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Asymmetric synthesis of β-pseudopeptides from chiral 3,4-aziridinolactams

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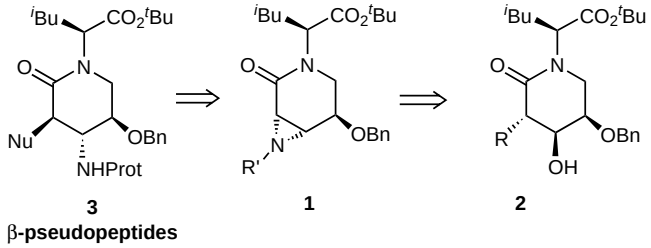
Abstract—The preparation of chiral 3,4-aziridinopiperidin-2-ones **1** and their reactivity with a range of nucleophiles has been studied. In all cases, nucleophilic attack on compounds **1** occurred exclusively at the C(3) centre, leading to the asymmetric synthesis of various β-pseudodipeptides.

1. Introduction

To extend our studies of 3-amino piperidin-2-ones as constrained dipeptide surrogates[1] and as β-turn mimetics[2] we have now prepared chiral 3,4-aziridinopiperidones **1** from hydroxylactams **2**, and have tested their reactivity with a selection of nucleophiles to obtain β-pseudopeptides of the type **3** (Scheme 1).

Aziridines **1** should follow the reactivity pattern reported for aziridine carboxylate esters.[3] Thus, heteroatomic nucleophiles would preferentially attack the acylated C(3) position,[4] whereas carbon nucleophiles would react at the C(4) centre.[5] The former reaction would lead to the formation of 4-amino piperidones, which can be regarded as β-pseudopeptides. The latter reaction would lead to 3-amino lactams, which we use as restricted pseudodipeptides. Another possibility was that the soft/hard character of the reagent would affect the regioselectivity of the process, as was observed previously when the reaction was performed in the presence of a Lewis acid.[6] The biological relevance of β-amino acids[7] and peptides of β-amino acids (β-peptides),[8] the structural interest in 4-amino lactams as β-turn mimetics,[9] and the fact that, despite the numerous asymmetric syntheses described for β-amino acids, ring opening of chiral azidirines had not previously been used to prepare aminovalerolactams, gave additional interest to this study. In addition, the 3,4-diamino-5-hydroxypiperidin-2-one motif is part of the natural antibiotic streptothricin F.[10]



Scheme 1.

2. Results and discussion

We planned to prepare the aziridine **1** from hydroxylactams **2** by mesylation of the C(4)-hydroxyl group followed by intramolecular nucleophilic attack (Scheme 1).

We first investigated the reaction on azidolactam **2a** ($R' = N_3$),[1a] which was transformed into mesylate **4a**, and then reduced, either with PPh_3 or by hydrogenation in the presence of Lindlar's catalyst, in order to obtain the aziridine **1** ($R' = H$) by spontaneous cyclisation of the primary amine **4b** (Scheme 2). Instead, we obtained pyridone **5**. We then tried to obtain aziridine **1** ($R' = H$) by direct treatment of compound **2a** with PPh_3, since it is known that *trans*-β-hydroxyiminophosphoranes can react to give 6,3-bicyclic aziridines.[11,12] However, in our

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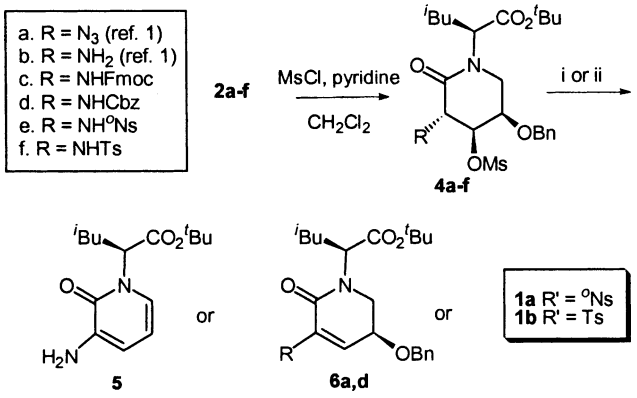


Scheme 2. *Reagents and conditions*: (i) H_2/Lindlar or PPh_3; (ii) K_2CO_3, CH_3CN, room temperature.

case the 3-amino piperidone **2b**[1a] was obtained as the only product, which demonstrated that the intermediate iminophosphorane had not evolved towards the 6,5-bicyclic intermediate.[13]

In view of these results, we tried to bias the reaction in favour of the substitution over the *syn*-elimination process by improving the nucleophilicity of the nitrogen atom on C(3). For this, we planned to use the 'amidate' of a derivative of the amino group on C(3), such as a carbamate. Compound **2b** was converted into the Fmoc and the Cbz carbamates **2c** and **2d**, which, after mesylation and treatment with K_2CO_3, led to pyridone **5** and to Δ^3-piperidinone **6d**, respectively. Since the Fmoc group was cleaved in the basic medium, this result suggested that the piperidinone with a free amino group on C(3) was prone to a second elimination, whereas if the amino group was masked the tetrahydropyridone was stable. This was proved by treatment of compound **2a** with K_2CO_3, which yielded the corresponding piperidinone **6a**.

One way to avoid the *syn*-elimination and reach our target aziridine **1** was to render the protons on the exocyclic nitrogen more acidic than the enolic C(3) proton. The 'amidate' anion would then be formed more quickly than the enolate and substitution on C(4) would be possible. For this purpose, amine **2b** was converted into the corresponding sulfonamides **2e** and **2f**, which after mesylation and treatment with K_2CO_3, afforded the desired aziridines **1a** (82% total yield) and **1b** (55% total yield).

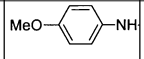
Interestingly, the ^1H NMR spectra of aziridines **1a** and **1b** show two double doublets corresponding to the protons on 6-position. The value of the coupling constants (see Section 4) indicate that the H-5 is pseudoequatorial, and therefore the benzyloxy substituent on C(5) is pseudoaxial. This conformation would be stabilised by the stereoelectronic effect between the oxygen atom on C(5) and the sulfonamide of the aziridine ring on 3- and 4-positions.[14]

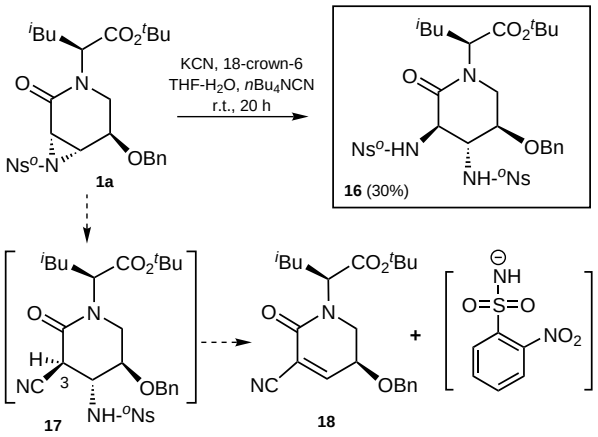
Once we had aziridines **1a** and **1b** in hand, we chose a set of nucleophiles that would not only give us sufficient information about the reactivity of the aziridines, but also provide products that interested us for future applications.

Reaction of aziridine **1a** with NaSMe gave compound **7** (^{o}Ns-{β-Met-Leu}-O^{t}Bu), a β-methionine derivative (Scheme 1 and Table 1, entry 1), while reaction of primary, secondary, and aromatic amines with compound **1a** gave the corresponding 3,4-diamino lactams (entries 2–9), as a consequence of regioselective attack on the C(3) acylated position.

When we used KCN as a carbon nucleophile, its reaction with nosylaziridine **1a** yielded compound **16** (Scheme 3), resulting from the incorporation of nosylamide at the 3-position. This result can only be

Table 1. Reaction of aziridine **1a** with diverse nucleophiles

Entry	Reagent	Solvent	Conditions	Product	Nu	Yield (%)
1	NaSMe	CH_3CN	rt, 1 h	**7**	CH_3S-	74
2	NaN_3	DMF	rt, 2 h	**8**	N_3-	79
3	^{p}(MeO)aniline	THF, Et_3N	rt, 20 h	**9**		68
4	$BnNH_2$	THF	rt, 2 h	**10**		76
5	piperidine	THF	rt, 1 h	**11**		77
6	morpholine	THF	rt, 1 h	**12**		82
7	Val-OMe	THF, Et_3N	rt, 12 h	**13**		63
8	phenylGly-OMe	THF	rt, 2 h	**14**		76
9	Gly-OEt	THF	rt, 4 h	**15**		76

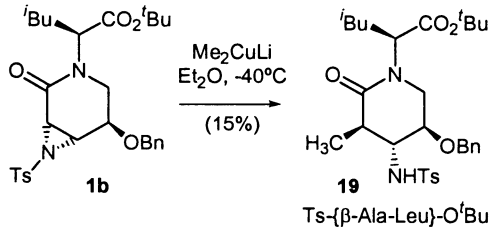


Scheme 3.

explained if the cyanide attacks the aziridine at C(3) to yield the corresponding 3-cyanolactam **17**. The C(3) proton would then be sufficiently acidic for the system to undergo its characteristic *syn*-elimination to give piperidinone **18**, and thus liberate the nosylamidate which would react as a nucleophile on the starting aziridine to give compound **16**. Unfortunately we could not isolate compounds **17** and/or **18** owing to their instability. When KCN was replaced by TMSCN/$Yb(TfO)_3$[15] to diminish the basicity of the medium, no reaction was observed.

