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Synthesis of Stereochemically and Skeletally Diverse Fused Ring Systems from Functionalized *C*-Glycosides

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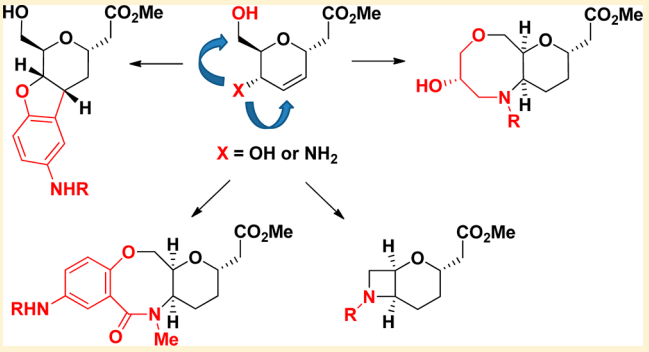
Supporting Information

ABSTRACT: A diversity-oriented synthesis (DOS) strategy was developed for the synthesis of stereochemically diverse fused-ring systems containing a pyran moiety. Each scaffold contains an amine and methyl ester for further diversification via amine capping and amide coupling. Scaffold diversity was evaluated in comparison to previously prepared scaffolds by a shape-based principal moments of inertia (PMI) analysis.



INTRODUCTION

As part of ongoing efforts to produce a stereochemically and skeletally diverse collection of small molecules, we sought to develop methods for the synthesis of a set of pyran-containing fused ring systems.[1] Pyrans are common subunits of natural products and biologically relevant small molecules.[2] To access pyran-containing fused ring systems, we envisioned utilizing a 2,3-unsaturated *C*-glycoside scaffold (**1** and **2**, Figure 1) previously reported by our group.[3] Having access to all eight stereoisomers of *C*-glycoside **1** and the corresponding allylic amine **2**, we aimed to develop synthetic pathways that would yield fused bi- and tricyclic ring systems. This paper descibes the synthesis of tricyclic compounds **3** and **4** via radical cyclization and nucleophilic aromatic substitution (S_NAr) reactions, and bicyclic compounds **5** and **6** through intramolecular Mitsunobu and epoxide ring-opening reactions. All skeletons resulting from these pathways retain functional handles that can be utilized for solid-phase library synthesis and future analogue development.

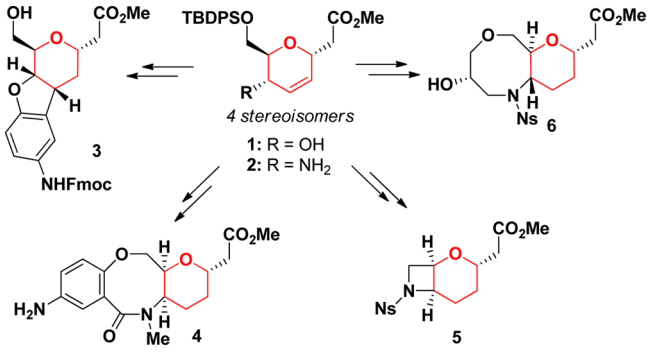


Figure 1. Synthesis of fused bi- and tricyclic ring systems from a *C*-glycoside template.

RESULTS AND DISCUSSION

The benzofuran motif is present in a wide range of natural products.[4] We aimed to access a [6,5,6] benzofuran scaffold (**3**, Scheme 1) starting from *C*-glycoside **1** via a 5-*exo*-*trig* radical cyclization.[5] This type of radical cyclization has been successfully employed in the construction of current drugs and numerous natural products including pregabalin[6] and morphine.[7] We anticipated that the radical cyclization step would occur by a regio- and stereoselective mode of addition onto the alkene, providing a *cis* relationship between C-4 and the newly formed stereogenic center at C-3.

The synthesis of benzofuran scaffold **3** began with an intermolecular S_NAr reaction between *C*-glycoside **1** and commercially available 2-bromo-1-fluoro-4-nitrobenzene **7** (Scheme 1). This reaction proceeded in the presence of sodium hydride in DMF with varying degrees of success (52−78% yield) across the diastereomers to afford **8a−d**. Selective reduction of the aryl nitro group using Zn metal[8] afforded the desired aniline **9a−d** in good yield. Initial attempts to effect the

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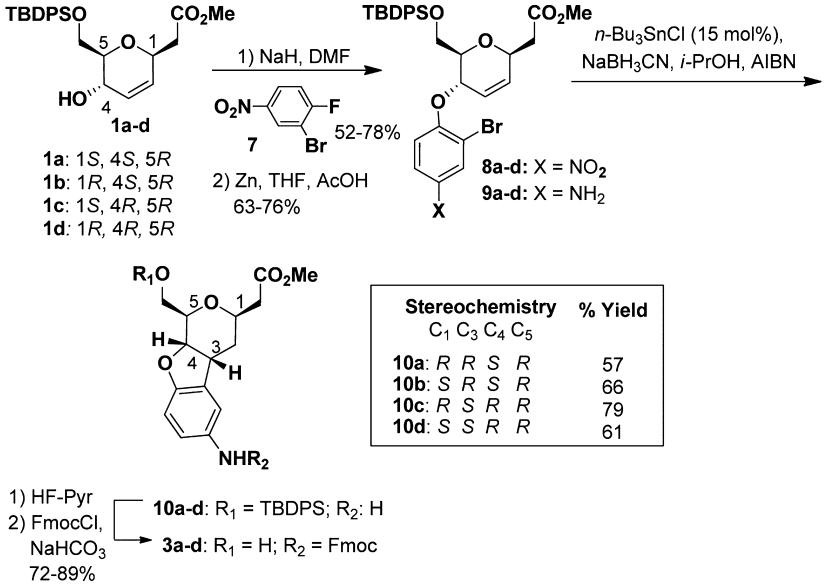
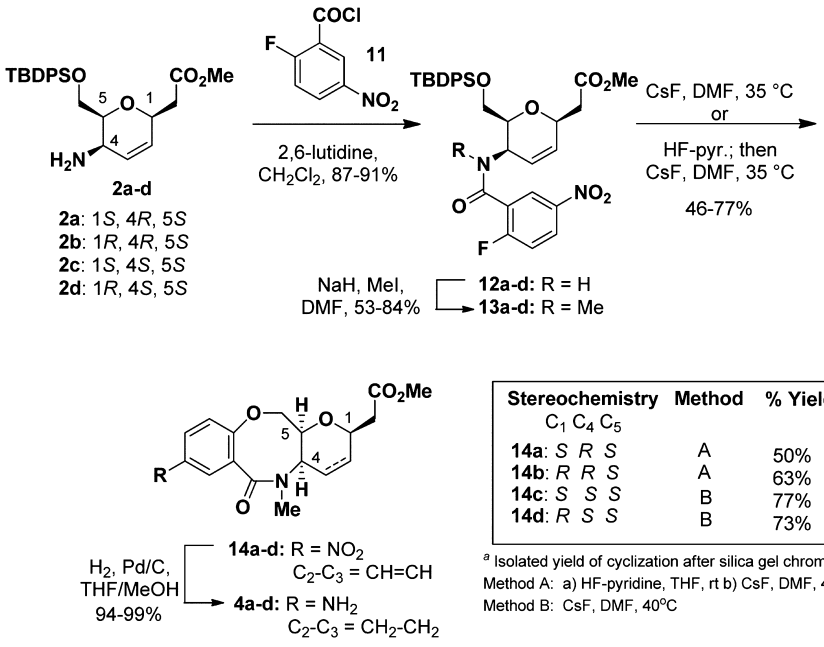
Scheme 1. Benzofuran Formation via a 5-*exo-trig* Cyclization



Stereochemistry C_1 C_3 C_4 C_5	% Yield
10a: *R R S R*	57
10b: *S R S R*	66
10c: *R S R R*	79
10d: *S S R R*	61

Scheme 2. Tricyclic Lactam Formation via Intramolecular S_NAr



Stereochemistry C_1 C_4 C_5	Method	% Yield[a]
14a: *S R S*	A	50%
14b: *R R S*	A	63%
14c: *S S S*	B	77%
14d: *R S S*	B	73%

[a] Isolated yield of cyclization after silica gel chromatography
Method A: a) HF-pyridine, THF, rt b) CsF, DMF, 40 °C
Method B: CsF, DMF, 40°C

5-*exo-trig* radical cyclization of **9a** by treatment with excess amounts of *n*-Bu_3SnH and catalytic AIBN in refluxing benzene were successful, affording the desired benzofuran **10a** in 53% yield. Concerns about toxicity and contamination by organo-tin reagents led us to explore the possibility of utilizing a catalytic amount of tin for the radical cyclization.[9] Using catalytic amounts of *n*-Bu_3SnCl and AIBN in the presence of $NaBH_3CN$ in *i*-PrOH[10] resulted in the formation of the cyclized product with similar efficiency as when using excess *n*-Bu_3SnH. Notably, we were able to perform this reaction on multigram scale for all stereoisomers yielding >20 g of each product. Finally, removal of the TBDPS group using HF·pyridine followed by Fmoc protection of the aniline yielded the desired benzofuran scaffolds **3a**−**d** in high yield.[11]

The intramolecular S_NAr reaction has been widely used in the context of diversity-oriented synthesis (DOS)[12] and small molecule synthesis in general.[13] We envisioned employing a S_NAr cyclization to produce a [6,8,6] tricyclic scaffold containing an 8-membered lactam starting from allylic amine **2**. Thus, amine **2** was first acylated with 2-fluoro-5-nitrobenzoyl chloride **11** to afford amide **12** (Scheme 2). Initially we attempted the S_NAr cyclization of **12** with a "one-pot" TBDPS deprotection/cyclization sequence using either TBAF or CsF; however, only dimerization and decomposition was observed. We hypothesized that the success of the intramolecular cyclization may be affected by the conformation of the amide bond. On the basis of observations by Smith and co-workers,[14] we decided to investigate the impact of an *N*-alkylated amide bond on intramolecular ring cyclization. Thus, amides **12a**−**d** were treated with methyl iodide in the presence of sodium hydride in DMF to afford *N*-methyl amide **13a**−**d**. Subsequent conversion of the alkylated amides to the cyclized products was

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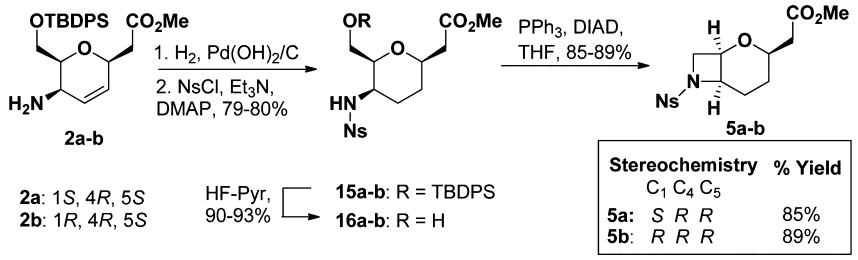
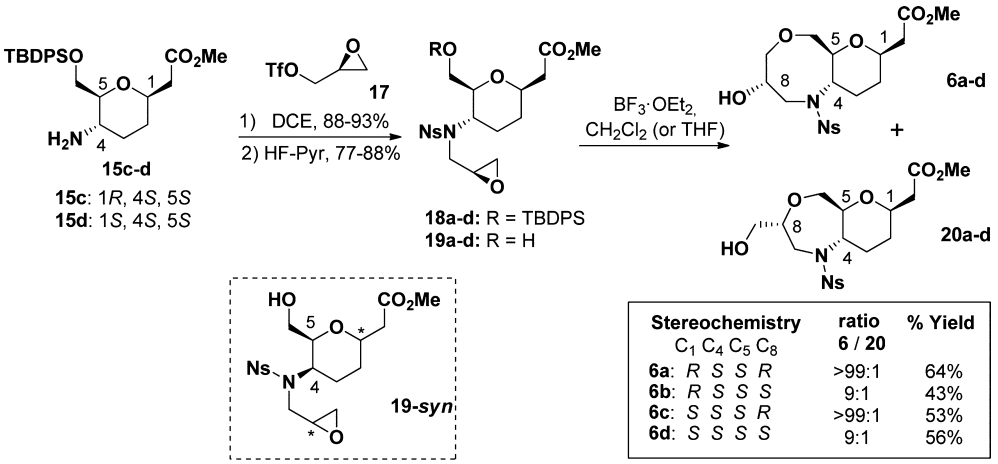
Scheme 3. Azetidine Formation via Intramolecular Mitsunobu



Scheme 4. Oxazacane Formation via Epoxide Opening/Ring-Closing Reaction



successful; however, the S_NAr reaction was found to have moderate stereochemical dependency. Upon treatment with cesium fluoride in DMF at 40 °C, TBDPS ethers **13c,d** underwent a smooth deprotection/cyclization sequence to produce lactams **14c,d**. Meanwhile, amides **13a,b** required a two-step sequence involving TBDPS removal with HF·pyridine followed by treatment with CsF to promote the S_NAr-mediated ring closure.[1a] Finally, hydrogenation of the cyclized products **14a−d**[15] reduced both the double bond and aryl nitro group, which afforded the desired tricyclic scaffolds **4a−d**.

