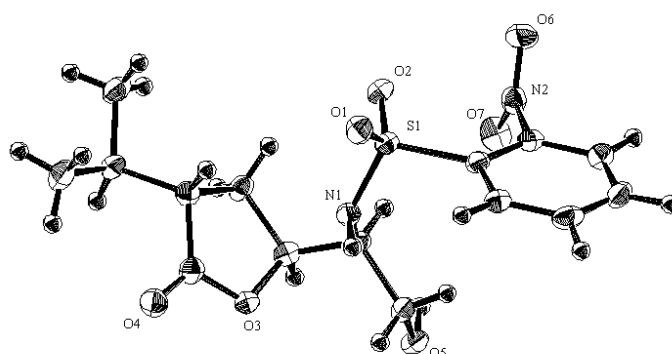
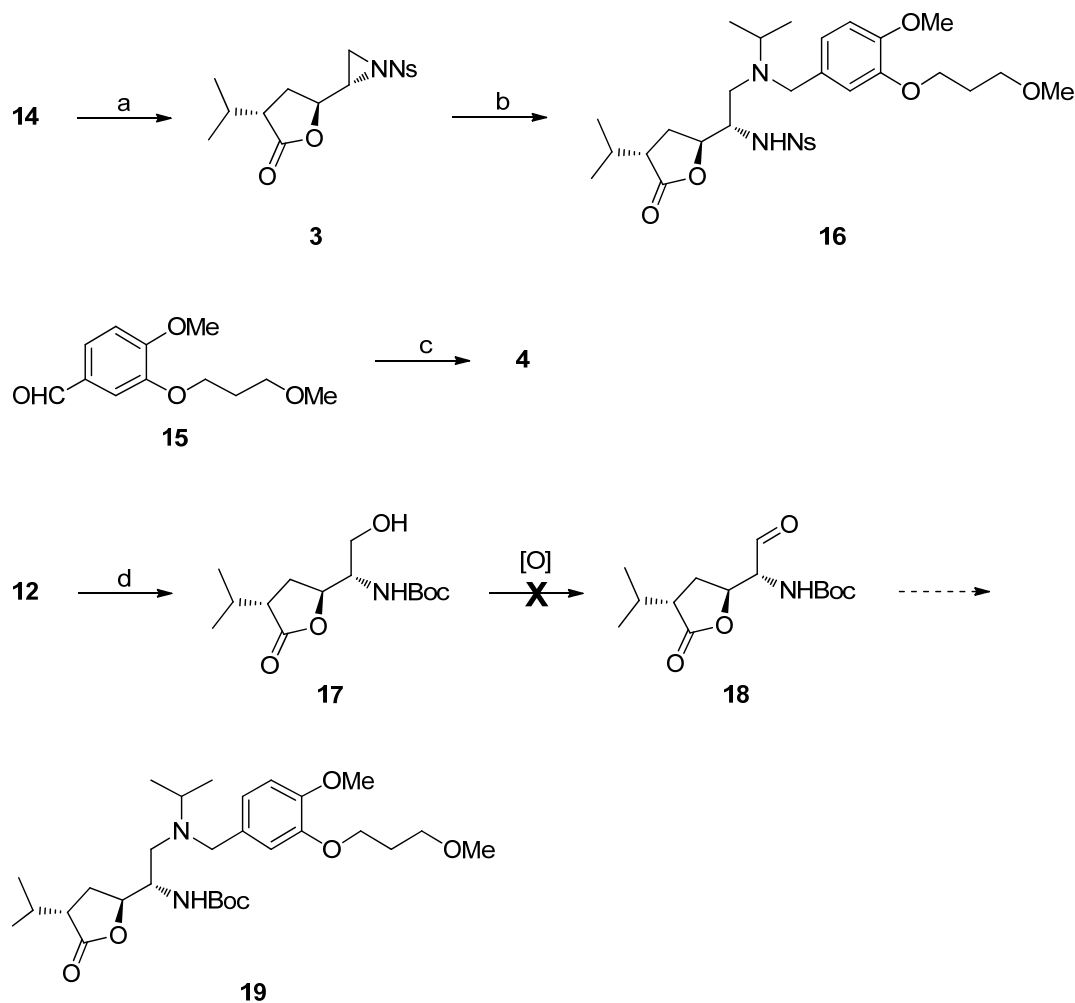


