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A Synthesis of (-)-Cytisine using a 6-*endo* aza-Michael Addition

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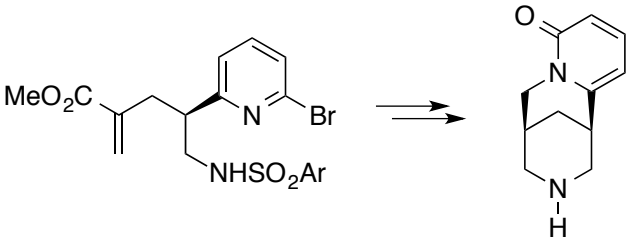

ABSTRACT: An asymmetric synthesis of (-)-cytisine has been achieved. The piperidine C-ring was formed using a stereodivergent intramolecular 6-*endo* aza-Michael addition. The B-ring was established by intramolecular pyridine *N*-alkylation. The absolute stereochemistry was established by an Evans acyl oxazolidinone enolate alkylation reaction that proceeded with an unexpected stereochemical outcome due to participation of the pyridine nitrogen lone pair.

Introduction

An asymmetric synthesis of (-)-cytisine has been achieved. The piperidine C-ring was formed using a stereodivergent intramolecular 6-*endo* aza-Michael addition. The B-ring was established by intramolecular pyridine *N*-alkylation. The absolute stereochemistry was established by an Evans acyl oxazolidinone enolate alkylation reaction that proceeded with an unexpected stereochemical outcome due to participation of the pyridine nitrogen lone pair.

Amongst the lupin alkaloids, cytisine **1** (Fig. 1) has received the most attention as it has been known for the longest time and has attracted attention due to its biological activities. This alkaloid has been the subject of a number of syntheses, the earliest of which is due to van Tamelen.[1] The chemistry of cytisine **1** has also been the subject of two reviews,[2] and a further synthesis has appeared since then.[3]

Van Tamelen's synthesis involved formation of a pyridinium salt to close the B-ring, and an intramolecular aza-Michael addition in a 6-*endo*-*trig* fashion to generate the C-ring by N-C2 bond formation. This addition involved the use of a vinyl pyridine as the Michael acceptor. We were interested in the use of a strategically quite distinct aza-Michael addition to form the N-C4 bond.[4] This particular disconnection appears underexploited.[2] In particular we were interested to understand the stereochemical outcome of this reaction and to know whether stereodivergent processes might be possible to form either the *cis* or *trans* disubstituted piperidines. A logical extension is to render this approach asymmetric.

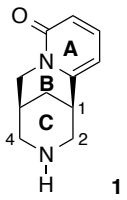

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FIGURE 1. Cytisine

Results and Discussion

Commercially available 2-bromo-6-methyl pyridine **2** was acylated on treatment with diethyl carbonate in the presence of base to give ester **3** (Scheme 1).[5] Alkylation of the corresponding enolate with 1-bromo-2-iodo-2-propene **4**[6] could then be easily achieved. The ester group was then reduced to give alcohol **6** which was converted into the toluene sulfonamide **8a** by a Mitsunobu-deacylation sequence.[7] Although the Mitsunobu reaction

proceeded excellently using di-*iso*-propylazodicarboxylate, separation of the product from the diacylhydrazine by-product was difficult and tedious. We, therefore, found it to be more practical to employ di-*t*-butylazodicarboxylate[8] and decompose the by-product by treatment with trifluoroacetic acid. We also prepared the corresponding *o*-nitrobenzene sulfonamide **8b**.[9,10] The only significant difference between the two series of reactions in the sequence was the unexpected lower reactivity of the nitro compounds in Mitsunobu reaction, converting **6b** to **8b**. At this point, the vinyl iodides **8** were converted into the required Michael acceptor. Palladium catalysed carbonylation at atmospheric pressure and at ambient temperature gave the acrylate derivatives **9ab** with no reaction observed at the bromine position.[11] We then attempted the base catalysed cyclisation (Table 1) of acrylate **9a**. While no reaction was observed using *i*-Pr_2NEt, treatment with DBU in THF at 60 °C gave a *ca.* 3:2 mixture of diastereoisomers of the piperidine products **10a** in favour of the *cis*-isomer (entry 1). The ratio increased to *ca.* 3:1 when the reaction was conducted in dioxane at reflux (entry 2). As the *cis* isomer would be expected to be the thermodynamic product, we were concerned that we might have reached the equilibrium position and further optimisation would be fruitless. Indeed, DFT calculations showed that the energy difference between the two isomers is 0.46 kcal/mol. This difference corresponds to the ratio obtained. We also examined the use of cesium carbonate in THF. At room temperature, an almost 1:1 ratio was obtained (entry 4). Lowering the temperature to -5°C gave a ca. 10:1 ratio in favour of the *trans* isomer of **10a** (entry 5). The intramolecular aza-Michael addition is, therefore, genuinely stereodivergent, giving different diastereoisomers as the major product under different conditions. Subsequently, however, we encountered difficulties in reproducing the result described in entry 5. We ascribe this to loss of activity of the cesium carbonate on repeated exposure to air, presumably due to hydration. Gratifyingly, a stereochemically similar result could be