We next investigated the possibility of azetidine ring formation **1e**,[16] to yield the [6,4] ring system **5** through an intramolecular Mitsunobu reaction. Starting from amines **2a,b**, the Mitsunobu precursors **16a,b** were obtained in three steps including hydrogenation, *N*-nosylation and TBDPS deprotection (Scheme 3). This material was then treated with PPh_3 and DIAD leading to the formation of the desired bicyclic azetidine **5a,b** in high yield. The product was easily isolated from the Mitsunobu byproducts, and the reaction could be carried out on multigram scale.

Finally, a number of interesting oxazapane and/or oxazacane ring systems were envisioned to be readily accessed through the use of chiral intermediate **15** (Scheme 4). We chose to explore the use of an epoxide-opening/ring-closing reaction, which would allow for the formation of a single diastereomeric product upon cyclization. A number of examples utilizing chiral epoxides as synthons for the assembly of complex small molecules, including both natural products[17] and library scaffolds,[18] have been well documented. Execution of this approach first required the incorporation of an epoxide into the *C*-glycoside template.

Initially, alkylation of sulfonamide **15a−d** with epichlorohydrin proved difficult when using the all *syn* stereoisomer, presumably due to steric hindrance. Ultimately, this was overcome using the (*R*)- or (*S*)-glycidol triflates (**17**)[19] (Scheme 4). Liberation of the primary alcohol by TBDPS deprotection gave compound **19**, the precursor to the epoxide-opening/ring-closing reaction. Previous reports of epoxide-opening/ring-closing reactions[17c] have mainly focused on the formation of smaller ring systems with varying degrees of *endo*/*exo* selectivity. Although the 7-*exo-tet* cyclization[20] is favored on the basis of Baldwin's rules, there is precedent for the 8-*endo-tet* cyclization to occur under basic conditions.[21] After a series of trial experiments, we found that the *endo*/*exo* selectivity of the Lewis-acid-mediated epoxide-opening/ring-closing reaction had a strong dependence on the stereochemical relationship between C-4 and C-5. With the *syn* configuration (**19-*syn***, not shown, see experimental details), mixtures of both the 7-membered oxazapane (**20**) and 8-membered oxazacane ring (**6**) systems were observed with selectivity ranging from 1:1 to 9:1 favoring the oxazapane depending on the stereoisomer used. Interestingly, with the *anti*-configuration (**19a−d**), the cyclization occurs smoothly via 8-*endo-tet* in the presence of $BF_3{\cdot}OEt_2$ in either CH_2Cl_2 or THF to give primarily the *endo* product, 8-membered oxazacane **6a−d**.[22] The stereochemistry at both C-1 of the pyran and of the epoxide has little impact on the regioselectivity of the reaction. The epoxide-opening/ring-closing reaction was run on a multigram scale with **19a−d**, obtaining acceptable yields of **6a−d** while not affecting selectivity.

In order to visualize the chemical space represented by the pyran-containing fused-ring systems as compared to our previously reported aldol-[1a−c] and azetidine-based[1e] pathways, we undertook a principal moments of inertia (PMI) analysis (Figure 2).[23] Through this shape-based analysis, we were able to visualize the differences between the three collections and

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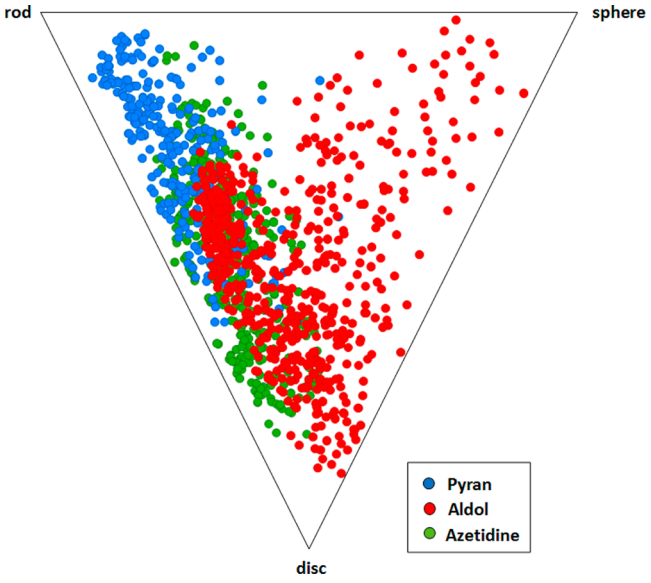

Figure 2. PMI analysis of pyran-containing scaffolds, along with previously reported scaffolds from aldol- and azetidine-based pathways.

observed that the fused ring systems access different chemical space than that occupied by the previously described scaffolds, especially compared to the aldol-based pathways, which included a variety of macrocycles.

CONCLUSIONS

In conclusion, we have reported the synthesis of a diverse set of fused-ring systems containing a pyran moiety. Utilizing all stereoisomers of a common *C*-glycoside intermediate, we are able to access all possible stereoisomers of each scaffold efficiently on multigram scale. Elaboration of these scaffolds to libraries suitable for high-throughput screening has been completed and will be the basis of future publications.

EXPERIMENTAL SECTION

General Methods. All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under a vacuum (~0.5 mmHg) and purged with N_2 prior to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to the footnoted references. ^{1}H and ^{13}C NMR spectra were recorded on 300 and/or 500 MHz spectrometers. All chemical shifts are reported in parts per million (δ) referenced to residual nondeuterated solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz; integration). Unless otherwise indicated, NMR data were collected at 25 °C. IR spectra were obtained with an FTIR spectrometer and are reported in cm^{-1}. Flash chromatography was performed using 40−60 μm silica gel (60 Å mesh) with the indicated solvent. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous potassium permanganate or ceric ammonium molybdate stain followed by heating. High-resolution mass spectra were obtained using a LC−MS coupled with a quadrupole.

Methyl 2-((2*S*,5*S*,6*R*)-5-(2-bromo-4-nitrophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 8a. To a solution of **1a** (25.0 g, 57.2 mmol, 1.0 equiv) in DMF (570 mL) was added 2-bromo-1-fluoro-4-nitrobenzene **7** (12.6 g, 57.2 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C, and sodium hydride (2.5 g, 62.9 mmol, 1.3 equiv) was added portion-wise over a period of 10 min. The reaction mixture was slowly warmed to rt and allowed to stir for 4 h. The reaction was then quenched with a saturated solution of aqueous ammonium chloride. DMF was removed in vacuo, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 0−15% EtOAc in hexanes), which provided 28.6 g (78%) of **8a** as a yellow oil. $[\alpha]_D^{20}$ +80.2 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (d, *J* = 2.7 Hz, 1H), 8.16 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.76−7.63 (m, 2H), 7.64−7.52 (m, 2H), 7.50−7.23 (m, 6H), 7.14 (d, *J* = 9.2 Hz, 1H), 6.05−5.97 (m, 2H), 5.31 (d, *J* = 8.3 Hz, 1H), 4.76 (t, *J* = 6.1 Hz, 1H), 4.05−3.92 (m, 2H), 3.86 (d, *J* = 8.3 Hz, 1H), 3.74 (s, 3H), 2.74−2.59 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 159.7, 141.9, 135.5, 133.2, 133.8, 127.8, 124.9, 124.7, 113.3, 113.0, 77.6, 72.0, 70.7, 62.9, 51.9, 40.2, 26.0, 19.4. HRMS (ESI+) calcd for $C_{31}H_{34}BrNNaO_7Si$ [M + +Na]$^+$: 662.1186. Found: 662.1181.

Methyl 2-((2*R*,5*S*,6*R*)-5-(2-bromo-4-nitrophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 8b. Following the above protocol, **1b** (29.5 g, 67 mmol, 1.0 equiv) was treated with 2-bromo-1-fluoro-4-nitrobenzene **7** (14.7 g, 67 mmol, 1.0 equiv) and sodium hydride (3.5 g, 87 mmol, 1.3 equiv) in DMF (890 mL). The reaction provided, after purification, 24.0 g (56%) of **8b** as a yellow oil. $[\alpha]_D^{20}$ +49.7 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, *J* = 2.7 Hz, 1H), 8.09 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.43−7.26 (m, 6H), 7.06 (d, *J* = 9.1 Hz, 1H), 5.99 (q, *J* = 10.4 Hz, 2H), 5.10 (d, *J* = 5.7 Hz, 1H), 4.79 (t, *J* = 6.0 Hz, 1H), 3.92 (dd, *J* = 7.1, 10.3 Hz, 3H), 3.72 (s, 3H), 2.78 (dd, *J* = 15.3, 8.6 Hz, 1H), 2.57 (dd, *J* = 15.3, 5.6 Hz, 1H), 1.15−0.82 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 159.4, 141.9, 135.7, 135.6, 133.2, 133.0, 132.9, 129.9, 129.6, 127.9, 124.7, 123.9, 113.1, 72.2, 70.2, 69.5, 52.1, 38.5, 26.9, 19.4. HRMS (ESI+) calcd for $C_{31}H_{34}BrNNaO_7Si$ [M + Na]$^+$: 662.1186. Found: 662.1180.

Methyl 2-((2*S*,5*R*,6*R*)-5-(2-bromo-4-nitrophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 8c. Following the above protocol, **1c** (10.0 g, 22.7 mmol, 1.0 equiv) was treated with 2-bromo-1-fluoro-4-nitrobenzene **7** (5.0 g, 22.7 mmol, 1.0 equiv) and sodium hydride (1.3 g, 31.8 mmol, 1.3 equiv) in DMF (280 mL). The reaction provided, after purification, 9.0 g (61%) of **8c** as a yellow oil. $[\alpha]_D^{20}$ −137.0 (*c* 0.9, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (d, *J* = 2.6 Hz, 1H), 8.18 (d, *J* = 9.1 Hz, 1H), 7.57 (dd, *J* = 18.8, 7.7 Hz, 4H), 7.47−7.26 (m, 6H), 7.06 (d, *J* = 9.1 Hz, 1H), 6.52−6.33 (m, 1H), 6.18 (d, *J* = 10.2 Hz, 1H), 4.90 (d, *J* = 4.5 Hz, 1H), 4.65 (t, *J* = 6.5 Hz, 1H), 4.13−4.03 (m, 1H), 4.02−3.89 (m, 2H), 3.70 (s, 3H), 2.71 (dd, *J* = 15.9, 7.2 Hz, 1H), 2.57 (dd, *J* = 16.0, 6.5 Hz, 1H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 159.8, 141.4, 136.7, 135.4, 133.2, 133.1, 129.7, 129.4, 127.7, 127.6, 125.1, 124.5, 121.6, 116.0, 113.0, 112.4, 71.6, 68.8, 62.3, 51.8, 39.6, 26.7, 19.1. HRMS (ESI+) calcd for $C_{31}H_{34}BrNNaO_7Si$ [M + Na]$^+$: 662.1186. Found: 662.1194.

Methyl 2-((2*R*,5*R*,6*R*)-5-(2-bromo-4-nitrophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 8d. Following the above protocol, **1d** (15.0 g, 34.0 mmol, 1.0 equiv) was treated with 2-bromo-1-fluoro-4-nitrobenzene **7** (7.49 g, 34.0 mmol, 1.0 equiv) and sodium hydride (1.12 g, 28.0 mmol, 1.3 equiv) in DMF (400 mL). The reaction provided, after purification, 11.4 g (52%) of **8d** as a yellow oil. $[\alpha]_D^{20}$ −116.2 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J* = 2.7 Hz, 1H), 8.08 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.48 (dd, *J* = 13.7, 7.9 Hz, 4H), 7.50−7.20 (m, 6H), 6.94 (d, *J* = 9.1 Hz, 1H), 6.35−6.09 (m, 2H), 4.77 (s, 2H), 3.98 (d, *J* = 4.6 Hz, 2H), 3.81 (d, *J* = 9.7 Hz, 1H), 3.59 (s, 3H), 2.64 (dd, *J* = 15.1, 8.9 Hz, 1H), 2.45 (dd, *J* = 15.1, 5.5 Hz, 1H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 159.8, 141.7, 135.7, 135.6, 135.6, 133.4, 133.2, 130.0, 129.6, 128.7, 127.9 (2), 124.7, 121.6, 113.2,

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112.6, 71.5, 69.6, 68.8, 62.1, 52.1, 37.5, 26.9, 19.3. HRMS (ESI+) calcd for $C_{31}H_{34}BrNNaO_7Si$ [M + Na]$^+$: 662.1186. Found: 662.1195.

Methyl 2-((2*S*,5*S*,6*R*)-5-(4-amino-2-bromophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 9a. To a solution of **8a** (27.3 g, 42.6 mmol) in THF (426 mL) and acetic acid (426 mL) was added zinc powder (41.8 g, 639 mmol, 15 equiv) in small portions at rt. The reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with CH_2Cl_2, filtered over Celite and washed with CH_2Cl_2. After filtration, the solvent was removed in vacuo. The organic residue was dissolved in CH_2Cl_2 (300 mL) and then washed with water (2 × 200 mL), brine (100 mL) and dried over Na_2SO_4. After filtration, excess solvent was removed in vacuo to afford a crude residue, which was purified by chromatography on silica gel (gradient: 0−60% EtOAc in hexanes) to provide 19.5 g (73%) of **9a** as a white foamy solid. $[\alpha]_D^{20}$ +59.3 (*c* 1.3, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.44−7.26 (m, 6H), 6.90−6.79 (m, 2H), 6.53 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.01 (d, *J* = 10.3 Hz, 1H), 5.85 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 4.67 (br s, 1H), 3.97 (s, 2H), 3.76 (d, *J* = 8.5 Hz, 1H), 3.69 (s, 3H), 3.50−3.13 (m, 2H), 2.71−2.40 (m, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 147.6, 142.0, 136.0, 135.7, 134.0, 133.6, 131.0, 129.7, 129.6, 127.7 (2), 127.1, 120.1, 118.0, 115.3, 114.3, 78.0, 71.8, 71.5, 63.4, 51.9, 40.5, 26.9, 19.5. HRMS (ESI+) calcd for $C_{31}H_{36}BrNNaO_5Si$ [M + Na]$^+$: 632.1444. Found: 632.1447.