We then tested organocuprates as carbon nucleophiles[16] on aziridine **1a**, but both MeMgBr in the presence of $CuBr{\cdot}SMe_2$ and Me_2CuLi under a variety of experimental conditions led to decomposition products. This result may stem from the reactivity of the *o*-nosyl substituent, which is prone to S*N*Ar reactions.

In order to circumvent this problem, we examined the reaction of Me_2CuLi on tosylaziridine **1b** (Scheme 4). Compound **19**, a conformationally constrained β-alanine derivative, was the only product that we could isolate, and this in low yield. Surprisingly, the product of the attack on C(4), which should be expected from the reaction of acylaziridines with organocuprates,[16] was not detected (Scheme 4).



Scheme 4.

3. Conclusion

In summary, we have prepared chiral 3,4-aziridinolactams **1a** and **1b** in two steps from 3-amino piperidones **2e** and **2f**, and have obtained several non-racemic β-pseudopeptides by stereo- and regioselective aziridine ring opening.

4. Experimental

4.1. General

Optical rotations were measured with a Perkin–Elmer 241 polarimeter, at 23°C. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, on a Varian Gemini-300 instrument. Chemical shifts are expressed in parts per million (δ) relative to Me_4Si. Mass spectra were determined on a Hewlett Packard 5988A mass spectrometer by electronic impact (EIMS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey–Nagel) and developed with the eluents described for column chromatography. The spots were located with ninhydrin, potassium hexachloroplatinate, or $KMnO_4$. Purification of reagents and solvents was performed according to standard methods. Microanalyses were performed on a Carlo Erba 1106 analyser at the Serveis Científico-Tècnics (Universitat de Barcelona).

4.2. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-(9-fluorenylmethoxy-carbonylamino)-4-hydroxypiperidin-2-one 2c

To a solution of compound **2b**[1] (282 mg, 0.69 mmol) in acetone (3 mL), $NaHCO_3$ (185 mg, 2.21 mmol) and FmocOSu (299 mg, 0.88 mmol) were added. The mixture was stirred at room temperature for 8 h. The solvent was evaporated, and the residue was chromatographed (AcOEt:hexane = 1:3). Compound **2c** was obtained as an oil (412 mg, 98%). $[\alpha]_D = -21$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3410 (OH, NH), 1725 (CO), 1656 (CO) cm^{-1}; ^1H NMR 0.88 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.92 (d, $J = 6$ Hz, 3H, $CH(CH_3)'_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 3.34 (dd, $J = 13$ and 3 Hz, 1H, H6), 3.42 (dd, $J = 13$ and 2 Hz, 1H, H-6′), 4.00–4.20 (m, 2H, H-4 and H-5), 4.24 (t, $J = 7$ Hz, 1H, CH-Fmoc), 4.40 (d, $J = 7$ Hz, 2H, CH_2-Fmoc), 4.60 (dd, $J = 9$ and 5 Hz, 1H, H-3), 4.70 and 4.86 (2d, $J_{AB} = 12$ Hz, 1H each, CH_2Ph), 5.16 (t, $J = 8$ Hz, 1H, NC*H*), 6.00 (d, $J = 4$ Hz, 1H, NH), 7.25-7.50 (m, 9H, Ph-H, Fmoc-H2 and Fmoc-H3), 7.61 (d, $J = 11$ Hz, 2H, Fmoc-H1), 7.78 (d, $J = 8$ Hz, 2H, Fmoc-H4); ^{13}C NMR 21.0 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)'_2$), 24.3 ($CH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 36.6 (CH_2), 44.1 (6-C), 46.9 (CH-Fmoc), 54.7 (NCH), 55.6 (3-C), 67.6 (CH_2-Fmoc), 72.8 (5-C), 72.9 (CH_2Ph), 73.5 (4-C), 81.9 ($C(CH_3)_3$), 120.3 (Fmoc-C4), 126.9 (Fmoc-C1), 128.0–128.5 (Ph-C2, Ph-C3, Ph-C4, Fmoc-C2, and Fmoc-C3), 137.7 (Ph-C1), 141.1 (Fmoc-C5), 143.5 (Fmoc-C6), 158.7 (CO carbamate), 167.8 (CO), 170.1 (CO). MS m/z (%): 628 (M^+, 2), 178 (100), 91 (37). Anal. calcd for $C_{37}H_{44}N_2O_7$: C, 70.68; H, 7.05; N, 4.46. Found: C, 70.47; H, 7.46; N, 4.09%.

4.3. (3*S*,4*S*,5*R*)-5-Benzyloxy-3-benzyloxycarbonylamino-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methyl-butyl]-4-hydroxypiperidin-2-one 2d

To a solution of compound **2b**[1] (282 mg, 0.69 mmol) in dry CH_2Cl_2 (2.5 mL), Et_3N (123 μL, 0.88 mmol) and benzyl chloroformate (125 μL, 0.88 mmol) were added sequentially. The mixture was stirred at room temperature for 8 h. The solvent was removed, and the residue was chromatographed (AcOEt:hexane = 1:2). Compound **2d** was obtained as an oil (232 mg, 65%). $[\alpha]_D = -17$ ($c = 1.2$, $CHCl_3$). IR (NaCl) 3420 (OH, NH), 1726 (CO), 1656 (CO) cm^{-1}. ^1H NMR 0.86 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.91 (d, $J = 7$ Hz, 3H, $CH(CH_3)_2'$), 1.42 (s, 9H, $C(CH_3)_3$), 1.45–1.65 (m, 3H, $CH(CH_3)_2$, CH_2), 3.32 (dd, $J = 13$ and 4 Hz, 1H, H-6), 3.39 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 3.90–4.10 (m, 2H, H-4 and H-5), 4.55 (br s, 1H, OH), 4.58 (dd, $J = 10$ and 5 Hz, 1H, H-3), 4.71 and 4.86 (2d, $J_{AB} = 12$ Hz, 1H each, CH_2Ph), 5.13 (m, 1H, NCH), 5.14 (s, 2H, CO_2CH_2Ph), 5.90 (br s, 1H, NH), 7.20–7.30 (m, 10H, Ph-H); ^{13}C NMR 21.1 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)_2'$), 24.3 ($CH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 36.5 (CH_2), 44.1 (C6), 54.7 (NCH), 55.6 (C3), 67.4 (CO_2CH_2Ph), 72.7 (C5), 72.8 (CH_2Ph), 73.5 (C4), 81.9 ($C(CH_3)_3$), 127.4–128.4 (Ph-C2, Ph-C3, Ph-C4), 135.8 and 137.8 (Ph-C1), 158.6 (CO carbamate), 167.8 (CO), 170.1 (CO). MS m/z (%) 540 (M^+, 1), 439 (11), 225 (9), 91 (100), 57 (25).

4.4. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-hydroxy-3-(*o*-nitro-benzensulfonamido)piperidin-2-one 2e

Operating as above, from compound **2b**[1] (470 mg, 1.15 mmol) in dry CH_2Cl_2 (4 mL), Et_3N (0.19 mL, 1.38 mmol) and *o*-NsCl (307 mg, 1.38 mmol), compound **2e** was obtained, after chromatography, as an oil (617 mg, 90%),. $[\alpha]_D = -105$ ($c = 1.1$, $CHCl_3$). IR (NaCl) 3500 (OH), 3300 (NH), 1730 (CO), 1661 (CO) cm^{-1}. ^1H NMR 0.69 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.85 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2'$), 1.39 (s, 9H, $C(CH_3)_3$), 1.50–1.60 (m, 3H, $CH(CH_3)_2$, CH_2), 1.70 (br s, 1H, OH), 3.25 (dd, $J = 13$ and 4 Hz, 1H, H-6), 3.39 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 4.10–4.20 (m, 2H, H-4 and H-5), 4.29 (d, $J = 9$ Hz, 1H, H-3), 4.71 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.87 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.91 (dd, $J = 9$ and 8 Hz, 1H, NCH), 6.60 (br s, 1H, NH), 7.36 (m, 5H, Ph), 7.67 (td, $J = 7$ and 2 Hz, 1H, Ns-H4), 7.73 (td, $J = 7$ and 2 Hz, 1H, Ns-H5), 7.98 (dd, $J = 7$ and 2 Hz, 1H, Ns-H6), 8.09 (dd, $J = 7$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 21.0 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)_2'$), 24.4 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 36.5 (CH_2), 44.2 (C6), 54.9 (NCH), 58.3 (C3), 71.4 (C4), 73.0 (C5), 73.1 (CH_2Ph), 82.1 ($C(CH_3)_3$), 125.8 (Ns-C3), 127.7 (Ph-C2), 127.9 (Ph-C4), 128.5 (Ph-C3), 130.8 (Ns-C6), 132.7 (Ns-C4), 133.4 (Ns-C1), 133.5 (Ns-C5), 137.6 (Ph-C1), 147.6 (Ns-C2), 167.0 (CO), 169.9 (CO). MS m/z (%): 592 (M^+, 1), 490 (23), 91 (100), 57 (46).