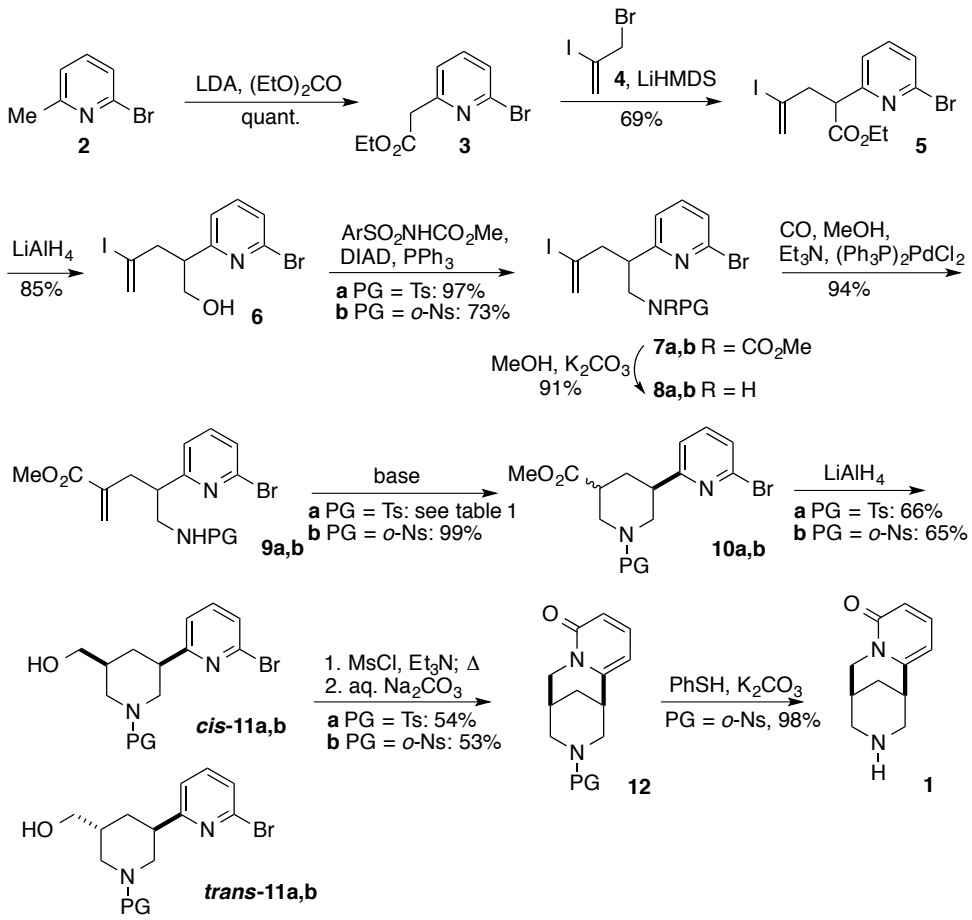
obtained using LHMDS in THF at 0°C (entry 6). The nosyl protected compound **9b** gave very similar results to the tosyl protected compound **9a** (entries 3 and 7).