Figure 2. X-Ray ORTEP of compound **14**

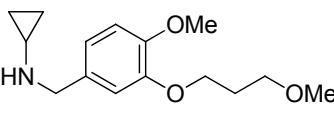
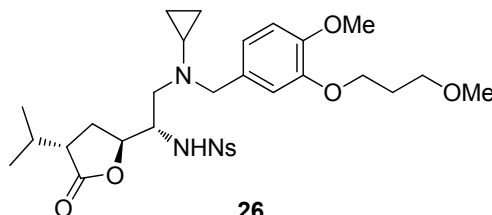
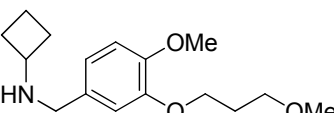
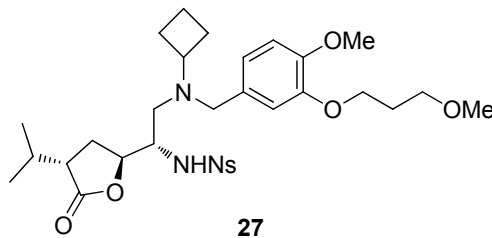
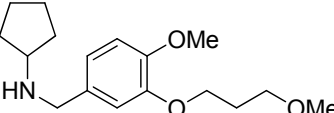
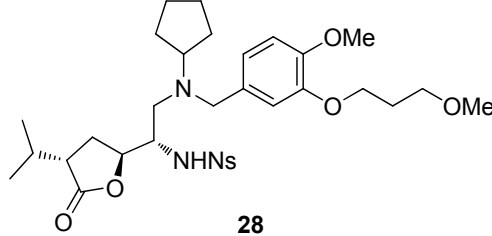
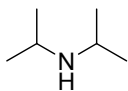
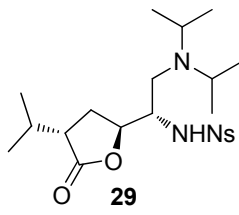
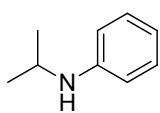
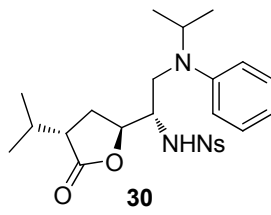
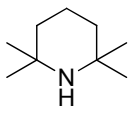
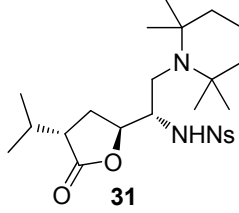
The left-hand aziridine **3** was formed by the Mitsunobu reaction of **14** with DEAD and Ph₃P in 93% yield (Scheme 4). On the other hand, the right-hand amine **4** was prepared by reductive amination of known benzaldehyde **15**¹² with isopropylamine in 92% yield. Then the final key coupling reaction, the ring

opening of **3** with secondary amine **4** was attempted. To our delight, the reaction was accomplished by only heating the solutions of **3** and **4** in toluene to afford the desired coupling product **16** in excellent yield (98%). Although reductive amination of aldehyde **18** with **4** was planned to obtain **19** as an alternative method, aldehyde **18** was not obtained by oxidation of alcohol **17**. To evaluate the feature of *N*-Ns-aziridine intermediate, we performed similar ring opening reactions of aziridine **3** with several amines (Table 1). Aziridine **3** smoothly reacted with several amines, even less nucleophilic and more hindered amines such as *N*-isopropylaniline (**24**) and 2,2,6,6-tetramethylpiperidine (**25**) than amine **4**, to produce coupling adducts in good yield. In addition, **3** was relatively stable and no decomposition was observed after several months of storage in a refrigerator. Meanwhile, we tried for similar reactions in two other popular *N*-protected aziridines with amine **4**. *N*-Boc-aziridine gave no desired product, and *N*-Cbz-aziridine gave a coupling product in moderate yield (data not shown). With these features, *N*-Ns-aziridine **3** was considered to be a useful intermediate for further chemical modifications of **2**.



Scheme 4. Reagents and conditions: (a) DEAD, Ph_3P , THF, 0 °C, 93%. (b) **4**, toluene, 110 °C, 98%. (c) isopropylamine, AcOH, $\text{NaBH}(\text{OAc})_3$, CH_2Cl_2 , rt, 92%. (d) (i) cat. Pd-C, H_2 , HCl, EtOH, rt (ii) Boc_2O , NaHCO_3 , dioxane- H_2O (1:1), rt.

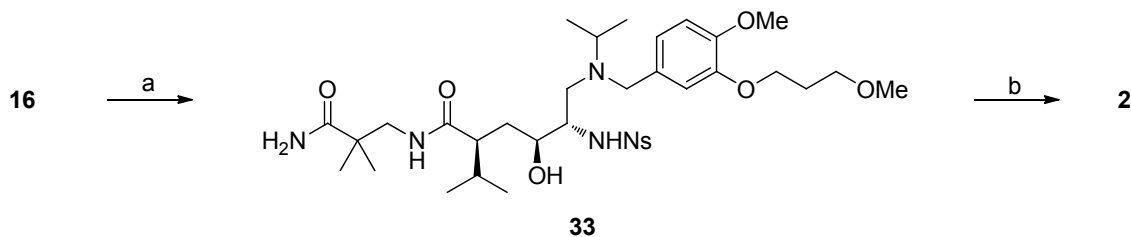
Table 1. Reaction of aziridine **3** with hindered amines

entry	amine	product	yield (%)
1	 20	 26	76
2	 21	 27	72
3	 22	 28	89
4	 23	 29	99
5	 24	 30	95
6	 25	 31	92

Next, the *N*-terminal amide bond formation with **16** and 3-amino-2,2-dimethylpropanamide (**32**)³ was attempted under neat condition in the presence of 2-hydroxypyridine as a catalyst to afford amide **33** in

73% yield.¹³ Finally, deprotection of the Ns group of **33** was accomplished with thiophenol and cesium carbonate in DMF to give P₁ N-isopropyl motif analogue **2** in 90% yield (Scheme 5).

In conclusion, we have described an efficient route to renin inhibitor **2** proceeding with high stereocontrol. With a practical synthetic route to 5-amino-6-dialkylamino-4-hydroxypentanamide derivatives in hand, further chemical modifications aimed at exploring novel renin inhibitors using this synthetic method are underway. The results of this work will be published elsewhere.