Methyl 2-((2*R*,5*S*,6*R*)-5-(4-amino-2-bromophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 9b. Following the above protocol, **8b** (24.0 g, 37.5 mmol, 1 equiv) was treated with zinc powder (36.8 g, 562 mmol, 15 equiv) in THF (375 mL) and acetic acid (375 mL). The reaction provided, after purification, 14.3 g (63%) of **9b** as a white foamy solid. $[\alpha]_D^{20}$ +38.6 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 6.1, 2.0 Hz, 4H), 7.47−7.26 (m, 6H), 6.87 (dd, *J* = 15.2, 5.7 Hz, 2H), 6.52 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.01 (d, *J* = 10.4 Hz, 1H), 5.88 (d, *J* = 10.3 Hz, 1H), 4.75 (br s, 2H), 3.91 (br s, 3H), 3.67 (s, 3H), 3.51 (br s, 1H), 2.78 (dd, *J* = 15.3, 8.8 Hz, 1H), 2.54 (dd, *J* = 15.3, 5.4 Hz, 1H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 147.3, 142.1, 135.9, 135.8, 133.7, 133.5, 131.1, 129.7, 127.8, 126.1, 120.1, 118.3, 115.2, 114.6, 72.8, 71.2, 69.4, 63.3, 51.9, 38.6, 26.9, 19.4. HRMS (ESI+) calcd for $C_{31}H_{36}BrNNaO_5Si$ [M + Na]$^+$: 632.1444. Found: 632.1439.

Methyl 2-((2*S*,5*R*,6*R*)-5-(4-amino-2-bromophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 9c. Following the general reaction protocol, **8c** (30.0 g, 46.8 mmol, 1 equiv) was treated with zinc powder (45.9 g, 702 mmol, 15 equiv) in THF (468 mL) and acetic acid (468 mL). The reaction provided, after purification, 21.0 g (73%) of **9c** as a white foamy solid. $[\alpha]_D^{20}$ −137.0 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73−7.57 (m, 4H), 7.45−7.22 (m, 6H), 6.83 (dd, *J* = 8.5, 5.7 Hz, 2H), 6.50 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.00 (dd, *J* = 16.0, 6.8 Hz, 2H), 4.62−4.43 (m, 2H), 4.14 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.95 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.84 (d, *J* = 4.8 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 2H), 2.69 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.52 (dd, *J* = 15.7, 6.5 Hz, 1H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 147.3, 142.1, 135.8, 134.7, 133.8, 129.7, 127.8, 124.2, 120.0, 119.3, 115.3, 115.0, 78.0, 71.8, 69.7, 63.4, 51.9, 39.9, 27.0, 19.4. HRMS (ESI+) calcd for $C_{31}H_{36}BrNNaO_5Si$ [M + Na]$^+$: 632.1444. Found: 632.1441.

Methyl 2-((2*R*,5*R*,6*R*)-5-(4-amino-2-bromophenoxy)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-yl)-acetate 9d. Following the above protocol, **8d** (15.0 g, 23.4 mmol, 1 equiv) was treated with zinc powder (23.0 g, 351 mmol, 15 equiv) in THF (234 mL) and acetic acid (234 mL). The reaction provided, after purification, 10.9 g (76%) of **9d** as a white foamy solid. $[\alpha]_D^{20}$ −23.9 (*c*, 1.1 $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72−7.53 (m, 4H), 7.46−7.23 (m, 6H), 6.91−6.69 (m, 2H), 6.62−6.42 (m, 1H), 6.12−5.88 (m, 2H), 4.90−4.68 (m, 1H), 4.56−4.45 (m, 1H), 4.12 (dt, *J* = 18.7, 7.0 Hz, 2H), 4.03−3.85 (m, 3H), 3.63 (s, 3H), 2.66 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.47 (dd, *J* = 15.0, 5.6 Hz, 1H), 1.10−0.86 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 147.4, 142.1, 135.8, 133.8 (2), 133.3, 129.8, 127.8 (2), 124.2, 120.1, 118.8, 115.1, 72.8, 69.9, 69.2, 62.5, 60.6, 52.0, 38.0, 27.0, 19.3. HRMS (ESI+) calcd for $C_{31}H_{36}BrNNaO_5Si$ [M + Na]$^+$: 632.1444. Found: 632.1441.

Methyl 2-((1*R*,3*R*,4a*R*,9a*S*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 10a. To a solution of **9a** (32.6 g, 53.4 mmol) in *i*-PrOH (530 mL) in a jacketed, 3-necked round-bottom flask (equipped with a reflux condenser and recirculating chiller) was added AIBN (1.7 g, 10.7 mmol) and tributyltin chloride (2.2 mL, 8.0 mmol). The reaction mixture was carefully degassed with Ar for 10 min prior to heating. The reaction mixture was then heated at 85 °C and was allowed to stir for 5 min. Simultaneously, a solution of $NaBH_3CN$ (5.0 g, 80.0 mmol) in *i*-PrOH (120 mL) and a solution of AIBN (1.7g, 10.7 mmol) in benzene (120 mL) were added slowly over 2 h. After 2 h, the reaction was cooled to rt. *i*-PrOH was removed in vacuo, and the residue was coevaporated with benzene (3 × 20 mL). The crude purple solid was diluted in EtOAc (200 mL) and extracted with a saturated solution of aqueous ammonium chloride (2 × 100 mL). The organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated. The resulting residue was diluted with MeCN (100 mL) and washed with hexanes (2 × 60 mL). The MeCN phase was then dried in vacuo to afford a pink residue, which was purified by chromatography on silica gel (gradient: 0−70% EtOAc in hexanes), which provided 28.5 g (57%) of **10a** as a white/pink foamy solid. $[\alpha]_D^{20}$ +36.4 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63−7.60 (m, 4H), 7.29−7.27 (m, 6H), 6.50−6.37 (m, 3H), 4.46 (t, *J* = 8.7 Hz, 1H), 3.80−3.77 (m, 3H), 3.69 (m, 1H), 3.64 (s, 3H), 3.40 (m, 3H), 2.59 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.45 (dd, *J* = 15.5, 5.2 Hz, 1H), 2.21 (d, *J* = 13.9 Hz, 1H), 1.78 (m, 1H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 152.5, 140.8, 135.8 (2), 133.9, 133.7, 129.59, 129.54, 129.5, 127.6, 115.0, 111.3, 110.6, 77.6, 77.0, 70.0, 64.9, 60.5, 51.8, 40.8, 39.5, 30.3, 26.9, 19.4. HRMS (ESI+) calcd for $C_{31}H_{38}NO_5Si$ [M + H]$^+$: 532.2519. Found: 532.2516.

Methyl 2-((1*R*,3*S*,4a*R*,9a*S*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 10b. Following the above protocol, **9b** (15.0 g, 24.6 mmol, 1 equiv) was treated with AIBN (1.6 g, 8.9 mmol) and tributyltin chloride (1.0 mL, 3.6 mmol) followed by $NaBH_3CN$ (2.3 g, 36.8 mmol) in *i*-PrOH (250 mL). The reaction provided, after purification, 8.8 g (66%) of **10b** as a white/pink foamy solid. $[\alpha]_D^{20}$ +54.9 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.55 (m, 4H), 7.40 (m, 5H), 6.57 (dd, *J* = 15.0, 5.2 Hz, 2H), 6.46 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.69−4.48 (m, 1H), 4.35 (td, *J* = 11.4, 5.0 Hz, 1H), 4.07−3.89 (m, 2H), 3.82 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.63 (s, 3H), 3.49−3.29 (m, 2H), 2.61 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.38 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.00 (ddd, *J* = 13.7, 5.7, 3.7 Hz, 1H), 1.49 (m 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 152.3, 140.4, 135.9, 135.8, 133.4, 133.4, 132.2, 129.8, 129.8, 127.9, 127.9, 115.2, 112.0, 110.2, 79.6, 77.5, 77.2, 77.0, 72.7, 68.2, 65.3, 51.8, 40.8, 38.9, 32.9, 27.0, 19.4. HRMS (ESI+) calcd for $C_{31}H_{37}NNaO_5Si$ [M + Na]$^+$: 554.2339. Found: 554.2345.

Methyl 2-((1*R*,3*R*,4a*S*,9a*R*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 10c. Following the above protocol, **9c** (20.0 g, 32.8 mmol, 1 equiv) was treated with AIBN (2.1 g, 13.1 mmol) and tributyltin chloride (1.3 mL, 4.9 mmol) followed by $NaBH_3CN$ (3.1 g, 49.1 mmol) in *i*-PrOH (430 mL). The reaction provided, after purification, 13.8 g (79%) of **10c** as a white/pink foamy solid. $[\alpha]_D^{20}$ −53.0 (*c* 0.9, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (t, *J* = 8.0 Hz, 4H), 7.39−7.37 (m, 6H), 6.63−6.37 (m, 3H), 4.38 (d, *J* = 9.9 Hz, 1H), 4.03 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.91 (m, 2H), 3.85−3.67 (m, 2H), 3.64 (s, 3H), 3.39 (s, 2H), 3.15−3.09 (m, 1H), 2.58−2.53 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.30−2.27 (dd, *J* = 14.9, 5.6, 1H), 2.07−1.89 (m, 1H), 1.27−1.18 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 152.1, 140.2, 135.9, 135.8, 134.2, 133.8, 129.8, 129.7,

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127.8, 115.0, 111.5, 110.8, 78.9, 78.0, 72.1, 63.9, 51.9, 40.9, 39.5, 35.4, 27.0, 19.4. HRMS (ESI+) calcd for $C_{31}H_{37}NNaO_5Si$ $[M + Na]^+$: 554.2339. Found: 554.2341.

Methyl 2-((1*R*,3*S*,4a*S*,9a*R*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 10d. Following the above protocol, **9d** (6.0 g, 9.8 mmol, 1 equiv) was treated with AIBN (0.6 g, 3.9 mmol) and tributyltin chloride (0.6 mL, 2.4 mmol) followed by $NaBH_3CN$ (0.9 g, 14.7 mmol) in *i*-PrOH (130 mL). The reaction provided, after purification, 3.2 g (61%) of **10d** as a white/pink amorphous solid. $[\alpha]_D^{20}$ −92.5 (*c*, 0.5 $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76−7.71 (m, 4H), 7.43−7.41 (m, 6H), 6.61−6.50 (m, 3H), 6.46 (dd, *J* = 8.3, 1.7 Hz, 1H), 5.00 (d, *J* = 5.9 Hz, 1H), 4.10−4.04 (m, 1H), 3.90−3.80 (m, 2H), 3.77−3.70 (m, 2H), 3.61 (s, 3H), 3.50 (s, 2H), 2.57−2.49 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.43−2.38 (dd, *J* = 15.7, 5.8 Hz, 1H), 2.10−1.95 (m, 1H), 1.90−1.80 (m, 1H), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 153.3, 140.0, 135.9, 135.8, 133.8, 133.7, 130.1, 129.8, 129.8, 127.8, 127.8, 115.8, 112.0, 109.7, 79.7, 77.5, 77.2, 77.0, 71.1, 67.4, 63.3, 51.8, 40.9, 37.9, 30.4, 27.0, 19.4. HRMS (ESI+) calcd for $C_{31}H_{37}NNaO_5Si$ $[M + Na]^+$: 554.2339. Found: 554.2335.

Methyl 2-((1*R*,3*R*,4a*R*,9a*S*)-6-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 3a. To a solution of **10a** (6.70 g, 12.6 mmol, 1 equiv) in THF (130 mL) was added HF·pyridine (70 wt %, 6.3 mL, 50 mmol, 4 equiv) at rt. The reaction was monitored by LC−MS until complete conversion of the starting material was observed. After stirring overnight, the reaction was quenched with TMSOMe (17.3 mL, 126 mmol), and excess of solvent was removed in vacuo to afford a crude oil, which was carried on to the next step without purification. To a solution of crude deprotected alcohol (3.70 g, 12.6 mmol) in dioxane (160 mL) was added a 10% aqueous $NaHCO_3$ solution (100 mL) until pH 6−7 was reached. The reaction mixture was cooled to 0 °C, and a solution of FmocCl (3.59 g, 13.9 mmol) in dioxane (20 mL) was added. The reaction was quenched with a saturated solution of aqueous ammonium chloride, and 1,4-dioxane was removed in vacuo. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were then washed with brine, separated and dried over $MgSO_4$. After filtration, the solvent was removed, and a crude pink solid was obtained. The solid was triturated in cold CH_2Cl_2 and then filtered and washed carefully with cold CH_2Cl_2 to give 4.7 g (72%) of the desired product **3a** as a white-gray amorphous solid. $[\alpha]_D^{20}$ +94.1 (*c* 0.8, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2950, 1723, 1615, 1548, 1490, 1449, 1439, 1219, 1150, 1054. ^1H NMR (500 MHz, DMSO-d_6, 100 °C): δ 9.10 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 6.6 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.40−7.31 (m, 3H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.61 (t, *J* = 8.7 Hz, 1H), 4.54−4.46 (m, 2H), 4.31−4.24 (m, 2H), 3.87−3.76 (m, 1H), 3.69−3.56 (m, 4H), 3.55−3.50 (m, 1H), 3.22−3.18 (m, 1H), 2.52−2.49 (m, 1H, obscured by solvent peak), 2.19 (d, *J* = 14.1, 1H), 1.99−1.89 (m, 1H), 1.38−1.32 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C, as a mixture of rotamers): δ 170.1, 154.4, 153.3, 143.4, 140.3, 132.2, 128.8, 128.3, 127.0, 126.6, 126.4, 124.5, 120.6, 119.4, 119.3, 115.1, 108.8, 108.4, 108.1, 77.0, 69.3, 65.2, 61.7, 50.5, 46.5, 38.0, 29.5, 29.4. HRMS (ESI+) calcd for $C_{30}H_{30}NO_7$ $[M + H]^+$: 516.2022. Found: 516.2027.