While it is easily understood that the *cis*-isomer of piperidine **10** will be thermodynamically more stable, the fact that the *trans*-isomer is kinetically favoured is less obvious. This phenomenon has been explained by Zimmerman in terms of protonation of *exo*-cyclic enols from the less hindered face.[12]

TABLE 1. The Intramolecular aza-Michael addition

entry	substrate	base	solvent	temperature/ °C	*trans*: *cis* ratio
1	**9a**	DBU[a]	THF	60	38:62
2	**9a**	DBU[a]	dioxane	100	27:73[c]
3	**9b**	DBU[a]	dioxane	100	37:63[c]
4	**9a**	Cs_2CO_3[b]	THF	RT	43:57
5	**9a**	Cs_2CO_3[b]	THF	-5	91:9
6	**9a**	LiHMDS[b]	THF	0	95:5[c]
7	**9b**	LiHMDS[b]	THF	0	95:5[c]

a. 0.5 equiv.; b. 1 equiv.; c. the products were obtained quantitatively in both cases.



SCHEME 1. Synthesis of (±)-Cytisine.

The esters **10** were found to be unstable during column chromatography on silica gel. The corresponding alcohols in the tosyl series, **11a**, obtained by $LiAlH_4$ reduction, could be separated. The *cis* isomer of **11a** was found to be crystalline and we were able to obtain an X-ray structure to confirm the stereochemistry.[13] To proceed with the synthesis, however, separation of the alcohols **11** was unnecessary. This has already been shown by van Tamelen.[1] Treatment of the alcohols **11ab** with mesyl chloride gave the mesylates. In contrast to an earlier mesylation of a pyridyl alcohol in this laboratory,[14] spontaneous cyclisation was not observed, presumably due to the bis-equatorial conformation. Cyclisation of only the *cis* isomer occurred on warming to 60°C in chloroform. The resulting pyridinium salt was then hydrolysed under mildly basic conditions to generate the pyridone **12**.[15] The

unreacted *trans*-mesylate and the pyridone **12** were easily separable. Initially working with the toluene sulfonamide **12a**, we now faced the need to deprotect the piperidine nitrogen atom. Reduction with magnesium in methanol resulted in a complex mixture indicating that reduction of the pyridone was also occurring. As this deprotection proceeds via an SET mechanism, we arranged for the measurement of the reduction potentials of a pyridone and a sulfonamide by cyclic voltametry. *N*-Methylpyridone and *N*-tosyl piperidine were selected as model compounds for this study. Both compounds underwent irreversible reduction and to our disappointment, the reduction potentials differed by a mere 30 mV (see S.I.). We, therefore, concluded that we would be unable to achieve a selective reduction. The synthesis of cytisine **1** was completed using the *o*-nitrobenzene sulfonamide protected material **12b**. Deprotection was then achieved in excellent yield by treatment with thiophenol in the presence of base. The spectroscopic data for the synthetic (±)-cytisine **1** were in excellent agreement with published data.

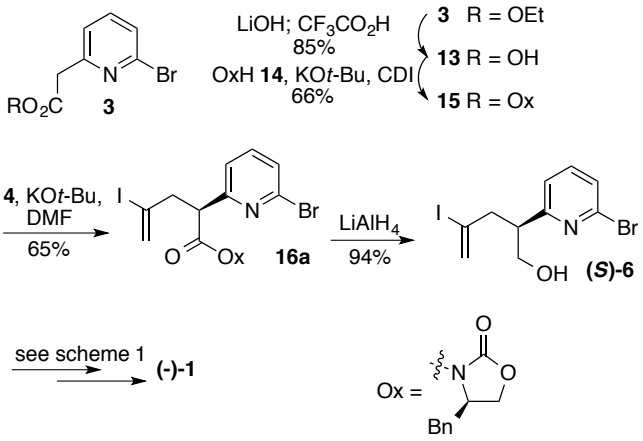
To convert our synthesis into an asymmetric synthesis, we returned to the ester alkylation step, intending to adapt this step using the methods of Evans (Scheme 2).[16] Ester **3** was hydrolysed using lithium hydroxide followed by precise neutralisation with trifluoroacetic acid. This careful control of reagent stoichiometry avoided the problems associated with the amphoteric nature of acid **13**. The resulting acid **13** was coupled with the (*R*)-oxazolidinone **14**. As formation of the acid chloride of **13** was challenging due to hydrochloride salt formation, we used carbonyl diimidazole to activate the acid group, followed by displacement with the potassium salt of oxazolidinone **14**. Pivaloyl chloride may also be employed and gives a similar yield. We then studied the diastereoselective alkylation of imide **15** with 1-bromo-2-iodo-2-propene **4** under various conditions (Table 2). It may be noted that, due to the presence of the pyridine moiety, weaker bases than those typically used in Evans chemistry can be used. No conversion to the product **16** was observed using