Scheme 5. Reagents and conditions: (a) 3-amino-2,2-dimethylpropanamide (**32**), 2-hydroxypyridine, 80 °C, 73%. (b) PhSH, Cs₂CO₃, DMF, rt, 90%.

EXPERIMENTAL

General

All chemicals, reagents and solvents were purchased from commercial sources (e.g., Aldrich Chemical Co., Inc., Tokyo Chemical Industry Co., LTD., KANTO CHEMICAL CO., INC., etc.) where available and used without further purification. ¹H NMR and ¹³C NMR spectra were obtained on a Varian Unity 400 and 500 MHz spectrometers. Mass spectral data were obtained on a VG Analytical 7070 E/HF mass spectrometer. Flash column chromatography was performed on silica gel 60 N (spherical, neutral), 40-50 μm, purchased from KANTO CHEMICAL CO., INC., or NH silica gel, 100-200 mesh, purchased from FUJI SILYSIA CHEMICAL LTD.

(1R)-3-Methylbutanoic acid 1-[(benzyloxy)methyl]prop-2-en-1-yl ester (7): A solution of isovaleryl chloride (19.9 mL, 163 mmol) in CH₂Cl₂ (20 mL) was added to a solution of **9** (24.3 g, 136 mmol), triethylamine (28.5 mL, 205 mmol) and 4-dimethylaminopyridine (1.65 g, 13.6 mmol) in CH₂Cl₂ (250 mL) under ice-cooling over 10 minutes, and the mixture was stirred at rt for 4 h. Water (0.75 mL, 42 mmol) was added to the reaction mixture, and the mixture was further stirred at rt for 15 min. The reaction mixture was concentrated under reduced pressure and diluted with 150 mL of water, followed by extraction with AcOEt. Then, the organic layer was washed with 1 N hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column

chromatography (eluent, *n*-hexane:AcOEt = 9:1) to obtain **7** (35.0 g, 95%) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.27 (m, 5H), 5.84 (ddd, *J* = 17.2, 10.6, 5.9 Hz, 1H), 5.54-5.49 (m, 1H), 5.33 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.24 (dt, *J* = 10.6, 1.2 Hz, 1H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 3.58 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.56 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.23 (d, *J* = 6.6 Hz, 2H), 2.17-2.07 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H). MS (FAB⁺): 263 (M+H)⁺.

(2*S*,4*E*)-6-(Benzyloxy)-2-isopropylhex-4-enoic acid (6): A solution of *n*-butyllithium (1.57 M in hexane solution, 94 mL, 0.15 mol) was added to a solution of diisopropylamine (23 mL, 0.16 mol) in THF (265 mL) under N₂ atmosphere and under ice-cooling over 45 min. The mixture was stirred at the same temperature for 20 min to prepare a solution of lithium diisopropylamide in THF. A solution of **7** (35 g, 0.13 mol) in THF (70 mL) was added to the solution above under cooling in a dry ice-acetone bath over 40 minutes, and the mixture was stirred at the same temperature for 20 min. Then, chlorotrimethylsilane (39 mL, 0.31 mol) was added to the reaction mixture over 20 min. The mixture was stirred at the same temperature for 20 min and then further stirred at rt for 3 h. After cooling in an ice bath, MeOH (27 mL, 0.67 mol) was added to the reaction mixture so that the internal temperature did not exceed 20 °C. The mixture was further stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and diluted with a 1 N sodium hydroxide aqueous solution (270 mL, 270 mmol), followed by extraction with *t*-butyl methyl ether. Then, the organic layer was extracted with a 1 N sodium hydroxide aqueous solution (68 mL, 68 mmol). All aqueous layers were combined and made acidic with 6 N hydrochloric acid (78 mL, 0.47 mol), followed by extraction with AcOEt. Then, the organic layer was washed with water and brine and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated under reduced pressure to obtain crude **6** (19.0 g, 54%, 91% ee) as a yellow liquid. [α]_D -9.9° (*c* 1.07, CHCl₃). Optically enriched (*S*)-**6** (13.2 g, 50.3 mmol) was then dissolved in CHCl₃ (25 mL) and treated with a solution of (+)-dehydroabietylamine (20.0 g, 70.1 mmol) in CHCl₃ (50 mL). After addition of *n*-hexane (750 mL), the salt was allowed to crystallize at rt. The solid material was collected by filtration, washed with *n*-hexane, dried, and dissolved in *t*-butyl methyl ether (80 mL). 1 N Sodium hydroxide aqueous solution (80 mL, 80 mmol) was added, and the mixture was stirred at rt for 30 min. After the aqueous layer was separated, organic layer was extracted with 1 N sodium hydroxide aqueous solution (20 mL, 20 mmol). All aqueous layers were combined and made acidic with 6 N hydrochloric acid (20 mL), followed by extraction with AcOEt (100 mL). Then, the organic layer was washed with water and brine and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated under reduced pressure to obtain **6** (11 g, 47% from **9**, 99% ee) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.27 (m, 5H), 5.72-5.62 (m, 2H), 4.47 (s, 2H), 3.99-3.91 (m, 2H), 2.40-2.20 (m, 3H),

1.96-1.88 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H). IR (ATR): 1732, 1703, 1454, 1372, 1214, 1165, 1096, 1064, 1027, 970, 736, 697 cm^{-1} . HRMS (ESI⁺): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 285.14666; found $[\text{M}+\text{Na}]^+$: 285.14618. The ee value of carboxylic acid **6** was determined by chiral HPLC analysis after conversion to the corresponding methyl ester with (trimethylsilyl)diazomethane and MeOH (column, CHIRALCEL OD-H ($4.6 \Phi \times 250$ mm); eluent, *n*-hexane:*i*-PrOH = 90:10; flow rate, 0.5 mL/min; wave length, 220 nm; t_R of (2*S*)-isomer, 14.7 min; t_R of (2*R*)-isomer, 16.2 min).

