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

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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 future diversification via amine capping and amide coupling. Scaffold diversity was evaluated in comparison to previously prepared scaffolds *via* 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 a common subunit in numerous 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**, 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 describes 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

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ring opening reactions. All skeletons resulting from these pathways retain functional handles that can be utilized for solid-phase library synthesis and future analog development.

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**) 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 pregabalin⁶ 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 metal⁸ afforded the desired aniline **9a-d** in good yield. Initial attempts to affect the 5-exo-trig radical cyclization of **9a** by treatment with excess amounts of *n*-Bu₃SnH 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*-Bu₃SnCl and AIBN in the presence of NaBH₃CN in *i*-PrOH¹⁰ resulted in the formation of the cyclized product with similar efficiency as when using excess *n*-Bu₃SnH. Notably, we were able to perform this reaction on multi-gram scale yielding >20 grams of 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. Based on observations by Smith and coworkers,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 successful, however, the S_NAr reaction was found to have moderate stereochemical dependency. On treatment with cesium fluoride in DMF at 35 °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 cesium fluoride 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 formation¹⁶ to yield [6,4] ring system **5** through an intramolecular Mitsunobu reaction. Starting from amines **2a-b**, the Mitsunobu precursor **16a-b** was obtained in three steps including hydrogenation, *N*-nosylation and TBDPS deprotection (Scheme 3). This material was then treated with PPh₃ 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 epoxide as synthons for the assembly of complex small molecules, including both natural products¹⁷ 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 by using the triflate derived from (*R*)- or (*S*)-glycidol (**17**)¹⁹ (Scheme 4). Liberation of the primary alcohol by TBDPS deprotection gave monocyclic compound **19**, the precursor to the epoxide-opening/ring closing reaction. Previous reports of epoxide-opening/ring closing reactions^{15c} have mainly focused on the formation of smaller ring systems with varying degrees of endo/exo selectivity. Although the 7-exo-tet cyclization²⁰ is favored based on Baldwin's rules, there is precedent for the 8-endo-tet cyclization to occur under basic conditions.²¹ After running 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**), mixtures of both the 7-(**20**) and 8-membered 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 BF₃·OEt₂ in either CH₂Cl₂ 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 effecting 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 are able to visualize the differences between the three collections and observed that the fused ring systems access different chemical space than 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 multi-gram 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 N₂ atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N₂ prior

to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to the footnoted references. ^1H and ^{13}C NMR spectra were recorded on 300 MHz 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 LCMS 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 $\times$ 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% to 15% EtOAc in hexanes), which provided 28.6 g (78%) of **8a** as a yellow oil. $[\alpha]_{\text{D}}^{20} +80.2$ (*c* 1.1, CHCl_3). IR ν_{max} (cm^{-1} , film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^1H 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 $\text{C}_{31}\text{H}_{34}\text{BrNNaO}_7\text{Si}$ [*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. $[\alpha]_{\text{D}}^{20} +49.7$ (*c* 1.0, CHCl_3). IR ν_{max} (cm^{-1} , film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ^1H 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 $\text{C}_{31}\text{H}_{34}\text{BrNNaO}_7\text{Si}$ [*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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₄BrNNaO₇Si [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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2930, 2856, 1740, 1582, 1519, 1478, 1343, 1272, 1113. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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, 112.6, 71.5, 69.6, 68.8, 62.1, 52.1, 37.5, 26.9, 19.3. HRMS (ESI+) calcd for C₃₁H₃₄BrNNaO₇Si [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 CH₂Cl₂, filtered over Celite and washed with CH₂Cl₂. After filtration, the solvent was removed *in vacuo*. The organic residue was dissolved in CH₂Cl₂ (300 mL) and then washed with water (2 × 200 mL), brine (100 mL) and dried over Na₂SO₄. After filtration, excess solvent was removed *in vacuo* to afford a crude residue, which was purified by chromatography on silica gel (gradient: 0% to 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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₆BrNNaO₅Si [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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₆BrNNaO₅Si [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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₆BrNNaO₅Si [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 CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2929, 2856, 1735, 1492, 1427, 1224, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₆BrNNaO₅Si [M+Na]⁺: 632.1444. Found: 632.1441.