LiHMDS or NaHMDS in THF at temperatures from -78°C to -60°C (entries 1-4). When a reaction using LiHMDS was allowed to warm to room temperature, decomposition was observed (entry 5). Alkylation was observed at -40 °C (entries 6-14). Diastereoselectivity varied from 58:44 (entry 6) to 82:18 (entries 13, 14). Conversion varied from 33% in THF/toluene (entry 6) to 93% in DMF (entry 14), showing the importance of a polar solvent. The optimum result was obtained using KO*t*-Bu in DMF at -40°C (entry 14) giving the major diastereoisomer **16a** in 65% isolated yield. It may be noted that the diastereoselectivity is eroded when the reaction time is prolonged, indicating some epimerisation occurs under the reaction conditions.[17]

TABLE 2. Diastereoselective Alkylation of Acyl Oxazolidinone 15.

entry	base	solvent	temperature/ °C	time/h	conversion /%	dr
1	LiHMDS	THF	-60	20	0	-
2	NaHMDS	THF	-60	20	0	-
3	KO*t*-Bu	THF	-78	20	0	-
4	NaO*t*-Bu	THF	-60	20	0	-
5	LiHMDS	THF	-78 to 25	20	100	dec.
6	KO*t*-Bu	PhMe/THF	-40	20	33	58:44
7	KHMDS	THF	-40	20	78	67:33
8	KO*t*-Bu	THF	-40	20	70	67:33
9	NaHMDS	DME/THF	-40	17	55	69:31
10	KO*t*-Bu	Pyr/THF	-40	20	88	70:30

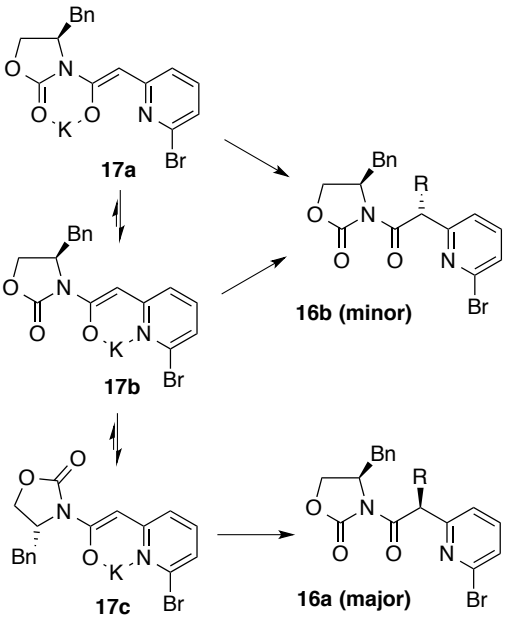
11	KO*t*-Bu	DME/THF	-40	20	81	72:28
12	KO*t*-Bu	DMF/THF	-40	20	93	82:18
13	KO*t*-Bu	DME/THF	-40	44	89	70:30
14	KO*t*-Bu	DMF	-40	20	93	82:18



SCHEME 2. Asymmetric alkylation chemistry.

These observations are in contrast with the usually highly reliable behavior of Evans' oxazolidones. Fortunately, the two diastereoisomers were separable and the major product **16a** of the alkylation reaction proved to be crystalline. Determination of the X-ray structure of **16a**[13] resulted in a final surprise, as the major diastereoisomer was found to have stereochemistry opposite to that predicted by the Evans model. In that model, the enolate counter ion is chelated between the enolate oxygen and the oxazolidonone carbonyl, as in chelate **17a**.[18] In the present case, a second, better donor is present: the pyridine nitrogen.[19] If the counter ion is chelated between the enolate oxygen and the pyridine nitrogen, the oxazolidone is then free to rotate, as shown in chelates **17b** and **17c** (Scheme 3). It may be postulated that rotation will occur to contra-align the carbonyl and enolate dipoles, resulting in selectivity opposite to the Evans' model. To the best of our knowledge, there is but a single

example of the alkylation of a pyridylacetyl oxazolidinone using the methodology of Evans.[20] We note that those authors did not report the degree of diastereoselectivity nor provide any independent confirmation of the sense of diastereoselectivity.