(3*S*,5*S*)-5-[(1*R*)-2-(Benzyloxy)-1-hydroxyethyl]-3-isopropylidihydrofuran-2(3*H*)-one (8): To a 2 L three-neck round-bottom flask was added the buffer (0.05 M sodium tetraborate decahydrate in 0.4 mM aq ethylenediaminetetraacetic acid disodium salt, 292 mL), dimethoxymethane (220 mL), acetonitrile (110 mL), carboxylic acid **6** (10.0 g, 37.9 mmol), tetra-*n*-butylammonium hydrogen sulfate (576 mg, 1.44 mmol), and ketone **11** (9.80 g, 37.9 mmol). The reaction mixture was cooled with an ice bath. A solution of Oxone[®] (32.6 g, 53.0 mmol) in aq ethylenediaminetetraacetic acid disodium salt (0.4 mM, 146 mL) and a solution of potassium carbonate (30.6 g, 221 mol) in water (146 mL) were added dropwise through two separate addition funnels over a period of 6 h. At this point, the reaction was quenched by the addition of AcOEt and water. The mixture was extracted with AcOEt, washed with brine, dried over anhydrous Na_2SO_4 , and purified by flash chromatography (eluent, *n*-hexane:AcOEt = 1:1) to afford a 91:9 mixture of alcohol (7.75 g, 71%) in which the (5*S*,1'*R*)-isomer **8** was predominant as determined by HPLC analysis (column, Inertsil ODS-3 ($4.6 \Phi \times 250$ mm); eluent, MeCN: aq 0.1% ammonium acetate = 50:50; flow rate, 1 mL/min; wave length, 220 nm; t_R of minor isomer, 11.8 min; t_R of major isomer, 12.5 min). Colorless oil. ¹H NMR (400 MHz, CDCl_3): δ *major isomer* 7.37-7.31 (m, 5H), 4.56 (d, $J = 4.7$ Hz, 2H), 4.44-4.40 (m, 1H), 3.88-3.83 (m, 1H), 3.63 (dd, $J = 9.8, 3.9$ Hz, 2H), 3.55 (dd, $J = 9.8, 6.3$ Hz, 2H), 2.64-2.58 (m, 1H), 2.41 (d, $J = 5.0$ Hz, 1H), 2.36-2.29 (m, 1H), 2.21-2.04 (m, 2H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H). IR (ATR): 1764, 1741, 1453, 1371, 1242, 1173, 1095, 1045, 1010, 969, 948, 912, 736, 698 cm^{-1} . HRMS (ESI⁺): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 301.14158; found $[\text{M}+\text{Na}]^+$: 301.14152.

(3*S*,5*S*)-5-[(1*R*)-2-(Benzyloxy)-1-methanesulfonyloxyethyl]-3-isopropylidihydrofuran-2(3*H*)-one (5): Methanesulfonyl chloride (177 μL , 2.29 mmol) was added to a solution of **8** (440 mg, 1.53 mmol) and triethylamine (464 mg, 4.59 mmol) in CH_2Cl_2 (15 mL) under ice-cooling, and the mixture was stirred at the same temperature for 1 h. Water was added to the reaction mixture, followed by extraction with CH_2Cl_2 . Then, the organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the solvent was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt = 3:1) to obtain a diastereomeric mixture of mesylate (528 mg,

97%) containing (5*S*,1'*R*)-isomer **5** as a major product. Colorless solid. ^1H NMR (400 MHz, CDCl_3): δ *major isomer* 7.39-7.30 (m, 5H), 4.82 (q, $J = 5.7$ Hz, 1H), 4.64-4.59 (m, 1H), 4.56 (s, 2H), 3.75 (dd, $J = 5.7, 1.8$ Hz, 2H), 3.04 (s, 3H), 2.65-2.59 (m, 1H), 2.38-2.31 (m, 1H), 2.18-2.09 (m, 2H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H). IR (ATR): 1771, 1352, 1172, 1096, 1026, 967, 918, 809, 738, 699, 524 cm^{-1} . HRMS (ESI $^+$): m/z calcd for $\text{C}_{17}\text{H}_{24}\text{NaO}_6\text{S}$ $[\text{M}+\text{Na}]^+$: 379.11913; found $[\text{M}+\text{Na}]^+$: 379.11840.

(3*S*,5*S*)-5-[(1*S*)-1-Azido-2-benzyloxyethyl]-3-isopropylidihydrofuran-2-one (12): Sodium azide (33 mg, 0.50 mmol) was added to a solution of **5** (150 mg, 0.42 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (3 mL) at rt, and the mixture was stirred at 60 $^\circ\text{C}$ for 1 d. The reaction mixture was cooled to rt and poured into ice water, followed by extraction with AcOEt. Then, the organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4 . After filtration, the solvent was evaporated under reduce pressure, and the residue was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt = 5:1) to obtain a diastereomeric mixture of azide (111 mg, 87%) containing (5*S*,1'*S*)-isomer **12** as a major product. Colorless liquid. ^1H NMR (500 MHz, CDCl_3): δ *major isomer* 7.38-7.29 (m, 5H), 4.61-4.53 (m, 3H), 3.79-3.73 (m, 2H), 3.66-3.63 (m, 1H), 2.75-2.70 (m, 1H), 2.20-2.10 (m, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H).