4.5. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-hydroxy-3-(*p*-toluensulfonamido)piperidin-2-one 2f

Operating as above, from lactam **2b**[1] (250 mg, 0.6 mmol) in dry CH_2Cl_2 (2 mL), Et_3N (92 μL, 0.66 mmol) and TsCl (125 mg, 0.66 mmol), tosylate **2f** was obtained, after chromatography, as an oil (258 mg, 75%). $[\alpha]_D = +54$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3483 (OH), 3258 (NH), 1731 (CO), 1652 (CO) cm^{-1}. ^1H NMR 0.69 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.84 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2'$), 1.38 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$ and CH_2), 2.40 (s, 3H, CH_3Ph), 3.23 (dd, $J = 13$ and 3 Hz, 1H, H-6), 3.58 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 3.90 (br s, 1H, OH), 3.97 (dd, $J = 9.6$ and 3.9 Hz, 1H, H-4), 4.04 (dd, $J = 10$ and 2.1 Hz, 1H, H-3), 4.06–4.15 (m, 1H, H-5), 4.67 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.84 (dd, $J = 10$ and 6 Hz, 1H, NCH), 4.90 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.89 (d, $J = 2$ Hz, 1H, NH), 7.25 (d, $J = 8$ Hz, 2H, Ts-H3), 7.28–7.40 (m, 5H, Ph), 7.78 (d, $J = 8$ Hz, 2H, Ts-H2); ^{13}C NMR 20.9 ($CH(CH_3)_2$), 21.5 (CH_3Ph), 23.0 ($CH(CH_3)_2'$), 24.3 ($CH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 36.4 (CH_2), 45.1 (C6), 55.4 (NCH), 56.7 (C3), 71.7 (C4), 72.8 (C5), 73.2 (CH_2Ph), 82.0 ($C(CH_3)_3$), 127.5–128.3 (Ph-C2, Ph-C3, Ph-C4, Ts-C3), 129.6 (Ts-C2), 134.4 (Ts-C4), 137.9 (Ph-C1), 143.9 (Ts-C1), 167.1 (CO), 169.8 (CO). MS m/z (%) 560 (M^+, 1), 459 (37), 91 (100), 57 (21). Anal. calcd for $C_{29}H_{40}N_2O_7S$: C, 62.12; H, 7.19; N, 5.00; S, 5.72. Found: C, 61.70; H, 7.07; N, 5.05; S, 5.91%.

4.6. (3*S*,4*S*,5*R*)-3-Azido-5-benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-methylsulfoxy-piperidin-2-one 4a

To a solution of azide **2a**[1] (200 mg, 0.46 mmol) in dry CH_2Cl_2 (2 mL), pyridine (75 μL, 0.92 mmol) and MsCl (0.18 mL, 2.3 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 3 h. The crude reaction mixture was washed with 0.1 M aqueous HCl and with 10% aqueous Na_2CO_3. The organic layer was concentrated to yield mesylate **4a** as a white solid (213 mg, 90%), which was used without further purification. $[\alpha]_D = -89$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 2118 (N_3), 1732 (CO), 1665 (CO) cm^{-1}. ^1H NMR 0.90 (d, $J = 4$ Hz, 3H, $CH(CH_3)_2$), 0.93 (d, $J = 4$ Hz, 3H, $CH(CH_3)_2'$), 1.44 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 3.14 (s, 3H, CH_3SO_3), 3.30 (dd, $J = 13$ and 4 Hz, 1H, H-6), 3.45 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 4.21 (br s, 1H, H-5), 4.54 (d, $J = 10$ Hz, 1H, H-3), 4.63 (dd, $J = 10$ and 2 Hz, 1H, H-4), 4.66 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.79 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.22 (dd, $J = 10$ and 7 Hz, 1H, NCH), 7.25–7.40 (m, 5H, Ph); ^{13}C NMR 21.3 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)_2'$), 24.3 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 36.5 (CH_2), 38.6 (CH_3SO_3), 43.6 (C6), 54.5 (NCH), 59.9 (C3), 72.0 (C5), 73.1 (CH_2Ph), 78.8 (C4), 82.3 ($C(CH_3)_3$), 127.8–128.6 (Ph-C2, Ph-C3, Ph-C4), 136.8 (Ph-C1), 166.3 (CO), 169.9 (CO). MS m/z (%) 510 (M^+, 1), 409 (14), 91 (100), 57 (36). Anal. calcd for $C_{23}H_{34}N_4O_7S$: C, 54.10; H, 6.71; N, 10.97; S, 6.28. Found: C, 53.81; H, 6.66; N, 10.64; S, 6.08%.

4.7. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-(9-fluorenylmethoxy-carbonylamino)-4-methylsulfoxypiperidin-2-one 4c

Operating as above, from lactam **2c** (412 mg, 0.68 mmol) in dry CH_2Cl_2 (3 mL), pyridine (82 μL, 1.09 mmol), and MsCl (211 μL, 2.71 mmol), an oil was obtained, which was chromatographed (AcOEt: hexane = 1:2) to yield mesylate **4c** as an oil (310 mg, 67%). $[\alpha]_D = -54$ ($c = 0.9$, $CHCl_3$). IR (NaCl) 3300 (NH), 1725 (CO), 1665 (CO) cm^{-1}. ^1H NMR 0.87 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.90 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2'$), 1.44 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.84 (s, 3H, CH_3SO_3), 3.30 (dd, $J = 13$ and 3 Hz, 1H, H-6), 3.47 (dd, $J = 13$ and 1 Hz, 1H, H-6′), 4.20 (t, $J = 7$ Hz, 1H, C*H*-Fmoc), 4.23–4.28 (m, 1H, H-5), 4.40–4.50 (m, 3H, H-3, CH_2-Fmoc), 4.68 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.79 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.18 (br s, 2H, NC*H*, H-4), 5.67 (d, $J = 7$ Hz, 1H, NH), 7.20–7.80 (m, 13H, Ph-H, Fmoc-H); ^{13}C NMR 21.2 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)_2'$), 24.2 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 36.6 (CH_2), 37.8 (CH_3SO_3), 43.7 (C6), 47.1 (*C*H-Fmoc), 53.6 (C3), 54.8 (N*C*H), 67.0 (CH_2-Fmoc), 72.3 (C5), 73.0 (CH_2Ph), 78.2 (C4), 82.1 ($C(CH_3)_3$), 119.9 (Fmoc), 124.9 (Fmoc), 127.0–128.5 (Ph-C2, Ph-C3, Ph-C4, Fmoc), 137.0 (Ph-C1), 141.2 (Fmoc), 143.7 (Fmoc), 156.4 (OCON), 167.1 (CO), 170.0 (CO). MS *m*/*z* (%): 605 (M^+−101, 2), 331 (13), 178 (96), 91 (100).

4.8. (3*S*,4*S*,5*R*)-5-Benzyloxy-3-benzyloxycarbonylamino-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-methylsulfoxypiperidin-2-one 4d

Operating as above, from lactam **2d** (232 mg, 0.43 mmol) in dry CH_2Cl_2 (2 mL), pyridine (52 μL, 0.64 mmol) and MsCl (133 μL, 1.71 mmol) mesylate **4d** was obtained, after chromatography, as an oil (229 mg, 86%). IR (NaCl) 3380 (NH), 1735 (CO), 1665 (CO) cm^{-1}. ^1H NMR 0.87 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.90 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2'$), 1.44 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.76 (s, 3H, CH_3SO_3), 3.31 (dd, $J = 13$ and 4 Hz, 1H, H-6), 3.48 (dd, $J = 13$ and 2 Hz, 1H, H-6′), 4.20–4.30 (m, 1H, H-5), 4.42 (dd, $J = 10$ and 7 Hz, 1H, H-3), 4.67 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.79 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.00–5.25 (m, 4H, H-4, CO_2CH_2Ph, NC*H*), 5.59 (d, $J = 7$ Hz, 1H, NH), 7.20–7.30 (m, 10H, CH_2Ph, CO_2CH_2Ph); ^{13}C NMR 21.3 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)_2'$), 24.2 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 36.6 (CH_2), 37.6 (CH_3SO_3), 43.8 (C6), 53.6 (N*C*H), 54.8 (C3), 67.1 (CO_2CH_2Ph), 72.4 (C5), 73.0 (CH_2Ph), 79.0 (C4), 82.1 ($C(CH_3)_3$), 127.7–128.4 (Ph-C2, Ph-C3, Ph-C4), 136.1 and 137.1 (Ph-C1), 156.0 (CO carbamate), 167.0 (CO), 170.0 (CO). MS *m*/*z* (%): 517 (M^+−101, 3), 331 (6), 91 (100), 57 (28).