Methyl 2-((1*R*,3*S*,4a*R*,9a*S*)-6-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 3b. Following the above protocol, **10b** (6.8 g, 12.7 mmol, 1 equiv) was treated with HF·pyridine (70 wt %, 7.9 mL, 64.0 mmol) in THF (130 mL). The crude alcohol was dissolved in 1,4-dioxane (160 mL), and 10% aqueous $NaHCO_3$ solution (100 mL) was added followed by a solution of FmocCl (6.6 g, 25.6 mmol) in 1,4-dioxane (20 mL). The reaction provided, after filtration, 5.84 g (89%) of **3b** as a white foamy solid. $[\alpha]_D^{20}$ +89.3 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2950, 1723, 1615, 1548, 1490, 1449, 1439, 1219, 1150, 1054. ^1H NMR (500 MHz, DMSO-d_6, 100 °C): δ 9.07 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.37−7.34 (m, 3H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 4.62−4.53 (m, 1H), 4.48 (d, *J* = 6.6 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 1H), 4.16 (dt, *J* = 16.5, 8.3 Hz, 1H), 3.87 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.73−3.57 (m, 5H), 3.56−3.40 (m, 1H), 2.54−2.36 (m, 2H), 2.08−1.91 (m, 1H), 1.40 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C): δ 170.2, 154.1, 153.3, 143.4, 140.3, 131.7, 131.3, 127.0, 126.5, 124.5, 119.4, 119.1, 115.8, 108.4, 79.0, 71.7, 66.6, 65.1, 61.3, 50.5, 46.5, 37.3, 31.8. HRMS (ESI+) calcd for $C_{30}H_{30}NO_7$ $[M + H]^+$: 516.2022. Found: 516.2021.

Methyl 2-((1*R*,3*R*,4a*R*,9a*R*)-6-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 3c. Following the above protocol, **10c** (7.5 g, 14.1 mmol, 1 equiv) was treated with HF·pyridine (70 wt %, 8.7 mL, 70.5 mmol) in THF (140 mL). The crude alcohol was dissolved in 1,4-dioxane (180 mL), and 10% aqueous $NaHCO_3$ solution (120 mL) was added, followed by a solution of FmocCl (7.3 g, 28.2 mmol) in 1,4-dioxane (20 mL). The reaction provided, after filtration, 6.2 g (85%) of **3c** as a white foamy solid. $[\alpha]_D^{20}$ −121.9 (*c* 0.8, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2950, 1723, 1615, 1548, 1490, 1449, 1439, 1219, 1150, 1054. ^1H NMR (500 MHz, DMSO-d_6, 100 °C): δ 9.06 (s, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 2H), 4.39 (d, *J* = 6.2 Hz, 1H), 4.35−4.22 (m, 2H), 3.79−3.70 (m, 3H), 3.69−3.48 (m, 4H), 3.40−3.23 (m, 1H), 2.56−2.32 (m, 2H), 1.98 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.03−0.98 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C): δ 170.0, 153.8, 153.3, 143.5, 140.4, 133.2, 131.7, 127.1, 126.4, 124.5, 119.4, 118.9, 115.2, 108.7, 78.7, 77.1, 71.0, 65.1, 60.8, 50.5, 46.5, 38.0, 34.4. HRMS (ESI+) calcd for $C_{30}H_{30}NO_7$ $[M + H]^+$: 516.2022. Found: 516.2027.

Methyl 2-((1*R*,3*S*,4a*R*,9a*R*)-6-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-b]benzofuran-3-yl)acetate 3d. Following the above protocol, **10d** (3.2 g, 6.0 mmol, 1 equiv) was treated with HF·pyridine (70 wt %, 3.0 mL, 24.0 mmol) in THF (60 mL). The crude alcohol was dissolved in dioxane (70 mL), and 10% aqueous $NaHCO_3$ solution (80 mL) was added, followed by a solution of FmocCl (1.6 g, 6.2 mmol) in 1,4-dioxane (10 mL). The reaction provided, after filtration, 2.4 g (82%) of **3d** as a white foamy solid. $[\alpha]_D^{20}$ −65.8 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2950, 1723, 1615, 1548, 1490, 1449, 1439, 1219, 1150, 1054. ^1H NMR (500 MHz, DMSO-d_6, 100 °C): δ 9.07 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.36−7.31 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 4.91 (d, *J* = 9.8 Hz, 1H), 4.47 (d, *J* = 6.7 Hz, 2H), 4.32−4.24 (m, 2H), 3.85−3.75 (m, 3H), 3.65−3.60 (m, 4H), 3.51−3.47 (m, 1H), 2.56−2.42 (m, 4H), 2.03 (s, 1H), 1.83−1.78 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.1, 155.0, 153.3, 143.4, 140.3, 131.4, 129.5, 127.0, 126.4, 124.5, 119.4, 119.3, 115.8, 107.6, 93.7, 70.2, 66.4, 65.1, 60.2, 50.4, 46.5, 36.5, 29.0. HRMS (ESI+) calcd for $C_{30}H_{30}NO_7$ $[M + H]^+$: 516.2022. Found: 516.2030.

Methyl 2-((2*S*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(2-fluoro-*N*-methyl-5-nitrobenzamido)-5,6-dihydro-2*H*-pyran-2-yl)acetate 13a. To a solution of **2a** (21.0 g, 47.8 mmol, 1.0 equiv) in CH_2Cl_2 (480 mL) at 0 °C was added 2,6-lutidine (11.1 mL, 96.0 mmol, 2.0 equiv) followed by 2-fluoro-5-nitrobenzoyl chloride **11** (11.7 g, 57.3 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 2 h. After complete conversion (determined by LC−MS) the reaction mixture was quenched with a saturated aqueous solution of aqueous ammonium chloride. The organic layer was washed with water, and the combined aqueous phases were extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by chromatography on silica gel, which provided 25.2 g of the amide (87%). The purified amide (21.0 g, 34.6 mmol, 1.0 equiv) was dissolved in dry DMF (700 mL) and neat methyl iodide (4.3 mL, 69.2 mmol, 2.0 equiv) was added to the solution. At 0 °C, sodium hydride (60% dispersion in mineral oil, 2.1 g, 51.9 mmol, 1.5 equiv) was added portion-wise to the mixture, over a period of 15 min. After 2 h at 0 °C, the reaction mixture was quenched with a saturated solution of ammonium chloride, and the layers were separated. The aqueous phase was extracted with ether, and the combined organic phases were washed with brine, dried with $MgSO_4$,

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filtered and concentrated to afford a crude material that was purified by silica gel chromatography (gradient: 0−30% EtOAc in hexanes) to afford **13a** as a pale yellow oil (18.0 g, 84% yield). $[\alpha]_D^{20}$ −42.7 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2931, 2857, 1739, 1641, 1533, 1350, 1112, 1097. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers, ratio 4:1): δ 8.26 (ddd, *J* = 9.0, 4.4, 2.9 Hz, 1H), 8.11 (ddd, *J* = 12.3, 5.3, 2.7 Hz, 1H), 7.75−7.67 (m, 2H), 7.65−7.57 (m, 1H), 7.45−7.33 (m, 6H), 7.24−7.12 (m, 2H), 6.17 (d, *J* = 10.0 Hz, 1H), 5.76 (ddd, *J* = 10.1, 5.5, 1.9 Hz, 1H), 5.25 (s, 1H), 4.62−4.41 (m, 1H), 4.01−3.86 (m, 2H), 3.78−3.70 (dd, *J* = 10.7, 7.4 Hz, 1H), 3.70 (s, 3H × 0.2), 3.66 (s, 3H × 0.8), 2.95 (s, 3H × 0.2), 2.69 (br s, 3H × 0.8), 2.63−2.43 (m, 2H), 1.06 (s, 9H × 0.8), 1.00 (s, 9H × 0.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 164.8, 144.5, 137.9, 135.7, 135.6, 135.4, 135.3, 133.6, 133.5, 129.7, 129.5, 129.0, 128.2, 127.7, 127.6, 127.5, 126.7, 126.6, 126.3, 126.0, 125.3, 125.2, 125.1, 123.6, 117.1, 116.8, 78.4, 71.9, 63.9, 51.8, 46.6, 39.6, 39.5, 33.6, 26.8, 26.7, 21.4, 19.3, 19.1. HRMS (ESI) calcd for $C_{33}H_{37}FN_2NaO_7Si$ $[M + Na]^+$: 643.2252. Found: 643.2250.

Methyl 2-((2*R*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-fluoro-*N*-methyl-5-nitrobenzamido)-5,6-dihydro-2*H*-pyran-2-yl)acetate 13b. Compound **13b** was prepared using the above protocol starting from **2b** (24.2 g, 55.0 mmol, 1.0 equiv) via treatment with 2,6-lutidine (12.8 mL, 110.0 mmol, 2.0 equiv) and 2-fluoro-5-nitrobenzoyl chloride **11** (13.5 g, 66.1 mmol, 1.2 equiv) in CH_2Cl_2 (550 mL) to provide 29.2 g (87%) of the amide. The methylation was performed on 23.6 g (38.8 mmol, 1.0 equiv) of the amide intermediate with sodium hydride (60% dispersion in mineral oil, 2.2 g, 54.4 mmol, 1.4 equiv) and methyl iodide (4.8 mL, 78.0 mmol, 2.0 equiv) in DMF (650 mL). The reaction provided, after purification, 19.1 g (79%) of **13b** as a pale yellow oil. $[\alpha]_D^{20}$ −96.8 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2926, 2852, 1736, 1640, 1532, 1349, 1093. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers, ratio 9:2): δ 8.29−8.20 (m, 1H), 8.17−8.04 (m, 1H), 7.69 (br t, *J* = 6.0 Hz, 3H), 7.55 (br dd, *J* = 14.1, 7.2 Hz, 1H), 7.47−7.29 (m, 6H), 7.20 (t, *J* = 8.6 Hz, 1H), 6.18 (br d, *J* = 9.9 Hz, 1H), 5.90−5.73 (m, 1H), 5.21 (br s, 1H), 4.85 (br s, 1H), 3.98 (br s, 1H), 3.87 (br dd, *J* = 11.0, 4.0 Hz, 1H), 3.76−3.65 (m, 4H), 2.99 (s, 3H × 0.2), 2.82−2.69 (m, 1H), 2.74 (s, 3H × 0.8), 2.64−2.35 (m, 1H), 1.05 (s, 9H × 0.8), 0.97 (s, 9H × 0.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 170.6, 164.8, 164.3, 162.8, 159.4, 144.5, 135.7, 135.6, 135.5, 135.3, 134.6, 133.5, 129.8, 129.7, 129.6, 127.7, 127.6, 126.7, 126.6, 126.3, 126.0, 125.2, 125.1, 123.1, 117.2, 116.8, 72.8, 72.5, 69.9, 69.7, 63.9, 51.9, 51.7, 46.1, 36.9, 36.7, 33.5, 33.4, 26.8, 19.2, 19.1. HRMS (ESI) calcd for $C_{33}H_{37}FN_2NaO_7Si$ $[M + Na]^+$: 643.2252. Found: 643.2250.