Methyl 2-((1*R*,3*R*,4*aR*,9*aS*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4*a*,9*a*-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 NaBH₃CN (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 co-evaporated 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 MgSO₄, 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% to 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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₈NO₅Si [M+H]⁺: 532.2519. Found: 532.2516.

Methyl 2-((1*R*,3*S*,4*aR*,9*aS*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4*a*,9*a*-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 NaBH₃CN (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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₇NNaO₅Si [M+Na]⁺: 554.2339. Found: 554.2345.

Methyl 2-((1*R*,3*R*,4*aS*,9*aR*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4*a*,9*a*-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 NaBH₃CN (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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2930, 2856, 1736, 1488, 1428, 1217, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (125 MHz, CDCl₃) δ 171.7, 152.1, 140.2, 135.9, 135.8, 134.2, 133.8, 129.8, 129.7, 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 C₃₁H₃₇NNaO₅Si [M+Na]⁺: 554.2339. Found: 554.2341.

Methyl 2-((1*R*,3*S*,4*aS*,9*aR*)-6-amino-1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3,4,4*a*,9*a*-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 NaBH₃CN (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 $\text{C}_{31}\text{H}_{37}\text{NNaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 554.2339. Found: 554.2335.

Methyl 2-((1*R*,3*R*,4*aR*,9*aS*)-6-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4*a*,9*a*-tetrahydro-1H-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 $\times$ 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 then filtered and washed carefully with cold CH_2Cl_2 to give 4.7 g (72%) of the desired product **3a** as a white-grey 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, $\text{DMSO}-d_6$, 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, $\text{DMSO}-d_6$, 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 $\text{C}_{30}\text{H}_{30}\text{NO}_7$ $[\text{M}+\text{H}]^+$: 516.2022. Found: 516.2027.

Methyl 2-((1*R*,3*S*,4*aR*,9*aS*)-6-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4*a*,9*a*-tetrahydro-1H-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, $\text{DMSO}-d_6$, 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, $\text{DMSO}-d_6$, 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*,4*aR*,9*aR*)-6-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4*a*,9*a*-tetrahydro-1H-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*,4*aR*,9*aR*)-6-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-1-(hydroxymethyl)-3,4,4*a*,9*a*-tetrahydro-1H-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 HFpyridine (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-2H-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 aqueous 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 , filtered and concentrated to afford a crude material that was purified by silica gel chromatography (gradient: 0% to 30% EtOAc in hexanes) to afford **13a** as a pale yellow oil (18.0 g, 84% yield). $[\alpha]_{\text{D}}^{20} -42.7$ (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, $3\text{H} \times 0.2$), 3.66 (s, $3\text{H} \times 0.8$), 2.95 (s, $3\text{H} \times 0.2$), 2.69 (br s, $3\text{H} \times 0.8$), 2.63 – 2.43 (m, 2H), 1.06 (s, $9\text{H} \times 0.8$), 1.00 (s, $9\text{H} \times 0.2$). ^{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 $\text{C}_{33}\text{H}_{37}\text{FN}_2\text{NaO}_7\text{Si}$ $[\text{M}+\text{Na}]^+$: 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. $[\alpha]_{\text{D}}^{20} -96.8$ (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, $3\text{H} \times 0.2$), 2.82 – 2.69 (m, 1H), 2.74 (s, $3\text{H} \times 0.8$), 2.64 – 2.35 (m, 1H), 1.05 (s, $9\text{H} \times 0.8$), 0.97 (s, $9\text{H} \times 0.2$). ^{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 $\text{C}_{33}\text{H}_{37}\text{FN}_2\text{NaO}_7\text{Si}$ $[\text{M}+\text{Na}]^+$: 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). $[\alpha]_{\text{D}}^{20} +13.6$ (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, $1\text{H} \times 0.5$), 8.15 (m, $3\text{H} \times 0.5$), 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, $1\text{H} \times 0.5$), 5.65 (d, $J = 10.2$ Hz, $1\text{H} \times 0.5$), 5.25 (br d, $J = 8.2$ Hz, $1\text{H} \times 0.5$), 4.66 – 4.50 (m, 1H), 4.16 (br s, $1\text{H} \times 0.5$), 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). ¹³C NMR (75 MHz, CDCl₃, 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 C₃₃H₃₇FN₂NaO₇Si [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 CH₂Cl₂ (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. [α]_D²⁰ +40.3 (*c* 1.0, CHCl₃). IR ν_{max} (cm⁻¹, film): 2931, 2857, 1737, 1643, 1533, 1349, 1111. ¹H NMR (300 MHz, CDCl₃, 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₃H₃₇FN₂NaO₇Si [M+Na]⁺: 643.2252. Found: 643.2245.