4.9. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-methylsulfoxy-3-(*o*-nitro-benzensulfonamido)piperidin-2-one 4e

Operating as above, from lactam **2e** (550 mg, 0.93 mmol) in dry CH_2Cl_2 (5 mL), pyridine (224 μL, 2.79 mmol), and MsCl (0.36 mL, 4.65 mmol), mesylate **4e** was obtained as an oil (570 mg, 91%). $[\alpha]_D = -72$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3300 (NH), 1730 (CO), 1667 (CO) cm^{-1}. ^1H NMR 0.70 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.86 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2'$), 1.42 (s, 9H, $C(CH_3)_3$), 1.40–1.60 (m, 3H, $CH(CH_3)_2$, CH_2), 3.25 (dd, $J = 13$ and 4 Hz, 1H, H-6), 3.27 (s, 3H, CH_3SO_3), 3.45 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 4.20–4.30 (m, 1H, H-5), 4.58 (dd, $J = 10$ and 8 Hz, 1H, H-3), 4.72 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.90 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.93 (t, $J = 9$ Hz, 1H, NC*H*), 5.08 (dd, $J = 10$ and 2 Hz, 1H, H-4), 6.47 (d, $J = 8$ 1H, NH), 7.27–7.38 (m, 5H, Ph), 7.67 (td, $J = 7$ and 2 Hz, 1H, Ns-H4), 7.72 (td, $J = 7$ and 2 Hz, 1H, Ns-H5), 7.98 (dd, $J = 7$ and 2 Hz, 1H, Ns-H6), 8.08 (dd, $J = 7$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 21.0 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)_2'$), 24.1 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 36.4 (CH_2), 39.0 (CH_3SO_3), 44.1 (C6), 54.7 (N*C*H), 56.4 (C3), 72.4 (C5), 73.7 (CH_2Ph), 79.6 (C4), 82.3 ($C(CH_3)_3$), 125.6 (Ns-C3), 127.9 (Ph-C2), 128.1 (Ph-C4), 128.5 (Ph-C3), 130.8 (Ns-C6), 132.8 (Ns-C4), 133.4 (Ns-C5), 134.4 (Ns-C1), 136.9 (Ph-C1), 147.4 (Ns-C2), 165.8 (CO), 169.7 (CO). MS *m*/*z* (%) 669 (M^+, 1), 568 (4), 472 (13), 223 (23), 91 (100), 57 (72). Anal. calcd for $C_{29}H_{39}N_3O_{11}S_2$: C, 52.01; H, 5.87; N, 6.27; S, 9.57. Found: C, 51.70; H, 5.91; N, 6.04; S, 9.16%.

4.10. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-methylsulfoxy-3-(*p*-toluensulfonamido)piperidin-2-one 4f

Operating as above, from lactam **2f** (500 mg, 0.89 mmol) in CH_2Cl_2 (5 mL), pyridine (215 μL, 2.67 mmol), and MsCl (207 μL, 2.67 mmol), mesylate **4f** was obtained as an oil (422 mg, 74%). $[\alpha]_D = +33$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3286 (NH), 1729 (CO), 1666 (CO) cm^{-1}. ^1H NMR 0.69 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.86 (d, $J = 7$ Hz, 3H, $CH(CH_3)_2'$), 1.38 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.40 (s, 3H, CH_3Ph), 3.19 (s, 3H, CH_3SO_3), 3.20 (dd, $J = 13$ and 4 Hz, 1H, H–6), 3.40 (dd, $J = 13$ and 3 Hz, 1H, H-6′), 4.24–4.28 (m, 1H, H-5), 4.31 (dd, $J = 9$ and 6 Hz, 1H, H-3), 4.68 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.90 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.89–4.93 (m, 1H, NC*H*), 4.99 (dd, $J = 9$ and 2 Hz, 1H, H-4), 5.43 (d, $J = 6$ Hz, 1H, NH), 7.26 (d, $J = 8$ Hz, 2H, Ts-H3), 7.3–7.4 (m, 5H, Ph), 7.79 (d, $J = 8$ Hz, 2H, Ts-H2); ^{13}C NMR 20.7 ($CH(CH_3)_2$), 21.4 (CH_3Ph), 23.1 ($CH(CH_3)_2'$), 24.2 ($CH(CH_3)_2$), 27.8 ($C(CH_3)_3$), 36.2 (CH_2), 38.7 (CH_3SO_3), 44.1 (C6), 55.7 (N*C*H), 55.0 (C3), 72.1 (C5), 73.1 (CH_2Ph), 78.5 (C4), 82.1 ($C(CH_3)_3$), 127.6–128.3 (Ph-C2, Ph-C3, Ph-C4, Ts-C3), 129.3 (Ts-C2), 135.7 (Ts-C4), 137.1 (Ph-C1), 143.5 (Ts-C1), 166.2 (CO), 169.7 (CO). MS *m*/*z* (%) 537 (M^+−101, 3), 223 (50), 111 (75), 91 (100).

4.11. 3-Amino-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-2-pyridone 5

To a solution of mesylate **4c** (262 mg, 0.38 mmol) in CH_3CN (25 mL), K_2CO_3 (158 mg, 1.14 mmol) was added. The suspension was stirred at 50°C for 1 h. The mixture was filtered, and the solvent of the solution was

evaporated. The resulting residue was chromatographed (AcOEt:hexane = 1:2) to yield compound **5** as an oil (64 mg, 60%). IR (NaCl) 3467 and 3350 (NH_2), 1733 (CO), 1650 (CO) cm^{-1}. ^1H NMR 0.92 (d, $J=9$ Hz, 3H, $CH(CH_3)_2$), 0.95 (d, $J=9$ Hz, 3H, $CH(CH_3)'_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.80–2.00 (m, 3H, $CH(CH_3)_2$), CH_2), 5.69 (dd, $J=15$ and 9 Hz, 1H, NC*H*), 6.11 (t, $J=10$ Hz, 1H, H-5), 6.52 (dd, $J=10$ and 3 Hz, 1H, H-4), 6.76 (dd, $J=10$ and 3 Hz, 1H, H-6); ^{13}C NMR 21.6 ($CH(CH_3)_2$), 23.1 ($CH(CH_3)'_2$), 24.8 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 40.0 (CH_2), 56.2 (NCH), 82.3 ($C(CH_3)_3$), 106.5 (C5), 112.0 (C4), 122.6 (C6), 137.2 (C3), 161.0 (CO), 170.0 (CO). MS *m/z* (%) 280 (M^+, 26), 224 (34), 181 (24), 168 (100).

4.12. (5*S*)-3-Azido-5-benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-Δ^3-piperidein-2-one 6a

Operating as above, from a solution of azide **4a** (84 mg, 0.16 mmol) in CH_3CN (3 mL), and K_2CO_3 (68 mg, 0.49 mmol) compound **6a** was obtained, after chromatography, as an oil (53 mg, 80%). $[\alpha]_D=+143$ ($c=1.0$, $CHCl_3$). IR (NaCl) 2117 (N_3), 1733 (CO), 1629 (CO) cm^{-1}. ^1H NMR 0.88 (d, $J=6$ Hz, 3H, $CH(CH_3)_2$), 0.93 (d, $J=6$ Hz, 3H, $CH(CH_3)'_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.60–1.80 (m, 3H, $CH(CH_3)_2$), CH_2), 3.48 (ddd, $J=13$, 4, and 1 Hz, 1H, H-6), 3.65 (dd, $J=13$ and 4 Hz, 1H, H-6′), 4.16 (br s, 1H, H-5), 4.55 (s, 2H, CH_2Ph), 5.27 (dd, $J=9$ and 6 Hz, 1H, NC*H*), 6.08 (dd, $J=5$ and 1 Hz, 1H, H-4), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR 21.3 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)'_2$), 24.2 ($CH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 37.6 (CH_2), 45.4 (C6), 54.2 (NCH), 67.5 (C5), 70.6 (CH_2Ph), 82.0 ($C(CH_3)_3$), 118.4 (C4), 127.5–128.5 (Ph-C2, Ph-C3, Ph-C4), 133.8 (C3), 137.4 (Ph-C1), 160.2 (CO), 170.6 (CO). MS *m/z* (%) 414 (M^+, 1), 313 (4), 91 (100).

4.13. (5*S*)-5-Benzyloxy-3-benzyloxycarbonylamino-*N*-[(1*S*)-1-(tert-butoxycarbonyl)-3-methylbutyl]-Δ^3-piperidein-2-one 6d

Operating as above, from lactam **4d** (80 mg, 0.13 mmol) in CH_3CN (10 mL), and K_2CO_3 (53 mg, 0.39 mmol), compound **6d** was obtained as an oil (55 mg, 82%). $[\alpha]_D=+43$ ($c=1.1$, $CHCl_3$). IR (NaCl) 3380 (NH), 1734 (CO), 1668 (CO) 1634 (CO) cm^{-1}. ^1H NMR 0.87 (d, $J=5$ Hz, 3H, $CH(CH_3)_2$), 0.90 (d, $J=5$ Hz, 3H, $CH(CH_3)'_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 3.48 (dd, $J=20$ and 4 Hz, 1H, H-6), 3.63 (dd, $J=20$ and 6 Hz, 1H, H-6′), 4.10–4.30 (m, 1H, H-5), 4.51 (d, $J=17$ Hz, 1H, CH_2Ph), 4.60 (d, $J=18$ Hz, 1H, CH_2Ph), 5.16 (s, 2H, CO_2CH_2Ph), 5.15–5.25 (m, 1H, NC*H*), 7.07 (d, $J=7$ Hz, 1H, H-4), 7.20–7.40 (m, 10H, CH_2Ph, CO_2CH_2Ph), 7.78 (s, 1H, NH); ^{13}C NMR 21.2 ($CH(CH_3)_2$), 23.4 ($CH(CH_3)'_2$), 24.1 ($CH(CH_3)_2$), 28.1 ($C(CH_3)_3$), 37.4 (CH_2), 45.2 (C6), 54.6 (NCH), 66.9 (CO_2CH_2Ph), 67.3 (C5), 70.1 (CH_2Ph), 81.9 ($C(CH_3)_3$), 111.9 (C4), 127.4–128.5 (Ph-C2, Ph-C3, Ph-C4), 129.6 (C3), 135.9 and 137.8 (Ph-C1), 153.1 (CO carbamate), 160.7 (CO), 170.4 (CO). MS *m/z* (%) 522 (M^+, 1), 421 (5), 375 (8), 91 (100), 57 (21). Anal. calcd for $C_{30}H_{38}N_2O_6$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.98; H, 7.48; N, 5.31%.