***N*-{(1*S*)-2-Hydroxy-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (14)**: A suspension of **12** (10.1 g, 33.5 mmol), a solution of 4 N hydrochloric acid in dioxane (16.7 mL, 66.8 mmol) and 10% palladium-carbon (50% wet, 3.57 g) in EtOH (170 mL) was stirred under H_2 atmosphere at rt for 6 h. Hydrogen in the reaction vessel was replaced by N_2 , and then the reaction mixture was diluted with EtOH. Palladium-carbon was separated by filtration and washed with EtOH. The solvent was evaporated from the filtrate under reduced pressure to obtain 8.50 g of crude aminoalcohol. Triethylamine (10.2 g, 101 mmol) and 2-nitrobenzenesulfonyl chloride (11.1 g, 50.1 mmol) were added to a solution of 8.50 g of crude aminoalcohol in a mixed solvent of THF (170 mL) and water (17 mL) at rt, and the mixture was stirred at rt for 12 h. The reaction mixture was concentrated under reduced pressure, followed by extraction with AcOEt. Then, the organic layer was washed with water, a saturated sodium bicarbonate aqueous solution and brine, and dried over Na_2SO_4 . After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent, AcOEt). Further, diisopropyl ether (110 mL) and AcOEt (10 mL) were added, and the precipitated solid was collected by filtration to obtain **14** (8.78 g, 70%) as a single stereoisomer. Colorless solid. ^1H NMR (500 MHz, CDCl_3): δ 8.15-8.11 (m, 1H), 7.92-7.88 (m, 1H), 7.77-7.74 (m, 2H), 5.85 (br d, $J = 8.3$ Hz, 1H), 4.64-4.61 (m, 1H), 3.72-3.62 (m, 3H), 2.69 (ddd, $J = 10.3, 6.8, 5.4$ Hz, 1H), 2.41 (ddd, $J = 13.7, 10.7, 5.4$ Hz), 2.20-2.10 (m, 2H), 1.99 (t, $J = 5.4$ Hz, 1H), 1.00 (d, $J = 6.8$ Hz, 3H),

0.93 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (500 MHz, CDCl_3), δ 178.5, 147.6, 134.3, 133.8, 133.0, 130.6, 125.5, 77.5, 62.4, 58.9, 45.1, 29.1, 26.1, 20.2, 18.3. IR (KBr): 3397, 1749, 1554, 1470, 1380, 1351, 1184, 1063, 1042, 971, 780, 745, 588, 559 cm^{-1} . HRMS (ESI^+): m/z calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{NaO}_7\text{S}$ $[\text{M}+\text{Na}]^+$: 395.08889; found $[\text{M}+\text{Na}]^+$: 395.08828. The ee value of **14** was determined by HPLC analysis (column, CHIRALPAK AD-H ($4.6\ \Phi \times 250$ mm); eluent, EtOH:*n*-hexane = 70:30; flow rate, 0.5 mL/min; wave length, 254 nm; t_R of (2'*S*,4'*S*,1*S*)-isomer, 5.6 min; t_R of (2'*R*,4'*R*,1*R*)-isomer, 8.8 min). Crystal data: $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_7\text{S}$, orthorhombic, space group $P2_12_12_1$, $a = 7.33552(18)$ Å, $b = 14.5482(3)$ Å, $c = 16.0057(4)$ Å, $V = 1708.10(7)$ Å³, $Z = 4$, $D_c = 1.448$ g/cm³, $\mu(\text{Cu-K}\alpha) = 20.639$ cm⁻¹. The number of reflections collected at 123 K was 19554, of which 3120 were independent and used for structure refinement with $R_1 = 0.0333$, $wR_2 = 0.0811$, and Flack parameter = 0.027(18). Full X-ray crystallographic data will be deposited at the Cambridge Crystallographic Data Centre.

(3*S*,5*S*)-3-Isopropyl-5-[(1*S*)-1-(2-nitrobenzenesulfonyl)aziridine-2-yl]dihydrofuran-2-one (3): A solution of diethyl azodicarboxylate in toluene (40%, 1.47 mL, 3.22 mmol) was added to a solution of **14** (1.0 g, 2.7 mmol) and triphenylphosphine (845 mg, 3.22 mmol) in THF (30 mL) under ice-cooling over 10 min, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent, toluene:acetone = 5:1) to obtain **3** (890 mg, 93%) as a colorless solid. ^1H NMR (400 MHz, CDCl_3): δ 8.14 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.83-7.73 (m, 3H), 4.74-4.70 (m, 1H), 3.26-3.23 (m, 1H), 2.83 (d, $J = 4.7$ Hz, 1H), 2.78 (dt, $J = 9.8, 4.7$ Hz, 1H), 2.65 (d, $J = 4.7$ Hz, 1H), 2.41-2.35 (m, 1H), 2.29 (dt, $J = 12.9, 9.4$ Hz, 1H), 2.18-2.10 (m, 1H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H). IR (KBr): 1778, 1548, 1369, 1336, 1168, 1114, 974, 933, 782, 770, 602 cm^{-1} . HRMS (ESI^+): m/z calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_6\text{S}$ $[\text{M}+\text{Na}]^+$: 377.07833; found $[\text{M}+\text{Na}]^+$: 377.07748.