SCHEME 3. Rationalisation of the unexpected outcome of alkylation.

With the alkylated compound **16a** in hand, we were able to carry out reductive cleavage of the oxazolidinone. This reaction occurred without epimerisation. The stereochemical purity of the alcohol **(*S*)-6** was determined to be ≥95% e.e. by formation of Mosher's esters.[21] The enantiomerically enriched material **(*S*)-6** was then carried through the steps described, using the *o*-nitrobenzene sulfonamide protecting group, to give (-)-cytisine **1**. In addition to the spectroscopic data, the melting point (151-153 °C; lit.[22] 154.5-155.5 °C) and optical rotation (-72 (c 0.5, $CHCl_3$; lit.[23] -76 (c 1.0, $CHCl_3$)) were now also in excellent agreement with those reported.

Conclusion

An asymmetric synthesis of (-)-cytisine has been completed using a stereodivergent 6-*endo*-*trig* intramolecular aza-Michael addition to establish the piperidine. As this is a truly stereodivergent reaction, it can in future be applied to other members of the lupin family. The absolute stereochemistry was established by an Evans asymmetric alkylation which proceeds with selectivity opposite to that expected due to an alternative competing chelation mode.

Experimental

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware. Anhydrous $CH_2Cl_2$was freshly distilled from CaH_2 under nitrogen, anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen, anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous ethanol and methanol were distilled from activated magnesium under nitrogen. All other chemicals were obtained commercially and used as received. Column chromatography was carried out on silica gel, 230-400 mesh. ^{1}H NMR spectra were recorded at 300 or 400 MHz (and the corresponding frequencies for ^{13}C) in $CDCl_3$. Chemical shifts are given in ppm and coupling constants in Hz ($CDCl_3$ ^{1}H: 7.26 ppm, ^{13}C: 77.23 ppm). Mass spectra were recorded in ESI+ mode with a TOF mass analyzer. Optical rotations were measured using a 10 mm path-length cell at 589 nm.

(-)-Cytisine **(-)-1:** A mixture of *N*-nosyl (-)-cytisine **(*R*,*R*)-12b** (70 mg, 0.186 mmol), thiophenol (0.057 mL, 0.56 mmol) and K_2CO_3 (77 mg, 0.56 mmol) in MeCN:DMF 4:1 (5 mL) was heated to 45°C for 30 min. The mixture was cooled to room temperature and transferred to a silica column and eluted using an eluent of $CHCl_3$:MeOH:NH_3(aq) 90:10:1 to give (-)-cytisine as a colorless crystalline compound (34 mg, 0.179 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.8, 6.7 Hz, 1H), 6.45 (d, *J* = 8.9 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 4.12 (d, *J* = 15.6 Hz, 1H), 3.90 (dd, *J* = 15.6, 6.6 Hz, 1H), 3.15 – 2.95 (m, 4H), 2.90 (br, 1H), 2.32 (br, 1H), 1.56 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 151.2, 138.9, 116.9, 105.1, 54.2, 53.2, 49.9, 35.8; FTIR (neat, cm^{-1}) υ_{max} 3279, 1643, 1537, 1155; MS (ESI+) *m/z* 191 (MH^+, 100), 403 ($2MNa^+$, 88); HRMS calcd for $C_{11}H_{15}N_2O$ (MH^+) 191.1184; found 191.1189; mp: 151-153 °C (lit.[22] 154.5-155.5 °C); $[\alpha]_D^{21}$ -72 (c 0.5 $CHCl_3$) (lit.[23] $[\alpha]_D^{23}$ -76 (c 1.0 $CHCl_3$)).