4.14. (3*S*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3,4-[*N*-(*o*-nitrobenzensulfonyl)aziridino]piperidin-2-one 1a

Operating as above, from lactam **4e** (570 mg, 0.85 mmol) in dry CH_3CN (60 mL) and K_2CO_3 (353 mg, 2.55 mmol), at room temperature for 2 h, aziridinolactam **1a** was obtained as an oil (488 mg, quantitative). $[\alpha]_D=-119$ ($c=1.1$, $CHCl_3$). IR (NaCl) 1729 (CO), 1666 (CO) cm^{-1}. ^1H NMR 0.74 (d, $J=6$ Hz, 3H, $CH(CH_3)_2$), 0.80 (d, $J=6$ Hz, 3H, $CH(CH_3)'_2$), 1.23 (s, 9H, $C(CH_3)_3$), 1.40–1.50 (m, 3H, $CH(CH_3)_2$, CH_2), 3.25 (dd, $J=19$ and 2 Hz, 1H, H-6), 3.45 (dd, $J=20$ and 4 Hz, 1H, H-6′), 3.73 (d, $J=6$ Hz, 1H, H-3), 3.76 (m, 1H, H-4), 4.20–4.30 (m, 1H, H-5), 4.59 (s, 2H, CH_2Ph), 5.24 (dd, $J=10$ and 6 Hz, 1H, NC*H*), 7.20–7.30 (m, 5H, Ph), 7.60–7.80 (m, 3H, Ns-H4, Ns-H5, Ns-H6), 8.13 (d, $J=8$ Hz, 1H, Ns-H3); ^{13}C NMR 21.2 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)'_2$), 23.7 ($CH(CH_3)_2$), 27.7 ($C(CH_3)_3$), 36.6 (CH_2), 40.9 (C4), 41.7 (C3), 41.8 (C6), 54.0 (NCH), 68.6 (C5), 71.6 (CH_2Ph), 81.6 ($C(CH_3)_3$), 124.6 (Ns-C3), 127.4 (Ph-C2), 128.0 (Ph-C4), 128.4 (Ph-C3), 131.1 (Ns-C6), 132.5 (Ns-C4), 134.8 (Ns-C5, Ns-C1), 136.9 (Ph-C1), 148.3 (Ns-C2), 162.6 (CO), 169.9 (CO). MS *m/z* (%) 472 (M^+-101, 23), 186 (7), 91 (100), 57 (53). Anal. calcd for $C_{28}H_{35}N_3O_8S$: C, 58.63; H, 6.15; N, 7.33; S, 5.59. Found: C, 58.20; H, 6.36; N, 7.18; S, 5.28%.

4.15. (3*S*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3,4-[*N*-(*p*-toluensulfonyl)aziridino]piperidin-2-one 1b

Operating as above, from lactam **4f** (140 mg, 0.22 mmol) in dry CH_3CN (15 mL), and K_2CO_3 (91 mg, 0.65 mmol), at room temperature for 12 h, aziridine **1b** (108 mg, 91%) was obtained as an oil. $[\alpha]_D=+54$ ($c=1.0$, $CHCl_3$). IR (NaCl) 1730 (CO), 1666 (CO) cm^{-1}. ^1H NMR 0.81 (d, $J=6$ Hz, 3H, $CH(CH_3)_2$), 0.86 (d, $J=6$ Hz, 3H, $CH(CH_3)'_2$), 1.30 (s, 9H, $C(CH_3)_3$), 1.50–1.60 (m, 3H, $CH(CH_3)_2$, CH_2), 2.43 (s, 3H, CH_3Ph), 3.20 (dt, $J=14$ and 1 Hz, 1H, H-6), 3.34 (dd, $J=14$ and 2 Hz, 1H, H-6′), 3.41 (d, $J=6$ Hz, 1H, H-3), 3.55 (ddd, $J=7$, 3, and 2 Hz, 1H, H-4), 4.10–4.20 (m, 1H, H-5), 4.59 (d, $J=12$ Hz, 1H, CH_2Ph), 4.65 (d, $J=12$ Hz, 1H, CH_2Ph), 5.17 (dd, $J=9$ and 6 Hz, 1H, NC*H*), 7.30–7.40 (m, 5H, Ph), 7.32 (d, $J=8$ Hz, 2H, Ts-H3), 7.81 (d, $J=8$ Hz, 2H, Ts-H2); ^{13}C NMR 21.2 ($CH(CH_3)_2$), 21.5 (CH_3Ph), 23.2 ($CH(CH_3)'_2$), 23.6 ($CH(CH_3)_2$), 27.7 ($C(CH_3)_3$), 36.3 (CH_2), 39.0 (C4), 39.9 (C3), 41.5 (C6), 53.8 (NCH), 68.6 (C5), 71.4 (CH_2Ph), 81.4 ($C(CH_3)_3$), 127.2–128.4 (Ph-C2, Ph-C3, Ph-C4, Ts-C3), 129.7 (Ts-C2), 133.7 (Ts-C4), 136.7 (Ph-C1), 145.0 (Ts-C1), 163.0 (CO), 169.7 (CO). MS *m/z* (%) 542 (M^+, 2), 441 (22), 91 (100). Anal. calcd for $C_{29}H_{38}N_2O_6S$: C, 64.18; H, 7.06; N, 5.16; S, 5.91. Found: C, 64.23; H, 6.74; N, 4.94; S, 5.73%.

4.16. (3*R*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-methylthio-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 7

To a solution of aziridinolactam **1a** (50 mg, 0.087 mmol) in dry CH_3CN (0.9 mL), NaSMe (6 mg, 0.087 mmol) was added. The mixture was stirred at room temperature until reaction completion (tlc monitoring, 1 h). The crude reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic layers were washed with brine, dried and evaporated. The resulting residue was chromatographed (AcOEt:cyclohexane = 3:8) to yield ^{o}Ns-{β-Met-Leu}-O^{t}Bu **7** (40 mg, 74%) as an oil. $[\alpha]_D = +39$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3336 (NH), 1729 (CO), 1652 (CO) cm^{-1}. ^{1}H NMR 0.89 (d, $J = 4$ Hz, 3H, CH(CH_3)$_2$), 0.91 (d, $J = 4$ Hz, 3H, CH(CH_3)$'_2$), 1.45 (s, 9H, C(CH_3)$_3$), 1.50–1.70 (m, 3H, CH(CH$_3$)$_2$, CH_2), 2.10 (s, 3H, SCH$_3$), 3.20 (dd, $J = 12$ and 9 Hz, 1H, H-6), 3.28 (d, $J = 4$ Hz, 1H, H-3), 3.45 (dd, $J = 12$ and 5 Hz, 1H, H-6′), 3.80 (m, 1H, H-4), 3.88 (m, 1H, H-5), 4.45 (d, $J = 12$ Hz, 1H, CH_2Ph), 4.50 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.11 (dd, $J = 11$ and 5 Hz, 1H, NCH), 5.99 (d, $J = 7$ Hz, 1H, NH), 7.10–7.30 (m, 5H, Ph), 7.58 (td, $J = 7$ and 2 Hz, 1H, Ns-H4), 7.63 (td, $J = 7$ and 2 Hz, 1H, Ns-H5), 7.75 (dd, $J = 7$ and 2 Hz, 1H, Ns-H6), 8.17 (dd, $J = 7$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 15.9 (SCH$_3$), 21.0 (CH(CH_3)$_2$), 23.3 (CH(CH_3)$'_2$), 25.0 (CH(CH$_3$)$_2$), 28.0 (C(CH_3)$_3$), 37.9 (CH_2), 43.6 (C6), 51.6 (C3), 54.5 (NCH), 59.2 (C4), 72.0 (CH_2Ph), 77.1 (C5), 82.3 (C(CH$_3$)$_3$), 125.3 (Ns-C3), 127.7 (Ph-C2), 127.9 (Ph-C4), 128.3 (Ph-C3), 131.0 (Ns-C6), 132.6 and 133.0 (Ns-C4 and Ns-C5), 134.9 (Ns-C1), 137.1 (Ph-C1), 147.7 (Ns-C2), 167.6 (CO), 171.0 (CO). MS m/z (%) 621 (M$^+$, 1), 520 (5), 318 (30), 272 (22), 186 (12), 91 (100), 57 (16). Anal. calcd for $C_{29}H_{39}N_3O_8S_2$: C, 56.02; H, 6.32; N, 6.76; S, 10.31. Found: C, 56.51; H, 6.54; N, 6.76; S, 10.29%.