Typical Procedure for the Preparation of Amines 4 and 20-22. *N*-[4-Methoxy-3-(3-methoxypropoxy)benzyl]propan-2-amine (4): Sodium triacetoxymethylborohydride (11.3 g, 53.5 mmol) was added to a solution of **15** (6.0 g, 27 mmol), isopropylamine (4.7 g, 80 mmol), and acetic acid (4.8 g, 80 mmol) in CH_2Cl_2 (135 mL) under ice-cooling, and the mixture was stirred at rt for 16 h. A saturated sodium bicarbonate aqueous solution was added to the reaction mixture, followed by extraction with CH_2Cl_2 . Then, the organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (eluent, CH_2Cl_2 :MeOH = 10:1) to obtain **4** (6.6 g, 92%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 6.90 (d, $J = 2.0$ Hz, 1H), 6.85-6.81 (m, 2H), 4.12 (t, $J = 6.4$ Hz, 2H), 3.85 (s, 3H), 3.71 (s, 2H), 3.57 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 3H), 2.87-2.82 (m, 1H), 2.13-2.08 (m, 2H), 1.09 (d, $J = 6.4$ Hz, 6H).

IR (ATR): 1512, 1464, 1441, 1423, 1260, 1232, 1160, 1025, 804, 764 cm^{-1} . HRMS (ESI^+): m/z calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 268.19127; found $[\text{M}+\text{H}]^+$: 268.19170.

***N*-[4-Methoxy-3-(3-methoxypropoxy)benzyl]cyclopropanamine (20)**: colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 6.88 (d, $J = 2.0$ Hz, 1H), 6.84 (dd, $J = 8.3, 2.0$ Hz, 1H), 6.82 (d, $J = 8.3$ Hz, 1H), 4.12 (t, $J = 6.4$ Hz, 2H), 3.85 (s, 3H), 3.76 (s, 2H), 3.58 (t, $J = 6.4$ Hz, 2H), 3.36 (s, 3H), 2.17-2.08 (m, 3H), 0.46-0.36 (m, 4H).

***N*-[4-Methoxy-3-(3-methoxypropoxy)benzyl]cyclobutanamine (21)**: colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 6.90 (d, $J = 1.6$ Hz, 1H), 6.83-6.82 (m, 2H), 4.12 (t, $J = 6.6$ Hz, 2H), 3.85 (s, 3H), 3.63 (s, 2H), 3.57 (t, $J = 6.3$ Hz, 2H), 3.35 (s, 3H), 3.32-3.25 (m, 1H), 2.25-2.19 (m, 2H), 2.14-2.07 (m, 2H), 1.73-1.64 (m, 4H).

***N*-[4-Methoxy-3-(3-methoxypropoxy)benzyl]cyclopentanamine (22)**: colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 6.90-6.81 (m, 3H), 4.12 (t, $J = 6.6$ Hz, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.57 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 2H), 3.13-3.08 (m, 1H), 2.13-2.08 (m, 2H), 1.88-1.82 (m, 2H), 1.73-1.66 (m, 2H), 1.57-1.33 (m, 5H).

Typical Procedure for the Preparation of Products 16 and 26-31. ***N*-{(1*S*)-2-{Isopropyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (16)**: A solution of *N*-Ns-aziridine **3** (0.19 g, 0.54 mmol) and amine **4** (0.18 g, 0.67 mmol) in toluene (7 mL) was stirred at 110 $^\circ\text{C}$ for 1.5 h. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, *n*-hexane:EtOAc = 1:1) to obtain compound **16** (299 mg, 98%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 8.01-7.99 (m, 1H), 7.89-7.87 (m, 1H), 7.77-7.71 (m, 2H), 6.82-6.81 (m, 2H), 6.75 (dd, $J = 7.8, 2.0$ Hz, 1H), 5.49-5.40 (br s, 1H), 4.80-4.76 (m, 1H), 4.12-4.09 (m, 2H), 3.87 (s, 3H), 3.60-3.57 (m, 2H), 3.49 (d, $J = 13.7$ Hz, 1H), 3.35 (s, 3H), 3.24 (d, $J = 14.1$ Hz, 1H), 2.83-2.77 (m, 1H), 2.71 (dd, $J = 13.2, 9.8$ Hz, 1H), 2.54-2.50 (m, 1H), 2.20 (dd, $J = 13.7, 5.9$ Hz, 1H), 2.14-2.01 (m, 5H), 1.96-1.90 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 6H). IR (ATR): 1768, 1735, 1541, 1511, 1362, 1236, 1163, 1115, 1044, 1025, 953, 852, 781, 741, 730, 655, 585, 557, 521 cm^{-1} . HRMS (ESI^+): m/z calcd for $\text{C}_{30}\text{H}_{43}\text{N}_3\text{NaO}_9\text{S}$ $[\text{M}+\text{Na}]^+$: 644.26258; found $[\text{M}+\text{Na}]^+$: 644.26177.