Methyl 2-((2*S*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-fluoro-*N*-methyl-5-nitrobenzamido)-5,6-dihydro-2*H*-pyran-2-yl)acetate 13c. Compound **13c** was prepared using starting from **2a** (20.3 g, 46.2 mmol, 1.0 equiv) via treatment with 2,6-lutidine (10.8 mL, 92.4 mmol, 2.0 equiv) and 2-fluoro-5-nitrobenzoyl chloride **11** (11.3 g, 55.5 mmol, 1.2 equiv) in CH_2Cl_2 (460 mL). This stereoisomer was not purified, and the crude mixture was used directly in the next step. The methylation was performed when the crude amide intermediate was reacted with sodium hydride (60% dispersion in mineral oil, 3.7 g, 92.0 mmol, 2.0 equiv) and methyl iodide (28.9 mL, 462 mmol, 10.0 equiv) in THF (750 mL). The reaction provided, after purification, 15.2 g of **13c** as a pale yellow oil (53% yield over two steps). $[\alpha]_D^{20}$ +13.6 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2926, 2852, 1737, 1643, 1532, 1348, 1111. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers, ratio 1:1): δ 8.29 (ddd, *J* = 9.0, 4.4, 2.9 Hz, 1H × 0.5), 8.15 (m, 3H × 0.5), 7.76−7.67 (m, 2H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.43−7.29 (m, 7H), 6.00 (d, *J* = 9.5 Hz, 1H), 5.75 (br d, *J* = 9.5 Hz, 1H × 0.5), 5.65 (d, *J* = 10.2 Hz, 1H × 0.5), 5.25 (br d, *J* = 8.2 Hz, 1H × 0.5), 4.66−4.50 (m, 1H), 4.16 (br s, 1H × 0.5), 3.88−3.72 (m, 3H), 3.70 (s, 3H × 0.5), 3.66 (s, 3H × 0.5), 2.89 (s, 3H × 0.5), 2.64 (s, 3H × 0.5), 2.70−2.51 (m, 1H), 2.51−2.36 (m, 1H), 1.04 (s, 9H × 0.5), 0.91 (s, 9H × 0.5). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers): δ 171.0, 170.7, 164.8, 159.5, 144.5, 135.8, 135.7, 135.3, 133.7, 133.5, 133.0, 129.8, 129.7, 129.6, 128.3, 127.7, 127.6, 126.9, 126.8, 126.5, 125.9, 125.3, 125.3, 125.2, 117.2, 116.9, 75.7, 75.4, 71.2, 64.0, 63.3, 51.8, 49.2, 40.1, 39.8, 32.0, 26.7, 19.3, 19.2. HRMS (ESI) calcd for $C_{33}H_{37}FN_2NaO_7Si$ $[M + Na]^+$: 643.2252. Found: 643.2245.

Methyl 2-((2*R*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-fluoro-*N*-methyl-5-nitrobenzamido)-5,6-dihydro-2*H*-pyran-2-yl)acetate 13d. Compound **13d** was prepared using the above protocol starting from **2d** (41.6 g, 95.0 mmol, 1.0 equiv) via treatment with 2,6-lutidine (22.0 mL, 189.0 mmol, 2.0 equiv) and 2-fluoro-5-nitrobenzoyl chloride **11** (23.1 g, 113.0 mmol, 1.2 equiv) in CH_2Cl_2 (1000 mL), to provide 52.0 g (91%) of the amide. The methylation was performed on 52.0 g (86.0 mmol, 1.0 equiv) of the amide intermediate with sodium hydride (60% dispersion in mineral oil, 4.8 g, 120.0 mmol, 1.4 equiv) and methyl iodide (10.7 mL, 171.0 mmol, 2.0 equiv) in DMF (1750 mL). The reaction provided, after purification, 40.1 g (75%) of **13d** as a yellow oil. $[\alpha]_D^{20}$ +40.3 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2931, 2857, 1737, 1643, 1533, 1349, 1111. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers 3:2): δ 8.35−8.02 (m, 2H), 7.75−7.65 (m, 2H), 7.52 (dd, *J* = 18.1, 7.2 Hz, 2H), 7.45−7.31 (m, 7H), 6.07 (br d, *J* = 10.3 Hz, 1H), 5.72 (br d, *J* = 10.2 Hz, 1H), 5.18 (s, 1H), 4.66 (br s, 1H), 3.97 (dd, *J* = 8.9, 4.3 Hz, 3H × 0.4), 3.90−3.78 (m, 3H × 0.6), 3.67 (s, 3H), 2.99 (br s, 3H × 0.4), 2.79 (s, 3H × 0.6), 2.66 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.54 (br dd, *J* = 14.9, 6.0 Hz, 1H), 1.07 (s, 9H × 0.6), 0.93 (s, 9H × 0.4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.6, 164.4, 164.2, 163.0, 159.6, 144.5, 135.7, 135.6, 135.3, 133.3, 133.2, 129.9, 129.8, 129.7, 127.7, 126.8, 126.7, 125.3, 125.2, 123.9, 117.2, 116.9, 74.1, 67.2, 63.4, 51.9, 51.8, 47.6, 39.2, 32.5, 32.5, 29.1, 26.8, 26.7, 19.2, 19.1. HRMS (ESI) calcd for $C_{33}H_{37}FN_2NaO_7Si$ $[M + Na]^+$: 643.2252. Found: 643.2245.

Methyl 2-((2*S*,4a*R*,12a*S*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 14a. A solution of HF·pyridine (70% by wt. in pyridine, 11.2 mL, 90.0 mmol, 4.0 equiv) was added via syringe at 0 °C to a solution of **13a** (14.0 g, 22.6 mmol, 1.0 equiv) in 250 mL THF. Once the addition was complete, the cold bath was removed allowing the reaction mixture to reach rt, and the mixture was stirred until complete conversion of the starting material was observed (4 h, LC−MS). The reaction was quenched at 0 °C with TMSOMe (24.9 mL, 180.4 mmol, 8.0 equiv), and solvent was removed in vacuo to afford a crude material (7.87 g, 20.6 mmol, 91% yield), which was used in the next step without further purification. A solution of the intermediate alcohol (7.87 g, 20.6 mmol, 1.0 equiv) in DMF (700 mL) was added via cannula at 0 °C to a flame-dried round-bottom flask containing dry CsF (31.3 g, 206.0 mmol, 10.0 equiv). The mixture was warmed to 40 °C overnight. The reaction was carefully quenched at 0 °C with brine (350 mL), and the compound was partitioned between brine and ether. The aqueous layer was extracted with ether (3×), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated to afford a crude material that was purified on silica gel (gradient: 0−60% EtOAc in hexanes) to afford **14a** (3.7 g, 10.2 mmol, 50% yield) as a yellow foamy solid. $[\alpha]_D^{20}$ −109.8 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2995, 2947, 2856, 1736, 1632, 1518, 1436, 1343, 1256, 1085. ^1H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.8 Hz, 1H), 8.10 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 1H), 6.18 (d, *J* = 10.1 Hz, 1H), 6.00−5.85 (m, 1H), 4.67 (s, 1H), 4.36 (dd, *J* = 12.6, 4.0 Hz, 1H), 4.26 (dd, *J* = 12.5, 9.5 Hz, 1H), 4.06−4.00 (m, 1H), 3.96 (ddd, *J* = 9.4, 3.9, 2.4 Hz, 1H), 3.72 (s, 3H), 3.08 (s, 3H), 2.64 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.55 (dd, *J* = 15.7, 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.3, 159.0, 141.6, 135.4, 128.7, 126.3, 122.3, 121.1, 120.1, 74.8, 72.2, 65.9, 52.0, 51.9, 38.8, 32.3. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_7$ $[M + H]^+$: 363.1187. Found: 363.1193.

Methyl 2-((2*R*,4a*R*,12a*S*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 14b. Compound **14b** was prepared using above protocol starting from **13b** (8.5 g, 13.7 mmol, 1.0 equiv). TBDPS deprotection was accomplished via treatment with HF·pyridine (70% by wt. in pyridine, 6.8 mL, 54.8 mmol, 4.0 equiv) in THF (150 mL), and the reaction was quenched with TMSOMe (18.8 mL, 137.0 mmol, 10.0 equiv) to afford the intermediate alcohol (4.8 g, 12.5 mmol) in 91% yield. Cyclization of the crude material (4.8 g, 12.5 mmol, 1.0 equiv) was conducted in DMF (420 mL) with CsF (19.0 g, 125.0 mmol, 10.0 equiv) at 40 °C for 5 h to afford **14b** (2.8 g, 7.8 mmol, 63% yield) as a yellow foamy solid. $[\alpha]_D^{20}$ −91.0 (*c* 1.1, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2952, 2900, 1736, 1634, 1518, 1437,

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1343, 1306, 1257, 1104. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, J = 2.8 Hz, 1H), 8.10 (dd, J = 9.2, 2.9 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 6.21 (dd, J = 10.0, 3.0 Hz, 1H), 5.98 (ddd, J = 8.8, 6.2, 2.1 Hz, 1H), 4.81 (ddt, J = 7.7, 5.1, 2.6 Hz, 1H), 4.34−4.20 (m, 2H), 4.06−3.96 (m, 2H), 3.74 (s, 3H), 3.07 (s, 3H), 2.74 (dd, J = 15.3, 9.4 Hz, 1H), 2.56 (dd, J = 15.3, 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168.3, 156.0, 141.7, 134.9, 128.9, 126.4, 122.1, 121.2, 120.1, 70.3, 69.2, 66.3, 52.1, 51.5, 37.2, 32.1. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_7$ [M + H]$^+$: 363.1187. Found: 363.1194.

Methyl 2-((2*S*,4a*S*,12a*S*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 14c. Cesium fluoride (CsF, 25.0 g, 165.0 mmol, 13.1 equiv) was added in one portion at 0 °C to a solution of **13c** (7.8 g, 12.6 mmol, 1.0 equiv) in DMF (1 L) under argon. The temperature was slowly raised to 40 °C, and the mixture was stirred at this temperature until complete conversion of the starting material was observed (LC−MS). The reaction was carefully quenched with brine (500 mL) at 0 °C and then partially concentrated. The crude mixture was partitioned between Et_2O and brine. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude material was then purified on silica gel (gradient: 0−50% EtOAc in hexanes) to afford **14c** (3.5 g, 9.7 mmol, 77% yield) as a yellow powder. $[\alpha]_D^{20}$ −42.5 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2943, 2847, 1735, 1636, 1518, 1437, 1345, 1327, 1255, 1092. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 2.8 Hz, 1H), 8.17 (dd, J = 9.1, 2.9 Hz, 1H), 7.09 (d, J = 9.1 Hz, 1H), 5.97 (dd, J = 10.3, 2.5 Hz, 1H), 5.84 (br d, J = 10.3 Hz, 1H), 4.76−4.66 (m, 1H), 4.45 (dd, J = 13.9, 2.6 Hz, 1H), 4.43−4.37 (m, 1H), 4.34 (dd, J = 13.8, 2.3 Hz, 1H), 3.80 (ddd, J = 10.0, 2.5, 2.5 Hz, 1H), 3.71 (s, 3H), 3.01 (s, 3H), 2.67 (dd, J = 16.0, 7.3 Hz, 1H), 2.52 (dd, J = 16.0, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 168.3, 161.2, 142.4, 132.6, 129.3, 126.7, 124.6, 122.8, 121.1, 73.3, 71.8, 69.7, 52.0, 51.8, 39.5, 29.5. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_7$ [M + H]$^+$: 363.1187. Found: 363.1190.

Methyl 2-((2*R*,4a*S*,12a*S*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 14d. Treatment of **13d** (6.3 g, 10.2 mmol, 1.0 equiv) with CsF (20.0 g, 132.0 mmol, 13.0 equiv) in DMF (800 mL) afforded **14d** (2.7 g, 7.5 mmol, 73% yield) as a yellow foamy solid. $[\alpha]_D^{20}$ −63.9 (c 1.2, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3008, 2947, 1735, 1635, 1518, 1438, 1345, 1324, 1255, 1093. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.14 (dd, J = 9.1, 2.8 Hz, 1H), 7.06 (d, J = 9.1 Hz, 1H), 5.99 (d, J = 10.4 Hz, 1H), 5.89 (d, J = 10.5 Hz, 1H), 4.82 (br s, 1H), 4.51−4.19 (m, 3H), 3.80 (d, J = 9.8 Hz, 1H), 3.72 (s, 3H), 2.99 (s, 3H), 2.73 (dd, J = 15.1, 9.1 Hz, 1H), 2.59 (dd, J = 15.0, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.4, 161.1, 142.2, 131.7, 129.6, 126.7, 124.7, 122.0, 120.9, 70.6, 69.2, 67.8, 52.0, 51.8, 38.4, 29.7. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_7$ [M + H]$^+$: 363.1187. Found: 363.1193.

Methyl 2-((2*R*,4a*R*,12a*S*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 4a. To a solution of **14a** (6.3 g, 17.5 mmol, 1.0 equiv) in THF:MeOH (3:1, 175 mL) under N_2 was added palladium on carbon (10 wt %, 0.5 g, 4.4 mmol, 0.3 equiv). The solution was purged with H_2 for 30 min, and the mixture was stirred overnight at rt under an atmosphere of H_2 (balloon). Celite was added to the reaction mixture, and after 30 min, the crude material was filtered through a plug of Celite and rinsed with a solution of 10% MeOH in CH_2Cl_2 (50 mL). The solvents were removed in vacuo, and the residue was purified by silica gel chromatography (gradient: 0−7% MeOH in CH_2Cl_2). Aniline **4a** was isolated as a red-brown powder (5.8 g, 17.4 mmol, 99% yield). $[\alpha]_D^{20}$ +21.6 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3434, 3347, 2950, 2895, 1732, 1612, 1494, 1436, 1201, 1045. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72−6.53 (m, 3H), 4.07 (d, J = 3.0 Hz, 1H), 4.05 (s, 1H), 3.84−3.99 (m, 1H), 3.84−3.72 (m, 2H), 3.68 (s, 3H), 3.58 (br s, 2H), 3.24 (s, 3H), 2.57 (dd, J = 15.5, 7.4 Hz, 1H), 2.44 (dd, J = 15.5, 5.3 Hz, 1H), 2.18−1.96 (m, 2H), 1.96−1.76 (m, 1H), 1.77−1.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.8, 147.6, 139.8, 121.1, 119.8, 119.5, 117.2, 78.8, 74.6, 65.2, 51.9, 50.6, 41.3, 32.1, 27.3, 24.2. HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ [M + Na]$^+$: 357.1421. Found: 357.1427.