4.17. (3*R*,4*R*,5*R*)-3-Azido-5-benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 8

To a solution of aziridine **1a** (44 mg, 0.076 mmol) in DMF (1 mL), NaN_3 (10 mg, 0.15 mmol) was added. The mixture was stirred at room temperature for 1 h. The crude reaction mixture was partitioned with H_2O and Et_2O. The organic layers, dried and evaporated, yielded compound **8** as an oil (37 mg, 79%). $[\alpha]_D = +16$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3327 (NH), 2114 (N_3), 1729 (CO), 1664 (CO) 1549 (NO_2) cm^{-1}. ^{1}H NMR 0.87 (d, $J = 6$ Hz, 3H, CH(CH_3)$_2$), 0.90 (d, $J = 7$ Hz, 3H, CH(CH_3)$'_2$), 1.42 (s, 9H, C(CH_3)$_3$), 1.50–1.70 (m, 3H, CH(CH$_3$)$_2$, CH_2), 3.10 (dd, $J = 13$ and 7 Hz, 1H, H-6), 3.51 (dd, $J = 13$ and 4 Hz, 1H, H-6′), 3.61 (dt, $J = 10$ and 8 Hz, 1H, H-4), 3.86 (td, $J = 7$ and 4 Hz, 1H, H-5), 4.05 (d, $J = 10$ Hz, 1H, H-3), 4.55 (s, 2H, CH_2Ph), 5.09 (dd, $J = 11$ and 5 Hz, 1H, NCH), 5.93 (d, $J = 8$ Hz, 1H, NH), 7.20–7.40 (m, 5H, CH$_2$Ph), 7.61 (td, $J = 7$ and 2 Hz, 1H, Ns-H4), 7.66 (td, $J = 7$ and 2 Hz, 1H, Ns-H5), 7.77 (dd, $J = 8$ and 2 Hz, 1H, Ns-H6), 8.13 (dd, $J = 8$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 21.3 (CH(CH_3)$_2$), 23.1 (CH(CH_3)$'_2$), 24.9 (CH(CH$_3$)$_2$), 28.0 (C(CH_3)$_3$), 37.4 (CH_2), 44.9 (C6), 54.9 (NCH), 59.2 (C4), 63.2 (C3), 72.4 (CH_2Ph), 74.8 (C5), 82.3 (C(CH$_3$)$_3$), 125.2 (Ns-C3), 127.9 (Ph-C2), 128.0 (Ph-C4), 128.4 (Ph-C3), 130.8 (Ns-C6), 132.9–133.3 (Ns-C4, Ns-C5), 134.7 (Ns-C1), 136.8 (Ph-C1), 147.3 (Ns-C2), 166.2 (CO), 170.2 (CO). MS m/z (%) 616 (M$^+$, 1), 515 (7), 238 (23), 91 (100). Anal. calcd for $C_{28}H_{36}N_6O_8S$: C, 54.53; H, 5.88; N, 13.63; S, 5.20. Found: C, 54.30; H, 5.55; N, 13.81; S, 4.95%.

4.18. (3*R*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-(*p*-methoxy-anilino)-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 9

To a solution of aziridine **1a** (40 mg, 0.069 mmol) in dry THF (0.7 mL), *p*-methoxyaniline (13 mg, 0.104 mmol) and Et_3N (96 μL, 0.069 mmol) were added. The mixture was stirred at room temperature until completion of the reaction (tlc monitoring, 8 h). The crude reaction mixture was partitioned between brine and CH_2Cl_2, and the organic layers were dried and evaporated. The resulting oil was chromatographed (AcOEt:cyclohexane = 3:7) to yield compound **9** as a yellow solid (33 mg, 68%). $[\alpha]_D = -115$ ($c = 0.5$, $CHCl_3$). IR (NaCl) 3410 (NH), 3360 (NH), 1732 (CO), 1676 (CO) cm^{-1}. ^{1}H NMR 0.82 (d, $J = 6$ Hz, 3H, CH(CH_3)$_2$), 0.89 (d, $J = 6$ Hz, 3H, CH(CH_3)$'_2$), 1.42 (s, 9H, C(CH_3)$_3$), 1.50–1.70 (m, 3H, CH(CH$_3$)$_2$, CH_2), 3.46 (dd, $J = 15$ and 5 Hz, 1H, H-6), 3.60–3.80 (m, 3H, H-3, H-4, H-6′), 3.70 (s, 3H, OCH_3), 4.09 (m, 1H, H-5), 4.71 (s, 2H, CH_2Ph), 5.12 (br s, 1H, NCH), 6.21 (br s, 1H, NH), 6.39 (d, $J = 9$ Hz, 2H, aniline-H2), 6.56 (d, $J = 9$ Hz, 2H, aniline-H3), 7.26–7.40 (m, 5H, Ph), 7.41–7.46 (m, 2H, Ns-H4, Ns-H5), 7.61 (dd, $J = 7$ and 2 Hz, 1H, Ns-H6), 7.98 (dd, $J = 7$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 21.4 (CH(CH_3)$_2$), 23.0 (CH(CH_3)$'_2$), 24.6 (CH(CH$_3$)$_2$), 29.7 (C(CH_3)$_3$), 38.0 (CH_2), 44.1 (C6), 54.7 (OCH_3), 55.8 (NCH), 59.9 and 60.6 (C3 and C4), 71.5 (CH_2Ph), 77.2 (C5), 82.2 (C(CH$_3$)$_3$), 114.5 (aniline-C2), 116.1 (aniline-C3), 125.0 (Ns-C3), 127.9 (Ph-C2), 128.0 (Ph-C4), 128.5 (Ph-C3), 131.2 (Ns-C6), 132.0–140.0 (Ns-C4, Ns-C5, Ns-C1, Ph-C1, aniline-C1, aniline-C4), 153.4 (Ns-C2), 169.7 (CO), 170.7 (CO). MS m/z (%) 697 (M$^+$+1, 1), 641 (12), 386 (29), 330 (100), 274 (44), 186 (45), 91 (72). Anal. calcd for $C_{35}H_{44}N_4O_9S$: C, 60.33; H, 6.36; N, 8.04; S, 4.60. Found: C, 59.90; H, 6.38; N, 7.84; S, 5.07%.

4.19. (3*R*,4*R*,5*R*)-3-Benzylamino-5-benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 10

Operating as above, from aziridine **1a** (40 mg, 0.069 mmol) in dry THF (1 mL), and benzylamine (11 μL, 0.10 mmol), compound **10** was obtained, after chromatography, as an oil (35 mg, 76%). $[\alpha]_D = -74$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3331 (NH), 3246 (NH), 1730 (CO), 1667 (CO) cm^{-1}. ^{1}H NMR 0.79 (d, $J = 6$ Hz, 3H, CH(CH_3)$_2$), 0.87 (d, $J = 6$ Hz, 3H, CH(CH_3)$'_2$), 1.45 (s, 9H, C(CH_3)$_3$), 1.50–1.70 (m, 3H, CH(CH$_3$)$_2$, CH_2), 1.90 (br s, 1H, NH), 3.14 (d, $J = 11$ Hz, 1H, H-3), 3.20 (dd,

$J=11$ and 4 Hz, 1H, H-4), 3.38 (dd, $J=14$ and 3 Hz, 1H, H-6), 3.49 (dd, $J=14$ and 4 Hz, 1H, H-6′), 3.64 (d, $J=12$ Hz, 1H, NHCH_2Ph), 3.96 (d, $J=12$ Hz, 1H, NHCH_2Ph′), 4.12 (d, $J=3$ Hz, 1H, H-5), 4.57 (d, $J=11$ Hz, 1H, OCH_2Ph), 4.62 (d, $J=11$ Hz, 1H, OCH_2Ph′), 5.13 (dd, $J=9$ and 5 Hz, 1H, NCH), 6.40 (br s, 1H, NH), 7.30–7.50 (m, 11H, OCH_2Ph, $NHCH_2Ph$, Ns-H4), 7.51 (td, $J=8$ and 1 Hz, 1H, Ns-H5), 7.61 (dd, $J=8$ and 1 Hz, 1H, Ns-H6), 7.90 (dd, $J=8$ and 1 Hz, 1H, Ns-H3); ^{13}C NMR 21.5 ($CH(CH_3)_2$), 22.8 ($CH(CH_3)_2'$), 24.6 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 37.8 (CH_2), 43.2 (C6), 52.7 ($NHCH_2Ph$), 54.5 (NCH), 60.0 (C3, C4), 71.6 (OCH_2Ph), 77.5 (C5), 82.0 ($C(CH_3)_3$), 125.0 (Ns-C3), 127.0–140.0 ($NHCH_2Ph$, OCH_2Ph, Ns-C1, Ns-C4, Ns-C5, Ns-C6), 147.9 (Ns-C2), 170.3 (CO), 170.6 (CO). MS m/z (%) 682 (M^++2, 1), 370 (10), 314 (21), 199 (28), 91 (100), 57 (28).

4.20. (3*R*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-(*o*-nitrobenzensulfonamido)-3-piperidinopiperidin-2-one 11

Operating as above, from aziridine **1a** (40 mg, 0.069 mmol) in dry THF (0.7 mL), and piperidine (0.01 mL, 0.104 mmol), compound **11** was obtained, after chromatography, as an oil (35 mg, 77%). $[\alpha]_D=-34$ ($c=1.0$, $CHCl_3$). IR (NaCl) 3350 (NH), 1730 (CO), 1650 (CO) cm^{-1}. ^{1}H NMR 0.87 (d, $J=6$ Hz, 6H, $CH(CH_3)_2$), 1.10–1.30 (m, 6H, $NCH_2CH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.52 (dt, $J=11$ and 5 Hz, 2H, NCH_2), 2.65 (dt, $J=11$ and 5 Hz, 2H, NCH_2'), 3.03 (d, $J=10$ Hz, 1H, H-3), 3.20 (dd, $J=13$ and 7 Hz, 1H, H-6), 3.41 (dd, $J=13$ and 4 Hz, 1H, H-6′), 3.64 (dd, $J=10$ and 7 Hz, 1H, H-4), 3.94 (br s, 1H, H-5), 4.59 (d, $J=11$ Hz, 1H, CH_2Ph), 4.63 (d, $J=11$ Hz, 1H, CH_2Ph), 5.07 (dd, $J=10$ and 5 Hz, 1H, NCH), 7.20–7.40 (m, 5H, CH_2Ph), 7.56 (td, $J=8$ and 1 Hz, 1H, Ns-H4), 7.63 (td, $J=7$ and 1 Hz, 1H, Ns-H5), 7.84 (dd, $J=8$ and 1 Hz, 1H, Ns-H6), 8.10 (dd, $J=8$ and 1 Hz, 1H, Ns-H3); ^{13}C NMR 21.2 ($CH(CH_3)_2$), 23.1 ($CH(CH_3)_2'$), 23.9 ($NCH_2CH_2CH_2$), 24.9 ($CH(CH_3)_2$), 26.9 ($NCH_2CH_2CH_2$), 28.0 ($C(CH_3)_3$), 37.3 (CH_2), 44.1 (C6), 50.4 (NCH_2), 53.9 (NCH), 57.4 (C4), 68.8 (C3), 72.2 (CH_2Ph), 76.5 (C5), 81.9 ($C(CH_3)_3$), 125.2 (Ns-C3), 127.8 (Ph-C2, Ph-C4), 128.3 (Ph-C3), 131.1–133.1 (Ns-C4, Ns-C5, Ns-C6), 134.6 (Ns-C1), 137.5 (Ph-C1), 147.7 (Ns-C2), 168.2 (CO), 170.8 (CO). MS m/z (%) 658 (M^+, 1), 624 (7), 348 (7), 177 (55), 84 (100).