Ethyl 2-(6-bromopyridin-2-yl)acetate **3***:* To a solution of diisopropylamine (15.4 mL, 110 mmol) in THF (30 mL) was added *n*-BuLi (71 mL, 107.5 mmol, 1.52 M) at -78°C and the mixture was stirred for 1 h. To the prepared LDA solution was cannulated a chilled solution of 2-bromo-6-methylpyridine (5.69 mL, 50 mmol) and diethyl carbonate (12.1 mL, 100 mmol) in THF (100 mL) while maintaining the temperature below -60°C. The mixture was stirred at -40°C for 16 h then quenched with 200 ml sat. aq. NH_4Cl solution. The mixture was extracted with 4x50 mL EtOAc and the combined organic layers were washed with 100 mL brine and dried over anhydrous $MgSO_4$, then filtered and concentrated *in vacuo*. The crude product is contaminated with residual diethyl carbonate which can be removed under vacuum or via column chromatography using hexane:EtOAc 4:1. The product was obtained as a yellow liquid (12.1 g, quantitative).[24]

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 155.8, 141.6, 139.0, 126.7, 123.0, 61.3, 43.4, 14.3; FTIR (neat, cm^{-1}) υ_{max} 3084, 2983, 1732, 1581, 1556, 1435, 1176, 1118, 1028; MS (ESI+) *m/z* 244 (MH^+, 100), 246 (MH^+, 97); HRMS calcd for $C_9H_{11}{}^{79}BrNO_2$ (MH^+) 243.9973; found 243.9982. HRMS calcd for $C_9H_{11}{}^{81}BrNO_2$ (MH^+) 245.9953; found 245.9960.

Ethyl 2-(6-bromopyridin-2-yl)-4-iodopent-4-enoate **5**: To a solution of **3** (3.77 g, 15.5 mmol) in THF (25 mL) at -78°C was added LiHMDS (16.3 mmol, 1M in THF) and stirred for 15 min. A solution of 3-bromo-2-iodoprop-1-ene **4**[6] (3.8 g, 15.5 mmol) in THF (14 ml) was added and the mixture was warmed up to 23°C overnight. It was quenched with sat. aq. NH_4Cl (20 mL) and extracted with 3x15 mL EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ then filtered and concentrated *in vacuo*. The resulting red oil was purified by column chromatography eluting with hexane:EtOAc 90:10 to give ester **5** (4.25 g, 10.4 mmol, 67%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 6.7 Hz, 1H), 6.01 (d, *J* = 1.4 Hz, 1H), 5.66 (d, *J* = 1.6 Hz, 1H), 4.20 – 4.13 (m, 2H), 3.18 (dd, *J* = 14.7, 7.1 Hz, 1H), 3.06 (dd, *J* = 14.9, 8.0 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 158.2, 141.8, 139.0, 128.8, 127.1, 122.6, 107.1, 61.5, 52.5, 46.8, 14.3 FTIR (neat, cm^{-1}) υ_{max} 2981, 1643, 1556 1435, 1242, 1126, 1018, 900, 769; MS (ESI+) *m/z* 410 (MH^+, ^{79}Br, 100), 412 (MH^+, 95); HRMS calcd for $C_{12}H_{14}{}^{79}BrINO_2$ 409.9253, found 409.9236.

(S)-2-(6-Bromopyridin-2-yl)-4-iodopent-4-en-1-ol **(S)-6**: To a solution of **16** (14.9 g, 27.5 mmol) in THF (150 mL) was added $LiAlH_4$ (2.1 g, 55 mmol) portionwise over 2 h at 0°C under a stream of N_2. The mixture was quenched by dropwise addition of sat. aq. $NaSO_4$ then filtered through celite and concentrated in vacuo. The crude product was purified by column chromatography eluting with hexane:EtOAc 85:15 to give alcohol **6** as a colourless oil (9.51 g, 26 mmol, 94%).

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 5.97 (d, *J* = 1.2 Hz, 1H), 5.68 (d, *J* = 1.4 Hz, 1H), 3.99 (dt, *J* = 11.1, 3.6 Hz, 1H), 3.89 (ddd, *J* = 11.1, 8.2, 5.4 Hz, 1H), 3.25 – 3.17 (m, 1H), 3.12 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.84 (ddd, *J* = 22.2, 14.3, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 141.7,

139.0, 128.5, 126.6, 123.0, 109.1, 64.2, 47.3, 47.0; FTIR (neat, cm^{-1}) υ_{max} 3062, 2931, 2877, 1612, 1581, 1550, 1435, 1157, 1126, 1064, 1026, 902, 794, 740; MS (ESI+) *m/z* 367 (MH^+, 100), 369 (MH^+, 91; HRMS calcd for $C_{10}H_{12}{}^{79}BrINO$ (MH^+) 367.9147; found 367.9149; $[\alpha]_D{}^{21}$ +103 (*c* 0.13, MeOH).