Methyl 2-((2*S*,4*aR*,12*aS*)-5-methyl-8-nitro-6-oxo-2,4*a*,5,6,12,12*a*-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 (4h, 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 mmoles, 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 35 °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 (3x) and the combined organic phases were dried over Na₂SO₄, filtered and concentrated to afford a crude material that was purified on silica gel (gradient: 0% to 60% EtOAc in hexanes) to afford **14a** (3.7 g, 10.2 mmol, 50% yield) as a yellow foamy solid. [α]_D²⁰ –109.8 (*c* 1.1, CHCl₃). IR ν_{max} (cm⁻¹, film) 2995, 2947, 2856, 1736, 1632, 1518, 1436, 1343, 1256, 1085. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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*,4*aR*,12*aS*)-5-methyl-8-nitro-6-oxo-2,4*a*,5,6,12,12*a*-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) 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, 1343, 1306, 1257, 1104. 1H 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*,4*aS*,12*aS*)-5-methyl-8-nitro-6-oxo-2,4*a*,5,6,12,12*a*-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 35 °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% to 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. 1H 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*,4*aS*,12*aS*)-5-methyl-8-nitro-6-oxo-2,4*a*,5,6,12,12*a*-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. 1H 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*,4*aR*,12*aS*)-8-amino-5-methyl-6-oxo-2,3,4,4*a*,5,6,12,12*a*-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% to 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. 1H 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*,4*aR*,12*aS*)-8-amino-5-methyl-6-oxo-2,3,4,4*a*,5,6,12,12*a*-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. 1H 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*,4*aS*,12*aS*)-8-amino-5-methyl-6-oxo-2,3,4,4*a*,5,6,12,12*a*-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. 1H 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*,4*aS*,12*aS*)-8-amino-5-methyl-6-oxo-2,3,4,4*a*,5,6,12,12*a*-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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film) 3437, 3350, 2950, 1733, 1623, 1493, 1437, 1206, 1095. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₂N₂NaO₅ [M+Na]⁺: 357.1421. Found: 357.1419.

Methyl 2-((2*R*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2H-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 N₂. 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 H₂ for 20 min before being placed under a static an atmosphere of H₂ (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 CH₂Cl₂ 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 CH₂Cl₂ (372 mL) at 0 °C (ice/water bath), and to this solution was added sequentially Et₃N (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% to 40% EtOAc in hexanes), which provided 19.0 g (82%) of **15a** as a yellow foamy solid. $[\alpha]_D^{20} -18.9$ (*c* 1.0, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2931 (w), 2857 (w), 1737 (m), 1540 (s), 1427 (m), 1352 (s), 1165 (s), 1111 (s). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₈N₂NaO₈SSi [M+Na]⁺: 649.2016. Found: 649.2012.