4.21. (3*R*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-morpholino-4-(*o*-nitro-benzensulfonamido)piperidin-2-one 12

Operating as above, from aziridine **1a** (40 mg, 0.069 mmol) in dry THF (1 mL) and morpholine (0.01 mL, 0.104 mmol), compound **12** was obtained, after chromatography, as an oil (37 mg, 82%). $[\alpha]_D=-17$ ($c=1.0$, $CHCl_3$). IR (NaCl) 3345 (NH), 1728 (CO), 1650 (CO) cm^{-1}. ^{1}H NMR 0.88 (d, $J=6$ Hz, 3H, $CH(CH_3)_2$), 0.89 (d, $J=7$ Hz, 3H, $CH(CH_3)_2'$), 1.43 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.60 (dt, $J=11$ and 5 Hz, 2H, NCH_2CH_2O), 2.75 (dt, $J=11$ and 5 Hz, 2H, NCH_2CH_2O'), 3.07 (d, $J=9$ Hz, 1H, H-3), 3.19 (dd, $J=13$ and 7 Hz, 1H, H-6), 3.39 (t, $J=5$ Hz, 4H, NCH_2CH_2O), 3.42 (dd, $J=13$ and 5 Hz, 1H, H-6′), 3.72 (t, $J=8$ Hz, 1H, H-4), 3.93 (td, $J=7$ and 5 Hz, 1H, H-5), 4.57 (s, 2H, CH_2Ph), 5.09 (dd, $J=11$ and 5 Hz, 1H, NCH), 5.97 (br s, 1H, NH), 7.20–7.40 (m, 5H, Ph), 7.58 (td, $J=7$ and 1 Hz, 1H, Ns-H4), 7.63 (td, $J=7$ and 2 Hz, 1H, Ns-H5), 7.81 (dd, $J=7$ and 2 Hz, 1H, Ns-H6), 8.10 (dd, $J=7$ and 2 Hz, 1H, Ns-H3); ^{13}C NMR 21.8 ($CH(CH_3)_2$), 23.1 ($CH(CH_3)_2'$), 25.0 ($CH(CH_3)_2$), 29.6 ($C(CH_3)_3$), 37.3 (CH_2), 44.3 (C6), 49.7 (NCH_2CH_2O), 54.1 (NCH), 56.9 (C4), 66.9 (NCH_2CH_2O), 68.8 (C3), 72.2 (CH_2Ph), 76.2 (C5), 82.1 ($C(CH_3)_3$), 125.2 (Ns-C3), 127.7 (Ph-C2), 127.9 (Ph-C4), 128.4 (Ph-C3), 130.9 (Ns-C6), 132.7 (Ns-C4), 133.2 (Ns-C5), 134.9 (Ns-C1), 137.3 (Ph-C1), 147.7 (Ns-C2), 167.7 (CO), 170.7 (CO). MS m/z (%) 662 (M^++2, 1), 561 (8), 186 (21), 91 (100), 57 (23).

4.22. (3*S*,4*S*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-[(1*S*)-1-(methoxycarbonyl)-2-methylpropilamino]-4-(*o*-nitrobenzensulfonamido)-piperidin-2-one 13

Operating as above, from aziridine **1a** (40 mg, 0.069 mmol) in dry THF (0.7 mL), Val-OMe (28 mg, 0.208 mmol), and Et_3N (96 μL, 0.069 mmol) compound **13** was obtained, after chromatography, as an oil (31 mg, 63%). $[\alpha]_D=-46$ ($c=1.0$, $CHCl_3$). IR (NaCl) 3320 (NH), 1731 (CO), 1676 (CO) cm^{-1}. ^{1}H NMR 0.77 (d, $J=6$ Hz, 3H, $CH_2CH(CH_3)_2$), 0.89 (d, $J=6$ Hz, 3H, $CH_2CH(CH_3)_2'$), 0.91 (t, $J=7$ Hz, 6H, $NHCHCH(CH_3)_2$), 1.41 (s, 9H, $C(CH_3)_3$), 1.45–1.65 (m, 3H, $CH_2CH(CH_3)_2$, CH_2), 1.85–1.95 (m, 1H, $NHCHCH(CH_3)_2$), 2.6 (br s, 1H, NH), 3.12 (d, $J=10$ Hz, 1H, H-3), 3.15 (d, $J=5$ Hz, 1H, $NHCHCH(CH_3)_2$), 3.31 (br s, 1H, H-4), 3.37 (dd, $J=15$ and 3 Hz, 1H, H-6), 3.48 (dd, $J=15$ and 4 Hz, 1H, H-6′), 3.66 (s, 3H, CO_2CH_3), 4.10 (br s, 1H, H-5), 4.47 and 4.56 (2d, $J_{AB}=12$ Hz, 1H each, CH_2Ph), 5.07 (dd, $J=10$ and 5 Hz, 1H, NCH), 6.39 (d, $J=3$ Hz, 1H, NH), 7.15–7.35 (m, 6H, Ph, Ns-H4), 7.57 (t, $J=8$ Hz, 1H, Ns-H5), 7.73 (d, $J=8$ Hz, 1H, Ns-H6), 7.92 (d, $J=8$ Hz, 1H, Ns-H3); ^{13}C NMR 18.2 ($NHCHCH(CH_3)_2$), 19.0 ($NHCHCH(CH_3)_2'$), 21.5 ($CH_2CH(CH_3)_2$), 22.9 ($CH_2CH(CH_3)_2'$), 24.5 ($CH_2CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 32.1 ($NHCHCH(CH_3)_2$), 37.7 (CH_2), 42.9 (C6), 51.5 (CO_2CH_3), 54.3 (NCH), 59.7 (C4), 61.4 ($NHCHCH(CH_3)_2$), 66.7 (C3), 71.3 (CH_2Ph), 76.8 (C5), 82.0 ($C(CH_3)_3$), 125.0 (Ns-C3), 127.4 (Ph-C2), 127.7 (Ph-C4), 128.3 (Ph-C3), 132.1 and 132.3 (Ns-C4 and Ns-C6), 133.0 (Ns-C1), 133.5 (Ns-C5), 137.3 (Ph-C1), 147.9 (Ns-C2), 170.0 (CO), 170.8 (CO), 174.3 (CO). MS m/z (%) 706 (M^++2, 1), 605 (6), 590 (13), 91 (100), 57 (36).

4.23. (3*R*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3-[(1*S*)-1-(methoxycarbonyl)-benzylamino]-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 14

Operating as above, from aziridine **1a** (40 mg, 0.069 mmol) in dry THF (0.7 mL), and phenylglycine methyl

ester (17 mg, 0.104 mmol) compound **14** was obtained, after chromatography, as an oil (39 mg, 76%). $[\alpha]_D = -136$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3325 (NH), 1722 (CO), 1663 (CO) cm^{-1}. ^1H NMR 0.73 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.82 (d, $J = 6$ Hz, 3H, $CH(CH_3')_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.20 (br s, 1H, NH), 3.10–3.20 (m, 2H, H-3, H-4), 3.42 (dd, $J = 15$ and 3 Hz, 1H, H-6), 3.52 (dd, $J = 15$ and 3 Hz, 1H, H-6′), 3.72 (s, 3H, CO_2CH_3), 4.23 (br s, 1H, H-5), 4.61 (s, 2H, CH_2Ph), 4.64 (s, 1H, NCHPh), 5.12 (dd, $J = 9$ and 5 Hz, 1H, NCH), 7.20–7.40 (m, 11H, CH_2Ph, NCHPh, Ns-H4), 7.58 (td, $J = 8$ and 1 Hz, 1H, Ns-H5), 7.77 (dd, $J = 8$ and 1 Hz, 1H, Ns-H6), 7.98 (dd, $J = 8$ and 1 Hz, 1H, Ns-H3); ^{13}C NMR 21.5 ($CH(CH_3)_2$), 22.7 ($CH(CH_3')_2$), 24.6 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 38.0 (CH_2), 42.9 (C6), 52.5 (CO_2CH_3), 54.6 (NCH), 58.8 (C4), 60.8 (NCHPh), 64.8 (C3), 71.6 (CH_2Ph), 77.9 (C5), 82.1 ($C(CH_3)_3$), 124.9 (Ns-C3), 127.0–138.0 (NCHPh, CH_2Ph, Ns-C1, Ns-C4, Ns-C5, Ns-C6), 148.1 (Ns-C2), 170.0 (CO), 170.7 (CO), 173.2 (CO). MS m/z (%) 738 (M^+, 1), 624 (7), 313 (63), 186 (20), 91 (100). Anal. calcd for $C_{37}H_{46}N_4O_{10}S$: C, 60.15; H, 6.28; N, 7.58; S, 4.34. Found: C, 60.09; H, 6.38; N, 7.35; S, 4.78%.