Methyl (2-(6-bromopyridin-2-yl)-4-iodopent-4-en-1-yl)(tosyl)carbamate (**7a**): A solution of alcohol **6** (2.86 g, 7.75 mmol), PPh_3 (2.33 g, 8.9 mmol), DTAD (2.05 g, 8.9 mmol) and methyl tosylcarbamate (2.04 g, 8.9 mmol) in THF (95 mL) was stirred at 23°C for 3 h then concentrated. The residue was dissolved in CH_2Cl_2 (60 mL) and TFA (30 ml) was added. The mixture was stirred at 23°C for 3 h, then concentrated and the residue was dissolved in CH_2Cl_2. It was washed with sat. aq. Na_2CO_3, then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography using a gradient of hexane:EtOAc 8:2 to 6:4 to give sulfonamide **7a** as a colourless oil which was carried through to the next step without further purification.

^1H NMR 400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.39 (m, 1H), 7.36 – 7.27 (m, 3H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.62 (d, *J* = 1.3 Hz, 1H), 4.15 (dd, *J* = 7.2, 3.2 Hz, 2H), 3.66 – 3.56 (m, 1H), 3.55 (s, 3H), 2.99 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.82 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 152.9, 144.9, 142.1, 138.7, 136.4, 129.5, 128,7, 128.6, 126.7, 123.9, 54.0, 50.8, 47.4, 46.8, 21.8; MS (ESI+) *m/z* 601 (MNa^+, 100), 603 (MNa^+, 90); HRMS calcd for $C_{19}H_{21}{}^{79}BrIN_2O_4S$ (MH^+) 578.9450; found 578.9447; HRMS calcd for $C_{19}H_{21}{}^{81}BrIN_2O_4S$ (MH^+) 580.9430; found 580.9443.

Methyl (R)-(2-(6-bromopyridin-2-yl)-4-iodopent-4-en-1-yl)((2-nitrophenyl)sulfonyl) carbamate **(*R*)-7b***:*

A solution of (***S*)-6** (4.4 g, 12 mmol), PPh_3 (3.39 g, 13.2 mmol), DTAD (3.0 g, 13.2 mmol) and methyl ((2-nitrophenyl)sulfonyl)carbamate (3.37 g, 13.2 mmol) in THF (150 mL) was

heated at reflux for 16 h then concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and TFA (25 ml) was added. The mixture was stirred until TLC indicated the disappearance of DTAD/reduced DTAD (about 3 h, TLC visualized with molybdate stain). The mixture was concentrated and the residue dissolved in CH_2Cl_2. It was washed with water and 2 M aq. NaOH, then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography using gradient elution with hexane:EtOAc 80:20, 65:35, 50:50. The product was obtained as a yellow oil that was contaminated with the unreacted nosyl carbamate. A portion of this material was carried through the next step without further purification.

^{1}H NMR (396 MHz, $CDCl_3$) δ 8.35 – 8.29 (m, 1H), 7.82 – 7.68 (m, 3H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 6.00 (d, *J* = 7.2 Hz, 1H), 5.64 (d, *J* = 1.2 Hz, 1H), 4.22 (dd, *J* = 14.8, 9.0 Hz, 1H), 4.11 (dd, *J* = 14.8, 5.7 Hz, 1H), 3.70 – 3.36 (m, 4H), 3.05 (dd, *J* = 14.3, 9.2 Hz, 1H), 2.86 (dd, *J* = 14.3, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 152.4, 148.2, 142.2, 138.8, 134.9, 134.8, 132.8, 132.0, 128.7, 126.8, 127.7, 124.1, 108.0, 54.3, 51.6, 47.3, 47.0; MS (ESI+) *m/z* 610 (MH^+, 100), 612 (MH^+, 92); HRMS calcd for $C_{18}H_{18}N_3O_6S^{79}BrI$ (MH^+) 609.9144 found 609. 9135, HRMS calcd for $C_{18}H_{18}N_3O_6S^{81}BrI$ (MH^+) 611.9124 found 611. 9113.