Methyl 2-((2*S*,5*R*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2H-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 CH₂Cl₂ (456 mL), Et₃N (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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2932 (w), 2858 (w), 1736 (s), 1541 (s), 1427 (m), 1360 (s), 1168 (s), 1111 (s). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₈N₂NaO₈SSi [M+Na]⁺: 649.2016. Found: 649.2012.

Methyl 2-((2*R*,5*R*,6*S*)-6-(hydroxymethyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2H-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 MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (gradient: 0% to 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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 3278 (w), 2953 (w), 1728 (m), 1541 (s), 1442 (m), 1344 (m), 1164 (s). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₀N₂NaO₈S [M+Na]⁺: 411.0838. Found: 411.0844.

Methyl 2-((2*S*,5*R*,6*S*)-6-(hydroxymethyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2H-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, CHCl₃). IR $\nu_{\max}$ (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, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₂₁N₂O₈S [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 PPh₃ (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% to 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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2952 (w), 1736 (m), 1544 (s), 1371 (m), 1168 (s). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₁₈N₂NaO₇S [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) PPh₃ (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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 2952 (w), 1735 (m), 1544 (s), 1371 (m), 1168 (s). ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₁₉N₂O₇S [M+H]⁺: 371.0913. Found: 371.0913.

Methyl 2-((2*R*,5*S*,6*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(2-nitrophenylsulfonamido)tetrahydro-2H-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 H₂ (balloon) for 10 min and left to stir under the H₂ atmosphere for 16 h. The reaction mixture was then filtered through Celite and the filter cake was washed with CH₂Cl₂ (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 CH₂Cl₂ (41 mL) was added Et₃N (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 CH₂Cl₂ (2 × 100 mL). The combined organic layers were washed with brine, dried over MgSO₄ and filtered. The organic layer was concentrated under reduced pressure and the crude residue was purified by chromatography on silica gel (gradient: 5% to 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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 3327, 2932, 2857, 1734, 1542, 1437, 1362, 1188, 1168, 1112. ¹H NMR (300 MHz, CDCl₃) 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* = 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₈N₂NaO₈SSi [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 Et₃N (15.9 mL, 114 mmol, 1.2 equiv), and 2-nitrobenzenesulfonyl chloride (23.2 g, 105 mmol, 1.1 equiv) in CH₂Cl₂ (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, CHCl₃). IR $\nu_{\max}$ (cm^{–1}, film) 3361, 2932, 2858, 1733, 1541, 1427, 1361, 1166, 1111. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₁H₃₈N₂NaO₈SSi [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 the (*S*)-glycidyl triflate [(*S*)-**17**] (4.3 g, 20.7 mmol, 2.0 eq). 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 CH₂Cl₂ (2 × 100 mL). The combined organic layers were washed with brine, dried over MgSO₄ and filtered. The organic layer was concentrated under reduced pressure and the crude residue was purified by chromatography on silica gel (gradient: 5% to 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, CHCl₃). IR $\nu_{\max}$ (cm^{–1}, film): 2932, 2857, 1740, 1545, 1437, 1373, 1265, 1113. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₄H₄₂N₂NaO₉SSi [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, CHCl₃). IR $\nu_{\max}$ (cm^{–1}, film): 2956, 2931, 2857, 1741, 1544, 1428, 1356, 1264, 1164, 1112. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₄H₄₃N₂O₉SSi [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-2H-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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film) 2931, 2857, 1734, 1543, 1360, 1165, 1110, 1006. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₄H₄₂N₂NaO₉SSi [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-2H-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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film) 2931, 2857, 1736, 1542, 1428, 1360, 1165, 1111. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₃₄H₄₃N₂O₉SSi [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-2H-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% to 5% MeOH in CH₂Cl₂), which provided 2.8 g (77%) of **19a** as a foamy solid. $[\alpha]_D^{22} -22.6$ (*c* 1.0, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 3436, 3350, 2933, 1689, 1609, 1450, 1396, 1241, 1193, 1081. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₅N₂O₉S [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-2H-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, CHCl₃). IR

$\nu_{\max}$ (cm⁻¹, film): 3485, 2951, 2874, 1732, 1541, 1373, 1349, 1260, 1163. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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, 31.5, 28.4. HRMS (ESI+) calcd for C₁₈H₂₅N₂O₉S [M+H]⁺: 445.1281. Found: 445.1281.