Methyl 2-((2*S*,4a*R*,12a*S*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 4b. Compound **4b** was prepared using the above protocol starting from **14b** (6.0 g, 16.4 mmol, 1.0 equiv) and Pd/C (10 wt %, 0.4 g, 4.1 mmol, 0.3 equiv) in THF:MeOH (3:1, 165 mL). The reaction provided, after purification, 5.2 g (94%) of **4b** as a red-brown powder. $[\alpha]_D^{20}$ +41.2 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3347, 2950, 1731, 1610, 1493, 1396, 1205, 1022. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 6.70 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 8.6, 2.5 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 4.66 (br s, 2H), 4.17−4.04 (m, 3H), 3.98 (dd, J = 12.9, 11.0 Hz, 1H), 3.71−3.66 (m, 1H), 3.61 (s, 3H), 3.14 (s, 3H), 2.58 (dd, J = 14.9, 7.8 Hz, 1H), 2.47 (dd, J = 15.1, 5.5 Hz, 1H), 1.85 (br app t, J = 15.0 Hz, 2H), 1.58 (br d, J = 8.1 Hz, 1H), 1.46−1.37 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C): δ 171.1, 169.4, 146.5, 143.7, 120.8, 118.5 (2), 114.7, 69.6, 68.8, 68.1, 57.1, 51.5, 39.4, 34.8, 28.3, 22.5. HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ [M + Na]$^+$: 357.1421. Found: 357.1426.

Methyl 2-((2*R*,4a*S*,12a*S*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 4c. Compound **4c** was prepared as described above starting from **14c** (6.3 g, 17.5 mmol, 1.0 equiv) and Pd/C (10 wt %, 0.5 g, 4.4 mmol, 0.3 equiv) in THF:MeOH (3:1, 180 mL). The reaction provided, after purification, 5.8 g (99%) of **4c** as a red-brown powder. $[\alpha]_D^{20}$ −32.0 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3427, 3349, 2951, 2873, 1733, 1616, 1493, 1436, 1202, 1091. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (d, J = 2.7 Hz, 1H), 6.79 (dd, J = 9.0 Hz, 1H), 6.69 (dd, J = 8.7, 2.8 Hz, 1H), 4.18 (dd, J = 13.8, 1.6 Hz, 1H), 4.06 (dd, J = 13.8, 1.9 Hz, 1H), 3.93−3.70 (m, 4H), 3.67 (s, 3H), 3.60 (d, J = 10.6 Hz, 1H), 3.01 (s, 3H), 2.65 (dd, J = 16.0, 7.1 Hz, 1H), 2.42 (dd, J = 16.0, 5.8 Hz, 1H), 2.02−1.75 (m, 3H), 1.39 (ddd, J = 24.3, 11.3, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.9, 149.8, 140.1, 121.7, 120.5, 120.1, 117.9, 76.4, 74.1, 68.5, 53.2, 51.8, 40.5, 30.6, 28.7, 27.0. HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ [M + Na]$^+$: 357.1421. Found: 357.1419.

Methyl 2-((2*S*,4a*S*,12a*S*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[b]pyrano[3,2-f][1,5]-oxazocin-2-yl)acetate 4d. Compound **4d** was prepared using the above protocol starting from **14d** (6.1 g, 17.0 mmol, 1.0 equiv) and Pd/C (10 wt %, 0.5 g, 4.2 mmol, 0.3 equiv) in THF:MeOH (3:1, 170 mL). The reaction provided, after purification, 5.5 g (98%) of **4d** as a red-brown powder. $[\alpha]_D^{20}$ +10.4 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3437, 3350, 2950, 1733, 1623, 1493, 1437, 1206, 1095. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (dd, J = 5.7, 2.9 Hz, 2H), 6.61 (dd, J = 8.8, 2.7 Hz, 1H), 4.42−4.30 m, 1H), 4.11 (d, J = 13.6 Hz, 1H), 3.89 (d, J = 13.5 Hz, 1H), 3.72 (d, J = 3.2 Hz, 2H), 3.60 (s, 3H), 3.48 (br s, 2H), 2.95 (s, 3H), 2.76 (dd, J = 14.4, 9.1 Hz, 1H), 2.41 (dd, J = 14.5, 6.0 Hz, 1H), 1.99−1.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.6, 149.6, 140.7, 128.4, 122.5, 120.7, 119.9, 117.4, 69.6, 69.2, 68.8, 53.8, 52.0, 36.5, 28.6, 27.6, 22.0. HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ [M + Na]$^+$: 357.1421. Found: 357.1419.

Methyl 2-((2*R*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 15a. A solution of **2a** (17.1 g, 38.9 mmol, 1.0 equiv) in MeOH (389 mL) was degassed for 20 min by sparging with dry N_2. To the solution was added $Pd(OH)_2$/C (20% by weight, 2.73 g, 3.89 mmol, 0.1 equiv), and the suspension was sparged with H_2 for 20 min before being placed under a static atmosphere of H_2 (balloon) at rt while stirring for 20 h. Upon completion of the reaction (LC−MS), the mixture was filtered through Celite. The filter cake was washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure to provide 16.45 g of crude product (96%), which was used in the next step without further purification. The crude material from above 16.45 g (37.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (372 mL) at 0 °C (ice/water bath), and to this solution was added sequentially Et_3N (15.7 mL, 112 mmol, 3.0 equiv), DMAP (0.46 g, 3.72 mmol, 0.1 equiv) and 2-nitrobenzenesulfonyl chloride (12.38 g, 55.9 mmol, 1.5 equiv). The reaction was stirred at 0 °C for 15 min before removing the ice bath and stirring for an additional 100 min. When the reaction was deemed complete by LC−MS, the reaction was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 0−40% EtOAc in hexanes),

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which provided 19.0 g (82%) of **15a** as a yellow foamy solid. $[\alpha]_D^{20}$ −18.9 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2931 (w), 2857 (w), 1737 (m), 1540 (s), 1427 (m), 1352 (s), 1165 (s), 1111 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 8.12−8.00 (m, 1H), 7.73−7.65 (m, 1H), 7.66−7.55 (m, 4H), 7.50 (dd, *J* = 3.4, 5.9 Hz, 2H), 7.48−7.32 (m, 6H), 5.81 (d, *J* = 8.7 Hz, 1H), 3.95−3.77 (m, 2H), 3.63 (s, 3H), 3.59 (d, *J* = 5.6 Hz, 1H), 3.48−3.35 (m, 1H), 3.38 (dd, *J* = 5.9, 10.5 Hz, 1H), 2.55 (dd, *J* = 7.2, 15.6 Hz, 1H), 2.39 (dd, *J* = 5.5, 15.6 Hz, 1H), 1.88 (d, *J* = 13.6 Hz, 1H), 1.71 (brs, 1H), 1.63−1.46 (m, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 147.4, 135.4, 135.4, 135.1, 133.1, 133.1, 133.0, 132.7, 129.9, 129.6, 129.6, 127.6, 127.6, 125.1, 80.1, 74.6, 63.4, 51.6, 49.2, 40.7, 29.3, 26.6, 25.3, 19.0. HRMS (ESI) calcd for $C_{31}H_{38}N_2NaO_8SSi$ $[M + Na]^+$: 649.2016. Found: 649.2012.

Methyl 2-((2*S*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 15b. Compound **15b** was prepared using the above protocol from **2b** (21 g, 47.7 mmol, 1.0 equiv) in MeOH (477 mL) and $Pd(OH)_2/C$ (20% by weight, 3.35 g, 4.77 mmol, 0.1 equiv), which provide 20.1 g of crude saturated amine (96%), which was used in the next step without further purification. The crude material from above (20.13 g, 45.6 mmol, 1.0 equiv) was subjected to a nosylation using CH_2Cl_2 (456 mL), Et_3N (19.22 mL, 137 mmol, 3.0 equiv), DMAP (0.55 g, 4.56 mmol, 0.1 equiv) and 2-nitrobenzenesulfonyl chloride (15.15 g, 68.4 mmol, 1.5 equiv), which provided, after purification, 23.6 g (83%) of **15b** as a yellow foamy solid. $[\alpha]_D^{20}$ +22.6 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2932 (w), 2858 (w), 1736 (s), 1541 (s), 1427 (m), 1360 (s), 1168 (s), 1111 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 8.11−8.00 (m, 1H), 7.71−7.63 (m, 1H), 7.63−7.49 (m, 6H), 7.40 (dt, *J* = 13.7, 6.7 Hz, 6H), 5.86 (d, *J* = 7.8 Hz, 1H), 4.33 (t, *J* = 6.9 Hz, 1H), 3.85−3.72 (m, 2H), 3.61 (obscured s, 2H), 3.59 (s, 3H), 2.64 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.41 (dd, *J* = 14.8, 6.5 Hz, 1H), 2.03−1.69 (m, 3H), 1.43−1.30 (m, 1H), 1.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 147.8, 135.7, 135.0, 133.4, 133.1, 133.0, 132.9, 130.4, 130.0, 129.9, 127.9, 125.3, 73.0, 69.2, 63.4, 51.8, 50.5, 37.6, 26.9, 25.8, 25.2, 19.2. HRMS (ESI) calcd for $C_{31}H_{38}N_2NaO_8SSi$ $[M + Na]^+$: 649.2016. Found: 649.2012.

Methyl 2-((2*R*,5*R*,6*S*)-6-(hydroxymethyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 16a. To a solution of **15a** (21.7 g, 34.6 mmol, 1.0 equiv) in THF (173 mL) at 0 °C (ice/water bath) in a plastic bottle was added HF·pyridine (70 wt %, 8.60 mL, 69.2 mmol, 2.0 equiv). The reaction was stirred, slowly warming to rt overnight for 20 h. The reaction was deemed complete by TLC and subsequently quenched with TMSOMe (38.2 mL, 277 mmol, 8.0 equiv). The mixture was stirred for an additional 30 min and then diluted with EtOAc and washed with aqueous saturated copper sulfate solution (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (gradient: 0−100% EtOAc in hexanes) to provide 12.1 g (90%) of **16a** as a pale yellow foamy solid. $[\alpha]_D^{20}$ −107.9 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3278 (w), 2953 (w), 1728 (m), 1541 (s), 1442 (m), 1344 (m), 1164 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 3.4, 5.8 Hz, 1H), 7.86 (dd, *J* = 3.5, 5.8 Hz, 1H), 7.80−7.73 (m, 2H), 5.83 (d, *J* = 9.0 Hz, 1H), 3.90−3.79 (m, 1H), 3.69 (s, 4H), 3.67−3.59 (m, 2H), 3.58−3.40 (m, 1H), 2.59 (dd, *J* = 7.3, 15.7 Hz, 1H), 2.43 (dd, *J* = 5.5, 15.8 Hz, 1H), 2.23−2.13 (m, 1H), 1.79−1.63 (m, 2H), 1.62−1.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 147.7, 134.5, 133.6, 132.9, 130.4, 125.3, 79.3, 74.4, 62.0, 51.7, 48.8, 40.6, 28.7, 25.4. HRMS (ESI) calcd for $C_{15}H_{20}N_2NaO_8S$ $[M + Na]^+$: 411.0838. Found: 411.0844.

Methyl 2-((2*S*,5*R*,6*S*)-6-(hydroxymethyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 16b. Compound **16b** was prepared following the above protocol using a solution of **15b** (23.59 g, 37.6 mmol, 1.0 equiv), THF (188 mL), HF·pyridine (70 wt %, 7.0 mL, 56.5 mmol, 1.5 equiv), TMSOMe (41.5 mL, 300 mmol, 8.0 equiv), which provided, after purification, 13.59 g (93%) of **16b** as a pale yellow foamy solid. $[\alpha]_D^{20}$ +23.3 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3395 (w), 2932 (w), 2857 (w), 1737 (m), 1541 (s), 1427 (m), 1360 (s), 1168 (s), 1112 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 5.9, 3.3 Hz, 1H), 7.84 (dd, *J* = 7.5, 3.8 Hz, 1H), 7.73 (dd, *J* = 5.7, 3.3 Hz, 2H), 5.76 (br s, 1H), 4.23−4.11 (m, 1H), 3.95−3.76 (m, 2H), 3.76−3.50 (m, 2H), 3.66 (s, 3H), 2.72 (br d, *J* = 6.1 Hz, 1H), 2.61 (dd, *J* = 15.9, 9.4 Hz, 1H), 2.42 (dd, *J* = 15.9, 4.4 Hz, 1H), 1.93−1.59 (m, 3H), 1.48−1.31 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 147.9, 134.3, 133.9, 133.1, 130.7, 125.6, 73.0, 67.1, 59.4, 52.1, 50.5, 37.9, 26.8, 25.7. HRMS (ESI) calcd for $C_{15}H_{21}N_2O_8S$ $[M + H]^+$: 389.1019. Found: 389.1022.