4.24. (3*R*,4*R*,5*R*)-5-Benzyloxy-3-(ethoxycarbonyl)-methylamino-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-(*o*-nitrobenzensulfonamido)piperidin-2-one 15

Ammonia was bubbled through a suspension of Gly-OEt.HCl (20 mg, 0.14 mmol) in dry THF (0.5 mL) for 15 min. The resulting suspension was filtered and the clear filtrate was added to a solution of aziridine **1a** (40 mg, 0.069 mmol) in dry THF (0.5 mL). Operating as above, compound **15** was obtained, after chromatography, as an oil (35 mg, 76%). $[\alpha]_D = -40$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3337 (NH), 1722 (CO), 1662 (CO) cm^{-1}. ^1H NMR 0.78 (d, $J = 6$ Hz, 3H, $CH(CH_3)_2$), 0.85 (d, $J = 6$ Hz, 3H, $CH(CH_3')_2$), 1.27 (t, $J = 7$ Hz, 3H, CH_2CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.45–1.65 (m, 3H, $CH(CH_3)_2$, CH_2), 2.10 (br s, 1H, NH), 3.17 (d, $J = 11$ Hz, 1H, H-3), 3.23 (dd, $J = 11$ and 4 Hz, 1H, H-4), 3.36 (dd, $J = 14$ and 3 Hz, 1H, H-6), 3.37 (d, $J = 18$ Hz, 1H, $NHCH_2$), 3.50 (dd, $J = 14$ and 3 Hz, 1H, H-6′), 3.53 (d, $J = 18$ Hz, 1H, $NHCH_2'$), 4.11 (dd, $J = 7$ and 3 Hz, H-5), 4.18 (q, $J = 7$ Hz, 2H, CH_2CH_3), 4.56 (s, 2H, CH_2Ph), 5.09 (dd, $J = 9$ and 5 Hz, 1H, NCH), 6.70 (br s, 1H, NH), 7.20–7.40 (m, 5H, CH_2Ph), 7.45 (td, $J = 8$ and 1 Hz, 1H, Ns-H4), 7.60 (td, $J = 8$ and 1 Hz, 1H, Ns-H5), 7.78 (dd, $J = 8$ and 1 Hz, 1H, Ns-H6), 8.01 (dd, $J = 8$ and 1 Hz, 1H, Ns-H3); ^{13}C NMR 14.1 (CH_2CH_3), 21.4 ($CH(CH_3)_2$), 22.8 ($CH(CH_3')_2$), 24.5 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 37.8 (CH_2), 43.4 (C6), 49.3 ($NHCH_2$), 54.5 (NCH), 60.3 (C3, C4), 61.0 (CH_2CH_3), 71.6 (CH_2Ph), 77.6 (C5), 82.1 ($C(CH_3)_3$), 125.1 (Ns-C3), 127.7 (Ph-C2), 127.8 (Ph-C4), 128.3 (Ph-C3), 131.2-133.4 (Ns-C1, Ns-C4, Ns-C5, Ns-C6), 137.4 (Ph-C1), 147.8 (Ns-C2), 169.8 (CO), 170.7 (CO), 171.8 (CO). MS m/z (%) 678 (M^++2, 1), 575 (1), 547 (5), 310 (15), 91 (100), 57 (36). Anal. calcd for $C_{32}H_{44}N_4O_{10}S$: C, 56.79; H, 6.55; N, 8.28; S, 4.74. Found: C, 57.06; H, 6.76; N, 7.78; S, 5.01%.

4.25. (3*R*,4*R*,5*R*)-5-Benzyloxy-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-3,4-bis(*o*-nitrobenzensulfonamido)piperidin-2-one 16

Operating as for the preparation of compound **9**, from aziridine **1a** (50 mg, 0.087 mmol) in THF:H_2O (10:1 0.5 mL), KCN (7 mg, 0.096 mmol) and Bu_4NCN (2 mg, 0.008 mmol) compound **16** (20 mg, 30%) was obtained, after chromatography, as an oil,. $[\alpha]_D = +6$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3335 (NH), 1730 (CO), 1678 (CO) cm^{-1}. ^1H NMR 0.76 (br s, 6H, $CH(CH_3)_2$), 1.34 (s, 9H, $C(CH_3)_3$), 1.40–1.60 (m, 3H, $CH(CH_3)_2$, CH_2), 3.30 (dd, $J = 14$ and 3 Hz, 1H, H-6), 3.54 (dd, $J = 14$ and 4 Hz, 1H, H-6′), 3.86 (dd, $J = 10$ and 5 Hz, 1H, H-4), 4.00–4.10 (m, 2H, H-3, H-5), 4.64 (s, 2H, CH_2Ph), 4.83 (dd, $J = 9$ and 5 Hz, 1H, NCH), 6.30 (br s, 1H, NH), 6.46 (d, $J = 6$ Hz, 1H, NH), 7.20–7.40 (m, 5H, CH_2Ph), 7.60–7.70 (m, 4H, Ns), 7.80–7.90 (m, 2H, Ns), 7.98 (dd, $J = 6$ and 3 Hz, 1H, Ns), 8.1 (m, 1H, Ns); ^{13}C NMR 21.3 ($CH(CH_3)_2$), 23.0 ($CH(CH_3')_2$), 24.3 ($CH(CH_3)_2$), 28.0 ($C(CH_3)_3$), 37.2 (CH_2), 43.9 (C6), 55.0 (NCH), 57.2 (C4), 59.6 (C3), 72.0 (CH_2Ph), 77.0 (C5), 82.2 ($C(CH_3)_3$), 125.6–134.5 (Ph, Ns), 136.9 (Ph-C1), 147.5 (Ns-C2, Ns-C2′), 166.5 (CO), 170.1 (CO). MS m/z (%): 776 (M^+, 1), 675 (2), 223 (32), 186 (45), 91 (100).

4.26. (3*R*,4*R*,5*R*)-5-Benzyloxy-3-methyl-*N*-[(1*S*)-1-(*tert*-butoxycarbonyl)-3-methylbutyl]-4-(*p*-toluensulfonamido)piperidin-2-one 19

To a suspension of CuI (111 mg, 0.58 mmol) in dry Et_2O (2 mL) cooled at 0°C, MeLi (1.6 M in Et_2O, 0.725 mL, 1.16 mmol) was added. The mixture was stirred at 0°C for 15 min after which, a yellow solid had appeared. A solution of aziridine **1b** (158 mg, 0.29 mmol) in dry Et_2O (4 mL) was then added dropwise. The mixture was stirred at 0°C for 2 h, and the reaction was quenched by adding 1 M aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated. The resulting residue was chromatographed (AcOEt:hexane = 1:4) to yield compound **19** as an oil (25 mg, 15%). $[\alpha]_D = +3$ ($c = 1.0$, $CHCl_3$). IR (NaCl) 3262 (NH), 1729 (CO), 1646 (CO) cm^{-1}. ^1H NMR 0.88 (d, $J = 7$ Hz, 6H, $CH(CH_3)_2$), 1.23 (d, $J = 7$ Hz, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.50–1.70 (m, 3H, $CH(CH_3)_2$, CH_2), 2.33 (quintuplet, $J = 7$ Hz, 1H, H-3), 2.38 (s, 3H, CH_3Ph), 3.10 (dd, $J = 13$ and 6 Hz, 1H, H-6), 3.40–3.50 (m, 2H, H-4, H-6′), 3.72 (q, $J = 6$ Hz, 1H, H-5), 4.44 (s, 2H, CH_2Ph), 4.89 (d, $J = 8$ Hz, 1H, NH), 5.16 (dd, $J = 10$ and 5 Hz, 1H, NCH), 7.20–7.40 (m, 5H, Ph), 7.22 (d, $J = 8$ Hz, 2H, Ts-H3), 7.74 (d, $J = 8$ Hz, 2H, Ts-H2); ^{13}C NMR 16.2 (CH_3), 21.3 ($CH(CH_3)_2$), 21.6 (CH_3Ph), 23.2 ($CH(CH_3')_2$), 24.9 ($CH(CH_3)_2$), 28.1 ($C(CH_3)_3$), 37.2 (CH_2), 42.9 (C3), 44.4 (C6), 54.4 (NCH), 58.3 (C4), 71.7 (CH_2Ph), 75.8 (C5), 82.0 ($C(CH_3)_3$), 127.0–128.4 (Ph-C2, Ph-C3, Ph-C4, Ts-C3), 129.5 (Ts-C2), 137.4 and 138.0 (Ts-C4 and Ph-C1), 143.4 (Ts-C1), 171.0 (CO), 171.2 (CO). MS m/z (%) 559 (M^+, 1), 457 (36), 91 (100), 57 (15). Anal. calcd for $C_{30}H_{42}N_2O_6S$: C, 64.49; H, 7.58; N, 5.01; S, 5.74. Found: C, 64.36; H, 7.63; N, 5.35; S, 5.78%.

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