***N*-{(1*S*)-2-{Cyclopropyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (26)**: Colorless oil. ^1H NMR (400 MHz,

CDCl₃): δ 8.09-8.06 (m, 1H), 7.89-7.87 (m, 1H), 7.76-7.70 (m, 2H), 6.78 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.65 (m, 1H), 5.41 (d, J = 8.2 Hz, 1H), 4.69-4.65 (m, 1H), 4.07 (t, J = 6.7 Hz, 2H), 3.86 (s, 3H), 3.70-3.64 (m, 1H), 3.57 (t, J = 6.1 Hz, 2H), 3.51 (d, J = 13.7 Hz, 1H), 3.40 (d, J = 13.7 Hz, 1H), 3.35 (s, 3H), 2.81 (dd, J = 13.1, 8.4 Hz, 1H), 2.63-2.58 (m, 1H), 2.36-2.31 (m, 1H), 2.23-1.96 (m, 5H), 1.65-1.60 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.48-0.36 (m, 2H), 0.28-0.23 (m, 1H), 0.18-0.12 (m, 1H).

***N*-{(1*S*)-2-{Cyclobutyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (27):** Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.07-8.06 (m, 1H), 7.91-7.89 (m, 1H), 7.77-7.75 (m, 2H), 6.80 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 1.5 Hz, 1H), 6.67 (dd, J = 8.1, 1.7 Hz, 1H), 5.56 (br s, 1H), 4.79-4.76 (m, 1H), 4.11 (t, J = 7.3 Hz, 2H), 3.86 (s, 3H), 3.58 (t, J = 6.4 Hz, 2H), 3.45-3.40 (m, 2H), 3.35 (s, 3H), 3.13 (d, J = 13.7 Hz, 1H), 3.00-2.94 (m, 1H), 2.61-2.51 (m, 2H), 2.17-2.02 (m, 5H), 1.97-1.85 (m, 3H), 1.74-1.67 (m, 1H), 1.61-1.46 (m, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H).

***N*-{(1*S*)-2-{Cyclopentyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (28):** Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.05-8.02 (m, 1H), 7.89-7.87 (m, 1H), 7.76-7.73 (m, 2H), 6.82 (d, J = 2.4 Hz, 1H), 6.80 (s, 1H), 6.74-6.72 (m, 1H), 5.56 (br s, 1H), 4.81-4.77 (m, 1H), 4.13-4.10 (m, 2H), 3.86 (s, 3H), 3.58 (t, J = 6.1 Hz, 2H), 3.54 (d, J = 13.7 Hz, 1H), 3.42-2.39 (m, 1H), 3.35 (s, 3H), 3.27 (d, J = 13.7 Hz, 1H), 3.00-2.92 (m, 1H), 2.73 (dd, J = 13.3, 9.4 Hz, 1H), 2.54-2.49 (m, 1H), 2.26 (dd, J = 13.3, 6.3 Hz, 1H), 2.14-1.89 (m, 5H), 1.63-1.32 (m, 7H), 1.20-1.13 (m, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

***N*-{(1*S*)-2-(Diisopropylamino)-1-[(2*S*,4*S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}-2-nitrobenzenesulfonamide (29):** Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.16-8.14 (m, 1H), 7.92-7.90 (m, 1H), 7.77-7.75 (m, 2H), 5.54 (br, 1H), 4.90-4.86 (m, 1H), 3.49-3.46 (m, 1H), 2.84-2.78 (m, 2H), 2.72-2.61 (m, 2H), 2.39-2.32 (m, 1H), 2.21-2.10 (m, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.7 Hz, 6H), 0.77 (d, J = 6.7 Hz, 6H). HRMS (ESI⁺): m/z calcd for C₂₁H₃₄N₃O₆S [M+H]⁺: 456.2168; found [M+H]⁺: 456.2164.

***N*-{(1*S*)-1-[(2*S*,4*S*)-4-Isopropyl-5-oxotetrahydrofuran-2-yl]-2-[isopropyl(phenyl)amino]ethyl}-2-nitrobenzenesulfonamide (30):** Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.94 (dd, J = 7.6, 1.8 Hz, 1H), 7.88 (dd, J = 7.6, 1.8 Hz, 1H), 7.75-7.66 (m, 2H), 7.14-7.10 (m, 2H), 6.83-6.79 (m, 1H), 6.59-6.57 (m, 2H), 7.43 (d, J = 7.4 Hz, 1H), 4.78-4.74 (m, 1H), 3.77-3.71 (m, 2H), 3.27 (dd, J = 11.5, 8.2 Hz, 1H),

3.05 (dd, $J = 14.5, 6.7$ Hz, 1H), 2.71-2.65 (m, 1H), 2.35-2.28 (m, 1H), 2.19-2.07 (m, 2H), 1.08 (d, $J = 6.7$ Hz, 3H), 0.99 (d, $J = 3.1$ Hz, 3H), 0.97 (d, $J = 3.1$ Hz, 3H), 0.93 (d, $J = 6.7$ Hz, 3H). HRMS (ESI⁺): m/z calcd for C₂₄H₃₂N₃O₆S [M+H]⁺: 490.20118; found [M+H]⁺: 490.20074.

***N*-[*(1S)*-1-[(*2S,4S*)-4-Isopropyl-5-oxotetrahydrofuran-2-yl]-2-(2,2,6,6-tetramethylpiperidin-1-yl)-ethyl]-2-nitrobenzenesulfonamide (31):** Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.20-8.17 (m, 1H), 7.91-7.89 (m, 1H), 7.77-7.74 (m, 2H), 6.24 (d, $J = 5.5$ Hz, 1H), 4.86-4.81 (m, 1H), 3.72-3.65 (m, 1H), 2.74 (dd, $J = 15.3, 8.6$ Hz, 1H), 2.63-2.57 (m, 1H), 2.41 (dd, $J = 15.1, 7.6$ Hz, 1H), 2.29-2.21 (m, 3H), 1.60-1.39 (m, 6H), 1.03-0.93 (m, 12H), 0.86 (s, 6H). HRMS (ESI⁺): m/z calcd for C₂₄H₃₈N₃O₆S [M+H]⁺: 496.2488; found [M+H]⁺: 496.2479.