Methyl 2-((2S,5S,6S)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*R*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2H-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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film) 3537, 2951, 1732, 1543, 1372, 1165. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄N₂NaO₉S [M+Na]⁺: 467.1100. Found: 467.1108.

Methyl 2-((2S,5S,6S)-6-(hydroxymethyl)-5-(2-nitro-*N*-((*S*)-oxiran-2-ylmethyl)phenylsulfonamido)tetrahydro-2H-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, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film) 3500, 2951, 1731, 1541, 1439, 1348, 1163. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄N₂NaO₉S [M+Na]⁺: 467.1100. Found: 467.1089.

Methyl 2-((3*R*,6*aS*,8*R*,10*aS*)-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 CH₂Cl₂ (112 mL) was added BF₃·Et₂O (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% to 90% EtOAc in hexanes) to provide 3.2 g (64%) of **6a** as a white powder. $[\alpha]_D^{22} +69.5$ (c 1.0, CHCl₃). IR $\nu_{\max}$ (cm⁻¹, film): 3516, 2951, 2874, 1735, 1532, 1439, 1346, 1160, 1058. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₅N₂O₉S [M+H]⁺: 445.1281. Found: 445.1276.

Methyl 2-((3*S*,6*aS*,8*R*,10*aS*)-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 BF₃-Et₂O (0.34 ml, 2.7 mmol, 0.2 equiv) in CH₂Cl₂ (270 mL). The reaction provided, after purification, 2.6 g (43%) of **6b** as a 9:1 mixture with **20b**. **6b** (white powder): [α]_D²² +122.5 (*c* 1.0, CHCl₃). IR ν_{max} (cm⁻¹, film): 3436, 2951, 2871, 1734, 1536, 1439, 1372, 1351, 1185, 1065. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₅N₂O₉S [M+H]⁺: 445.1281. Found: 445.1271.

Methyl 2-((3*R*,6*aS*,8*S*,10*aS*)-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 BF₃-Et₂O (0.30 ml, 2.4 mmol, 0.2 equiv) in CH₂Cl₂ (236 mL). The reaction provided, after purification, 2.8 g (53%) of **6c** as a white powder. [α]_D²² +149.8 (*c* 1.0, CHCl₃). IR ν_{max} (cm⁻¹, film) 3516, 2950, 1733, 1542, 1439, 1344, 1160. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄N₂NaO₉S [M+Na]⁺: 467.1100. Found: 467.1107.

Methyl 2-((3*S*,6*aS*,8*S*,10*aS*)-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 BF₃-Et₂O (0.24 ml, 1.9 mmol, 0.2 equiv) in CH₂Cl₂ (189 mL). The reaction provided, after purification, 2.35 g (56%) of **6d** as a 9:1 mixture with **20d** as a white powder: [α]_D²² +146.0 (*c* 1.0, CHCl₃). IR ν_{max} (cm⁻¹, film) 3432, 2950, 1732, 1542, 1439, 1371, 1348, 1161. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₅N₂O₉S [M+H]⁺: 445.1281. Found: 445.1293.

Supplementary Material

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

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

Scheme 1. Benzofuran formation *via* a 5-*exo*-trig cyclization.

Scheme 2. Tricyclic lactam formation *via* intramolecular $\text{S}_{\text{N}}\text{Ar}$.

Scheme 3. Azetidine formation *via* intramolecular Mitsunobu.

Scheme 4. Oxazacane formation *via* epoxide opening/ring-closing reaction.