Methyl 2-((1*R*,3*R*,6*R*)-7-((2-nitrophenyl)sulfonyl)-2-oxa-7-azabicyclo[4.2.0]octan-3-yl)acetate 5a. To a solution of alcohol **16a** (12.1 g, 31.2 mmol, 1.0 equiv) and PPh_3 (16.3 g, 62.3 mmol, 2.0 equiv) in THF (312 mL) at 0 °C (ice/water bath) was added DIAD (13.5 mL, 68.5 mmol, 2.2 equiv) dropwise over 5 min. The reaction was stirred, slowly warming to rt over 1 h until the reaction was deemed complete by LC−MS. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 0−100% EtOAc in hexanes), to afford 9.84 g (85%) of **5a** as a white foamy solid. $[\alpha]_D^{20}$ −108.6 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2952 (w), 1736 (m), 1544 (s), 1371 (m), 1168 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.86−7.73 (m, 2H), 7.66 (d, *J* = 9.0 Hz, 1H), 4.28 (brs, 1H), 4.23 (t, *J* = 4.8 Hz, 1H), 3.93 (dd, *J* = 4.6, 8.5 Hz, 1H), 3.67 (s, 4H), 3.61 (d, *J* = 8.6 Hz, 1H), 2.58 (dd, *J* = 8.0, 15.8 Hz, 1H), 2.44 (dd, *J* = 4.8, 15.7 Hz, 1H), 2.18 (d, *J* = 11.6 Hz, 1H), 1.76 (dd, *J* = 8.5, 17.4 Hz, 2H), 1.55 (d, *J* = 9.4 Hz, 1H), 1.24 (t, *J* = 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 148.7, 134.0, 131.6, 130.9, 129.7, 124.1, 70.6, 66.5, 60.7, 57.2, 51.6, 40.8, 25.3, 24.6. HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_7S$ $[M + Na]^+$: 393.0732. Found: 393.0730.

Methyl 2-((1*R*,3*S*,6*R*)-7-((2-nitrophenyl)sulfonyl)-2-oxa-7-azabicyclo[4.2.0]octan-3-yl)acetate 5b. Compound **5b** was obtained following the above procedure using **16b** (13.53 g, 34.8 mmol, 1.0 equiv) PPh_3 (18.27 g, 69.7 mmol, 2.0 equiv), DIAD (15.1 mL, 77.0 mmol, 2.2 equiv) in THF (348 mL). Purification of the reaction mixture afforded 11.46 g (89%) of **5b** as a white foamy solid. $[\alpha]_D^{20}$ −86.2 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2952 (w), 1735 (m), 1544 (s), 1371 (m), 1168 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 7.2, 3.2 Hz, 1H), 7.75−7.64 (m, 2H), 7.64−7.56 (m, 1H), 4.56−4.39 (m, 2H), 4.31 (td, *J* = 6.3, 2.7 Hz, 1H), 4.05 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.94 (dd, *J* = 9.3, 2.6 Hz, 1H), 3.61 (s, 3H), 2.53 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.38 (dd, *J* = 15.2, 4.9 Hz, 1H), 2.08−1.81 (m, 3H), 1.44−1.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 148.5, 134.1, 131.9, 130.7, 130.5, 124.2, 67.1, 63.5, 61.9, 56.3, 51.7, 39.4, 23.4, 21.4. HRMS (ESI) calcd for $C_{15}H_{19}N_2O_7S$ $[M + H]^+$: 371.0913. Found: 371.0913.

Methyl 2-((2*R*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 15c. To allylic amine **2c** (4.5 g, 10.2 mmol) under Ar was added ethanol (100 mL) and Pd/C (10 wt %, 0.1 g, 1.0 mmol, 0.1 equiv). The solution was subsequently purged with H_2 (balloon) for 10 min and left to stir under the H_2 atmosphere for 16 h. The reaction mixture was then filtered through Celite, and the filter cake was washed with CH_2Cl_2 (3 × 75 mL). The filtrate was then concentrated to give the primary amine, which was used in the next reaction without further purification. To a solution of the saturated primary amine (4.5 g, 10.2 mmol, 1.0 equiv) in CH_2Cl_2 (41 mL) was added Et_3N (1.7 mL, 12.2 mmol, 1.2 equiv) followed by 2-nitrobenzenesulfonyl chloride (2.5 g, 11.2 mmol, 1.1 equiv). The reaction was stirred at rt until analysis of the reaction mixture by LC−MS showed that all starting material had been consumed (∼1 h). The reaction was quenched with a saturated solution of aqueous ammonium chloride (100 mL). The organic layer was separated, and the aqueous layer was then washed with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 5−50% EtOAc in hexanes), which provided 5.5 g (86%) of **15c** as a yellow foamy solid. $[\alpha]_D^{22}$ +8.3 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3327, 2932, 2857, 1734, 1542, 1437, 1362, 1188, 1168, 1112. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 6.9 Hz, 1H), 8.04−7.97 (m, 1H), 7.80−7.27 (m, 13H), 5.26 (d, *J* = 8.3 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 1H), 3.82−3.70 (m, 2H), 3.62 (s, 3H), 3.43 (s, 1H), 3.30 (s, 1H), 2.44 (ddd, *J* =

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20.9, 15.5, 6.4 Hz, 2H), 1.96 (d, J = 12.1 Hz, 1H), 1.68 (d, J = 11.9 Hz, 1H), 1.48 (s, 1H), 1.41−1.34 (m, 2H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 147.8, 135.9, 135.8, 134.89, 134.86, 133.9, 133.55, 133.48, 133.0, 132.4, 131.3, 130.6, 129.9, 129.67, 129.62, 127.9, 127.7, 127.7, 125.4, 124.9, 81.0, 76.8, 73.8, 69.1, 63.9, 51.8, 50.9, 40.8, 31.8, 30.6, 26.9, 26.7, 22.1, 19.4, 14.9. HRMS (ESI+) calcd for $C_{31}H_{38}N_2NaO_8SSi$ $[M + Na]^+$: 649.2016. Found: 649.2020.

Methyl 2-((2*S*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 15d. Compound **15d** was prepared as described above using allylic amine (*R*,*S*,*S*)-**2d** (41.4 g, 94 mmol) and 10% Pd/C (10.0 g, 9.42 mmol, 0.1 equiv) in MeOH (942 mL). The resulting crude amine (42.0 g, 95.0 mmol) was treated with Et_3N (15.9 mL, 114 mmol, 1.2 equiv) and 2-nitrobenzenesulfonyl chloride (23.2 g, 105 mmol, 1.1 equiv) in CH_2Cl_2 (476 mL) to afford 54.9 g (92%) of the desired amine **15d** as a yellow foamy solid. $[\alpha]_D^{22}$ −50.6 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3361, 2932, 2858, 1733, 1541, 1427, 1361, 1166, 1111. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13−8.01 (m, 1H), 7.86−7.77 (m, 1H), 7.65 (dd, J = 11.2, 4.3 Hz, 1H), 7.60−7.48 (m, 5H), 7.46−7.30 (m, 6H), 5.97 (d, J = 8.2 Hz, 1H), 3.99−3.65 (m, 5H), 3.62 (s, 4H), 2.42 (ddd, J = 20.9, 15.5, 6.3 Hz, 2H), 1.73 (s, 2H), 1.53 (s, 2H), 1.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 147.9, 135.6, 135.5, 134.7, 133.5, 133.0, 132.9, 132.9, 130.7, 130.0, 129.9, 127.9, 127.8, 125.4, 77.0, 68.0, 61.8, 51.7, 48.8, 40.4, 26.9, 25.2, 24.3, 19.2. HRMS (ESI) calcd for $C_{31}H_{38}N_2NaO_8SSi$ $[M + Na]^+$: 649.2016. Found: 649.2011.

Methyl 2-((2*R*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitro-*N*-((*R*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 18a. To a solution of sulfonamide **15c** (6.5 g, 10.4 mmol, 1.0 equiv) in 1,2-dichloroethane (42 mL) was added cesium carbonate (13.5 g, 41.5 mmol, 4.0 equiv) followed by (*S*)-glycidyl triflate [(*S*)-**17**] (4.3 g, 20.7 mmol, 2.0 equiv). The reaction mixture was stirred at rt until deemed completion (~1 h) and then quenched with 100 mL of a saturated solution of aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was then washed with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 5−55% EtOAc in hexanes), which provided 6.4 g (90%) of pure **18a** as a yellow oil. $[\alpha]_D^{22}$ −10.3 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2932, 2857, 1740, 1545, 1437, 1373, 1265, 1113. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 9.0 Hz, 1H), 7.70−7.31 (m, 13H), 3.90−3.27 (m, 7H), 3.62 (s, 3H), 3.05 (dd, J = 6.1, 14.9 Hz, 1H), 2.94 (bs, 1H), 2.76 (t, J = 3.1 Hz, 1H), 2.58−2.47 (m, 2H), 2.38 (dd, J = 6.1, 17.8 Hz, 1H), 1.83−1.70 (m, 2H), 1.48−1.35 (m, 1H), 0.97 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 147.6, 135.8, 135.7, 133.8, 131.7, 131.3, 129.6, 129.5, 127.6, 124.2, 79.6, 73.4, 63.9, 51.7, 51.3, 46.3, 40.7, 39.5, 31.5, 27.5, 26.8, 19.2. HRMS (ESI+) calcd for $C_{34}H_{42}N_2NaO_9SSi$ $[M + Na]^+$: 705.2278. Found: 705.2299.

Methyl 2-((2*R*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitro-*N*-((*S*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 18b. Following the above protocol, **15c** (15.9 g, 50.8 mmol, 1.0 equiv) was treated with (*R*)-glycidyl triflate [(*R*)-**17**] (10.5 g, 50.8 mmol, 2.0 equiv), cesium carbonate (33.1 g, 102 mmol, 4.0 equiv) in 1,2-dichloroethane (100 mL). The reaction provided, after purification, 15.0 g (93%) of **18b** as a yellow oil. $[\alpha]_D^{22}$ −86.8 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 2956, 2931, 2857, 1741, 1544, 1428, 1356, 1264, 1164, 1112. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 8.4 Hz, 4H), 7.43−7.32 (m, 8H), 7.15 (d, J = 8.4 Hz, 1H), 4.41 (dd, J = 12.1, 3.2 Hz, 1H), 4.03 (dd, J = 12.1, 6.1 Hz, 1H), 3.91−3.69 (m, 2H), 3.58 (s, 3H), 3.41 (d, J = 11.2 Hz, 1H), 3.39−3.29 (m, 1H), 3.26−3.17 (m, 1H), 3.08−3.02 (m, 1H), 2.82 (dt, J = 9.0, 4.5 Hz, 2H), 2.66 (dd, J = 4.8, 2.6 Hz, 1H), 2.60−2.37 (m, 3H), 2.29−1.95 (m, 1H), 1.84 (d, J = 13.3 Hz, 1H), 1.48 (d, J = 12.4 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 155.0, 147.3, 135.9, 135.8, 133.7, 133.5, 132.9, 131.8, 131.4, 129.8, 129.7, 127.8, 127.7, 124.4, 80.0, 79.2, 74.1, 68.7, 63.7, 55.2, 51.9, 49.1, 47.9, 46.7, 44.73, 40.9, 31.8, 29.4, 26.8, 19.3. HRMS (ESI+) calcd for $C_{34}H_{43}N_2O_9SSi$ $[M + H]^+$: 683.2459. Found: 683.2468.

Methyl 2-((2*S*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitro-*N*-((*R*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 18c. Following the above protocol, (*S*,*S*,*S*)-**15d** (10.0 g, 16.0 mmol, 1.0 equiv) was treated with (*S*)-glycidyl triflate [(*S*)-**17**] (6.6 g, 31.9 mmol, 2.0 equiv), cesium carbonate (20.8 g, 63.8 mmol, 4.0 equiv) in DCE (64 mL). The reaction provided, after purification, 10.1 g (93%) of **18c** as a yellow oil. $[\alpha]_D^{22}$ +3.2 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2931, 2857, 1734, 1543, 1360, 1165, 1110, 1006. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (dd, J = 7.3, 1.5 Hz, 1H), 7.71−7.57 (m, 4H), 7.57−7.46 (m, 2H), 7.45−7.28 (m, 7H), 4.43 (s, 1H), 4.06−3.93 (m, 1H), 3.92−3.66 (m, 3H), 3.62 (s, 3H), 3.49 (dd, J = 11.1, 6.6 Hz, 1H), 3.01 (dd, J = 15.8, 7.0 Hz, 1H), 2.93−2.71 (m, 2H), 2.67−2.48 (m, 2H), 2.13−1.84 (m, 2H), 1.79−1.52 (m, 2H), 1.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 147.8, 135.8, 135.8, 133.8, 133.7, 133.6, 133.2, 131.7, 131.3, 129.69, 129.61, 127.69, 127.65, 124.3, 72.8, 68.9, 64.3, 55.3, 51.8, 51.3, 47.9, 46.2, 36.4, 28.3, 26.9, 22.8, 19.3. HRMS (ESI) calcd for $C_{34}H_{42}N_2NaO_9SSi$ $[M + Na]^+$: 705.2278. Found: 705.2296.