***tert*-Butyl {(1*S*)-2-hydroxy-1-[(*2S,4S*)-4-isopropyl-5-oxotetrahydrofuran-2-yl]ethyl}carbamate (17):** Title compound was obtained in the same manner as described for compound **14** except for the use of di-*tert*-butyl dicarbonate and sodium bicarbonate in dioxane-water (1:1) at the stage of the reaction with 2-nitrobenzenesulfonyl chloride. Colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 4.86 (br, 1H), 4.71-4.67 (m, 1H), 3.83-3.71 (m, 3H), 2.60-2.56 (m, 1H), 2.28-2.22 (m, 1H), 2.19-2.10 (m, 3H), 1.45 (s, 9H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H).

(*2S,4S,5S*)-*N*-(3-Amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-6-{isopropyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}-5-[(2-nitrophenyl)sulfonyl]amino}hexanamide (33): **32** (134 mg, 1.15 mmol) and 2-hydroxypyridine (11 mg, 0.1 mmol) were added to a solution of **16** (0.24 g, 0.38 mmol) in triethylamine (3.8 mL), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to rt and then concentrated under reduced pressure and further stirred at 80 °C for 9 h. The reaction mixture was cooled and then water was added, followed by extraction with CH₂Cl₂. Then, the organic layer was dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, CH₂Cl₂:MeOH = 20:1) to obtain **33** (206 mg, 73%) as a colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 8.03-8.01 (m, 1H), 7.82-7.81 (m, 1H), 7.74-7.68 (m, 2H), 6.84-6.78 (m, 3H), 6.38 (t, $J = 6.4$ Hz, 1H), 6.16 (br s, 1H), 5.87 (br s, 1H), 5.32 (br s, 1H), 5.03 (br s, 1H), 4.16-4.09 (m, 2H), 3.85 (s, 3H), 3.68-3.56 (m, 4H), 3.42-3.38 (m, 2H), 3.36 (s, 3H), 3.23-3.19 (m, 2H), 3.05-2.99 (m, 1H), 2.84 (dd, $J = 13.6, 6.8$ Hz, 1H), 2.59 (dd, $J = 13.6, 3.9$ Hz, 1H), 2.14-2.09 (m, 2H), 1.96-1.92 (m, 1H), 1.29-1.23 (m, 2H), 1.19 (s, 6H), 1.08-1.03 (m, 1H), 1.00 (d, $J = 4.4$ Hz, 3H), 0.99 (d, $J = 4.4$ Hz, 3H), 0.74 (d, $J = 6.4$ Hz, 3H), 0.61 (d, $J = 6.8$ Hz, 3H). IR (KBr): 1665, 1541, 1513, 1466, 1365, 1261, 1233, 1167, 1124, 586 cm⁻¹. HRMS (ESI⁺): m/z calcd for C₃₅H₅₆N₅O₁₀S [M+H]⁺: 738.37479; found [M+H]⁺: 738.37566.

(2S,4S,5S)-5-Amino-N-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-6-{isopropyl[4-methoxy-3-(3-methoxypropoxy)benzyl]amino}hexanamide fumarate (2): Cesium carbonate (0.11 g, 0.33 mmol) was added to a solution of **33** (0.21 g, 0.28 mmol) and thiophenol (60 μ L, 0.56 mmol) in DMF (2.8 mL) under N₂ atmosphere at rt, and the mixture was stirred at the same temperature for 12 h. Brine was added to the reaction mixture, followed by extraction with CH₂Cl₂. Then, the organic layer was dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent, CH₂Cl₂:MeOH:Et₃N = 20:1:0 - 10:1:0 - 100:10:1) to afford **2** (132 mg, 90%). Fumaric acid (28 mg, 0.24 mmol) was added to a solution of **2** (128 mg, 0.24 mmol) in MeOH (1 mL), and the mixture was stirred at rt for 5 min. The reaction mixture was concentrated under reduced pressure, and CH₂Cl₂ (0.5 mL) was added to the residue. Et₂O (5 mL) was further added and the solid was collected by filtration to obtain fumarate as a colorless solid. ¹H NMR (500 MHz, CD₃OD): δ 7.72 (t, J = 6.1 Hz, 1H), 6.95-6.92 (m, 3H), 6.69 (s, 2H), 4.08 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.62 (d, J = 3.9 Hz, 2H), 3.59 (t, J = 6.1 Hz, 2H), 3.38-3.29 (m, 6H), 3.07-3.01 (m, 1H), 2.68-2.55 (m, 3H), 2.29-2.24 (m, 1H), 2.06-2.01 (m, 2H), 1.82-1.75 (m, 1H), 1.68-1.63 (m, 1H), 1.50-1.43 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 2.9 Hz, 3H), 0.93 (d, J = 2.4 Hz, 3H). IR (KBr): 2962, 1663, 1608, 1516, 1470, 1267, 1190, 1166, 1122, 1025, 984, 804, 648 cm⁻¹. MS (FAB⁺): 553 (M+H)⁺.

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