Methyl 2-((2*S*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-5-(2-nitro-*N*-((*S*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 18d. Following the above protocol, **15d** (20.1 g, 32.0 mmol, 1.0 equiv) was treated with (*R*)-glycidyl triflate [(*R*)-**17**] (13.2 g, 64.0 mmol, 2.0 equiv), cesium carbonate (41.7 g, 128.0 mmol, 4.0 equiv) in DCE (128 mL). The reaction provided, after purification, 19.3 g (88%) **18d** as a yellow oil. $[\alpha]_D^{22}$ −74.5 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 2931, 2857, 1736, 1542, 1428, 1360, 1165, 1111. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.86 (m, 1H), 7.53 (dd, J = 15.6, 6.7 Hz, 4H), 7.46−7.29 (m, 8H), 4.54−4.40 (m, 1H), 3.96 (d, J = 16.4 Hz, 1H), 3.79 (t, J = 7.9 Hz, 1H), 3.63 (s, 3H), 3.40 (d, J = 10.7 Hz, 2H), 3.17−3.02 (m, 1H), 3.02−2.77 (m, 3H), 2.62 (dd, J = 15.2, 6.6 Hz, 1H), 2.56−2.48 (m, 1H), 2.46−2.14 (m, 2H), 2.04−1.90 (m, 2H), 1.78−1.59 (m, 1H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 147.4, 135.7, 133.65, 133.61, 133.4, 132.9, 131.6, 131.3, 129.8, 129.6, 127.76, 127.72, 124.3, 71.6, 69.2, 64.0, 55.0, 52.4, 51.8, 48.0, 46.4, 36.1, 28.5, 26.8, 24.8, 19.2. HRMS (ESI) calcd for $C_{34}H_{43}N_2O_9SSi$ $[M + H]^+$: 683.2459. Found: 683.2444.

Methyl 2-((2*R*,5*S*,6*S*)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*R*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 19a. To a solution of **18a** (5.6 g, 8.2 mmol, 1.0 equiv) in THF (41 mL) was added HF·pyridine (70 wt %, 6.1 mL, 49.2 mmol, 6.0 equiv) at rt. The reaction mixture was stirred at rt for 2 h. The mixture reaction was quenched with TMSOMe (17.0 mL, 123.0 mmol, 15.0 equiv), and stirring was continued for 1 h. The solvent was then removed under reduced pressure, and the crude residue was purified by chromatography on silica gel (gradient: 0−5% MeOH in CH_2Cl_2), which provided 2.8 g (77%) of **19a** as a foamy solid. $[\alpha]_D^{22}$ −22.6 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3436, 3350, 2933, 1689, 1609, 1450, 1396, 1241, 1193, 1081. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20−8.02 (m, 1H), 7.73−7.58 (m, 3H), 4.11−3.75 (m, 4H), 3.65 (s, 3H), 3.62−3.43 (m, 3H), 3.18−3.12 (m, 1H), 2.93−2.85 (m, 1H), 2.63−2.32 (m, 3H), 2.15−2.08 (m, 1H), 1.91−1.37 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 134.2, 132.0, 131.9, 130.9, 124.6, 124.3, 81.2, 78.3, 75.3, 74.6, 74.1, 70.3, 62.2, 51.9, 40.7, 31.7, 31.3, 28.7, 27.7. HRMS (ESI+) calcd for $C_{18}H_{25}N_2O_9S$ $[M + H]^+$: 445.1281. Found: 445.1288.

Methyl 2-((2*R*,5*S*,6*S*)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*S*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 19b. Following the above protocol, **18b** (11.0 g, 16.1 mmol, 1.0 equiv) was treated with HF·pyridine (70 wt %, 10.0 mL, 81.0 mmol, 5.0 equiv) in THF (81 mL). The reaction provided, after purification, 6.3 g (88%) of **19b** as a foamy solid. $[\alpha]_D^{22}$ −62.5 (c 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3485, 2951, 2874, 1732, 1541, 1373, 1349, 1260, 1163. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24−8.00 (m, 1H), 7.71−7.56 (m, 3H), 3.98 (dd, J = 16.3, 2.6 Hz, 1H), 3.88−3.76 (m, 1H), 3.64 (s, 4H), 3.61−3.39 (m, 3H), 3.19−3.11 (m, 2H), 2.96−2.81 (m, 2H), 2.60 (dd, J = 4.5, 2.6 Hz, 1H), 2.46 (ddd, J = 20.8, 15.5, 6.5 Hz, 2H), 2.18−1.98 (m, 2H), 1.87−1.79 (m, 2H), 1.59−1.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 147.7, 133.9, 133.1, 131.86, 131.83, 124.4, 78.1, 73.9, 62.0, 54.2, 51.8, 51.7, 47.6, 46.6, 40.4,

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31.5, 28.4. HRMS (ESI+) calcd for $C_{18}H_{25}N_2O_9S$ $[M + H]^+$: 445.1281. Found: 445.1281.

Methyl 2-((2*S*,5*S*,6*S*)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*R*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 19c. Following the above protocol, **18c** (10.0 g, 14.6 mmol, 1.0 equiv) was treated with HF·pyridine (70 wt %, 5.5 mL, 43.9 mmol, 3.0 equiv) in THF (146 mL). The reaction provided, after purification, 5.7 g (88%) of **19c** as a foamy solid. $[\alpha]_D^{22}$ +77.1 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3537, 2951, 1732, 1543, 1372, 1165. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.80−7.57 (m, 3H), 4.40 (s, 1H), 4.16 (d, *J* = 16.0 Hz, 1H), 4.03−3.91 (m, 1H), 3.89−3.70 (m, 2H), 3.67 (s, 3H), 3.24−3.06 (m, 1H), 3.00−2.72 (m, 3H), 2.71−2.41 (m, 3H), 2.08−1.80 (m, 2H), 1.76−1.55 (m, 2H), 1.53−1.35 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 148.0, 134.2, 132.0, 131.8, 124.5, 72.0, 69.0, 62.3, 54.3, 51.9, 51.8, 48.0, 46.1, 35.9, 28.3, 21.8. HRMS (ESI) calcd for $C_{18}H_{24}N_2NaO_9S$ $[M + Na]^+$: 467.1100. Found: 467.1108.

Methyl 2-((2*S*,5*S*,6*S*)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*S*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2*H*-pyran-2-yl)acetate 19d. Following the above protocol, **18d** (19.3 g, 28.3 mmol, 1.0 equiv) was treated with HF·pyridine (70 wt %, 10.5 mL, 85.0 mmol, 3.0 equiv) in THF (283 mL). The reaction provided, after purification, 9.9 g (79%) of **19d** as a foamy solid. $[\alpha]_D^{22}$ −57.8 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3500, 2951, 1731, 1541, 1439, 1348, 1163. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18−8.05 (m, 1H), 7.77−7.60 (m, 3H), 4.36 (s, 1H), 4.16 (d, *J* = 16.2 Hz, 1H), 3.92−3.75 (m, 1H), 3.62 (s, 4H), 3.47−3.31 (m, 1H), 3.25−3.07 (m, 2H), 3.03−2.78 (m, 3H), 2.72−2.61 (m, 1H), 2.54 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.39−2.16 (m, 1H), 2.08−1.88 (m, 3H), 1.80−1.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 147.8, 134.1, 133.1, 132.0, 131.9, 124.5, 70.8, 69.2, 61.8, 53.9, 52.2, 51.9, 48.1, 46.6, 35.9, 28.4, 24.3. HRMS (ESI) calcd for $C_{18}H_{24}N_2NaO_9S$ $[M + Na]^+$: 467.1100. Found: 467.1089.

Methyl 2-((3*R*,6a*S*,8*R*,10a*S*)-3-hydroxy-1-((2-nitrophenyl)-sulfonyl)decahydropyrano[2,3-c][1,5]oxazocin-8-yl)acetate 6a. To **19a** (5.0 g, 11.3 mmol) in CH_2Cl_2 (112 mL) was added BF_3-Et_2O (1.6 mL, 12.4 mmol, 1.1 equiv) at rt. After 2 h, the reaction was concentrated under reduced pressure to afford a light brown residue, which was purified by chromatography on silica gel (gradient: 40−90% EtOAc in hexanes) to provide 3.2 g (64%) of **6a** as a white powder. $[\alpha]_D^{22}$ +69.5 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3516, 2951, 2874, 1735, 1532, 1439, 1346, 1160, 1058. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.83−7.47 (m, 3H), 3.99−3.68 (m, 6H), 3.63 (s, 3H), 3.58−3.47 (m, 3H), 3.41−3.21 (m, 2H), 2.41 (ddd, *J* = 20.9, 15.5, 6.5 Hz, 2H), 1.68 (d, *J* = 16.3 Hz, 2H), 1.52−1.21 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 148.2, 134.4, 132.0, 131.1, 128.5, 124.4, 81.2, 77.4, 75.2, 73.4, 69.6, 58.8, 51.9, 51.8, 40.6, 31.4, 27.1. HRMS (ESI+) calcd for $C_{18}H_{25}N_2O_9S$ $[M + H]^+$: 445.1281. Found: 445.1276.

Methyl 2-((3*S*,6a*S*,8*R*,10a*S*)-3-hydroxy-1-((2-nitrophenyl)-sulfonyl)decahydropyrano[2,3-c][1,5]oxazocin-8-yl)acetate 6b. Following the above protocol, **19b** (6.0 g, 13.5 mmol, 1.0 equiv) was treated with BF_3-Et_2O (0.34 mL, 2.7 mmol, 0.2 equiv) in CH_2Cl_2 (270 mL). The reaction provided, after purification, 2.6 g (43%) of **6b** as a 9:1 mixture with **20b**. **6b** (white powder): $[\alpha]_D^{22}$ + 122.5 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film): 3436, 2951, 2871, 1734, 1536, 1439, 1372, 1351, 1185, 1065. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.73−7.62 (m, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 4.10−4.02 (m, 1H), 3.90−3.75 (m, 5H), 3.64 (s, 3H), 3.62−3.40 (m, 3H), 2.95 (b, 1H), 2.50 (dd, *J* = 15.5, 7.6 Hz, 1H), 2.35 (dd, *J* = 15.5, 5.3 Hz, 2H), 1.72−1.26 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 148.1, 134.2, 134.1, 131.9, 130.9, 128.5, 124.30, 80.9, 75.2, 74.6, 70.1, 58.7, 51.9, 47.9, 40.7, 31.3, 27.7. HRMS (ESI+) calcd for $C_{18}H_{25}N_2O_9S$ $[M + H]^+$: 445.1281. Found: 445.1271.

Methyl 2-((3*R*,6a*S*,8*S*,10a*S*)-3-hydroxy-1-((2-nitrophenyl)-sulfonyl)decahydropyrano[2,3-c][1,5]oxazocin-8-yl)acetate 6c. Following the general reaction protocol, **19c** (5.3 g, 11.8 mmol, 1.0 equiv) was treated with BF_3-Et_2O (0.30 mL, 2.4 mmol, 0.2 equiv) in CH_2Cl_2 (236 mL). The reaction provided, after purification, 2.8 g (53%) of **6c** as as a white powder. $[\alpha]_D^{22}$ +149.8 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3516, 2950, 1733, 1542, 1439, 1344, 1160. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.1 Hz, 1H), 7.80−7.56 (m, 3H), 4.47−4.23 (m, 1H), 4.00−3.71 (m, 4H), 3.67 (s, 3H), 3.63−3.43 (m, 3H), 2.80 (dd, *J* = 14.5, 8.2 Hz, 2H), 2.48 (dd, *J* = 14.5, 6.9 Hz, 2H), 2.05−1.80 (m, 2H), 1.69 (s, 1H), 1.59−1.45 (m, 1H), 1.42−1.15 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 148.2, 134.3, 131.9, 130.9, 128.4, 124.4, 77.3, 73.4, 73.2, 70.0, 69.5, 52.0, 35.9, 28.4, 23.1. HRMS (ESI) calcd for $C_{18}H_{24}N_2NaO_9S$ $[M + Na]^+$: 467.1100. Found: 467.1107.

Methyl 2-((3*S*,6a*S*,8*S*,10a*S*)-3-hydroxy-1-((2-nitrophenyl)-sulfonyl)decahydropyrano[2,3-c][1,5]oxazocin-8-yl)acetate 6d. Following the above protocol, **19d** (4.2 g, 9.5 mmol, 1.0 equiv) was treated with BF_3-Et_2O (0.24 mL, 1.9 mmol, 0.2 equiv) in CH_2Cl_2 (189 mL). The reaction provided, after purification, 2.35 g (56%) of **6d** as a 9:1 mixture with **20d** as a white powder: $[\alpha]_D^{22}$ +146.0 (*c* 1.0, $CHCl_3$). IR ν_{max} (cm^{-1}, film) 3432, 2950, 1732, 1542, 1439, 1371, 1348, 1161. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16−7.98 (m, 1H), 7.80−7.65 (m, 2H), 7.64−7.52 (m, 1H), 4.36 (dd, *J* = 13.7, 6.8 Hz, 1H), 4.17−3.98 (m, 1H), 3.97−3.70 (m, 4H), 3.66 (s, 3H), 3.63−3.39 (m, 3H), 3.03 (s, 1H), 2.83 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.57−2.28 (m, 2H), 1.97−1.82 (m, 1H), 1.80−1.43 (m, 2H), 1.42−1.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 148.0, 134.1, 134.0, 131.9, 130.8, 124.2, 74.4, 72.8, 70.0, 69.9, 59.1, 52.0, 35.9, 28.2, 23.6. HRMS (ESI) calcd for $C_{18}H_{25}N_2O_9S$ $[M + H]^+$: 445.1281. Found: 445.1293.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic information (CIF) for **3c**, **14b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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