N-(2-(6-Bromopyridin-2-yl)-4-iodopent-4-en-1-yl)-4-methylbenzenesulfonamide (**8a**): A mixture of **7a** (3.5 g, 6.04 mmol) and K_2CO_3 (1.08 g, 7.85 mmol) in MeOH (61 mL) was stirred for 16 h at 25°C until the opaque mixture turned clear and TLC indicated the consumption of starting material. Sat. aq. NH_4Cl was added and MeOH was evaporated. The residue was extracted 4x with chloroform. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give sulphonamide **8a** as a yellow oil (2.93 g, 5.62 mmol, 88%) over 2 steps from **6**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.44 (m, *J* = 7.7 Hz, 1H), 7.30 (m, 3H), 7.06 (d, *J* = 7.1 Hz, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.64 (d, *J* = 1.4 Hz, 1H), 5.33 (t, *J* = 6.0 Hz, 1H), 3.36 – 3.15 (m, 3H), 2.79 – 2.62 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 143.5, 141.9, 139.1, 136.8, 129.9, 129.0, 127.2, 126.8, 123.3, 107.8, 48.2, 45.3, 44.9, 21.7; FTIR (neat, cm^{-1}) υ_{max} 3284, 1555, 1440, 1327, 1222, 1157, 1091, 900; MS (ESI+) *m/z* 521 (MH^+, ^{79}Br), 523 (MH^+, ^{81}Br); HRMS calcd for $C_{17}H_{19}{}^{79}BrIN_2O_2S$ (MH^+) 520.9392; found 520.9395; HRMS calcd for $C_{17}H_{19}{}^{81}BrIN_2O_2S$ 52(MH^+) 2.9368; found 522.9975.

(R)-N-(2-(6-Bromopyridin-2-yl)-4-iodopent-4-en-1-yl)-2-nitrobenzenesulfonamide **(*R*)-8b***:* A mixture of **(*R*)-7b** (1.6 g, 2.62 mmol) and K_2CO_3 (0.471 g, 3.4 mmol) in MeOH (25 mL) was stirred for 2 h at 25°C until the opaque mixture turned clear and TLC indicated the consumption of starting material. Sat. aq. NH_4Cl was added and MeOH was evaporated. The residue was extracted 4x with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give sulphonamide **8b** was obtained as a yellow oil (1.4 g, 2.54 mmol, 67%) over 2 steps from **(*S*)-6**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.4 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.89 (t, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 1.4 Hz, 1H), 3.49 (qdd, *J* = 10.3, 7.1, 5.3 Hz, 2H), 3.31 (ddd, *J* = 15.0, 7.8, 4.3 Hz, 1H), 2.82 – 2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 148.1, 142.3, 139.0, 133.9, 133.7, 133.1, 131.2, 129.1, 127.1, 125.6, 123.2, 107.7, 48.3, 45.9, 45.3; MS (ESI+) *m/z* 552 (MH^+, 100), 554 (MH^+, 89); 574 (MNa^+, 20), 576 (MNa^+, 17); HRMS calcd for $C_{16}H_{16}{}^{79}BrIN_3O_4S$ (MH^+) 551.9090; found 551.9083; $[\alpha]_D{}^{21}$ +34 (*c* 0.12, MeOH)

Methyl 4-(6-bromopyridin-2-yl)-2-methylene-5-((4-methylphenyl)sulfonamido)pentanoate (**9a**): A solution of **8a** (2.8 g, 5.37 mmol), $Pd(PPh_3)_2Cl_2$ (188 mg, 0.26 mmol), and Et_3N (1.5

mL, 10.7 mmol) in MeOH (55 mL) was stirred overnight at 25°C under 1 atm of CO. The mixture was concentrated and the residue was dissolved in $CHCl_3$ then washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated is vacuo. The crude product was purified by column chromatography eluting with hexane:EtOAc 60:40 to give ester **9a** as an orange oil (2.27 g, 5.01 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.27 (m, 3H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.12 (d, *J* = 1.1 Hz, 1H), 5.45 (m, 2H), 3.72 (s, 3H), 3.35 – 3.22 (m, 1H), 3.22 – 3.11 (m, 2H), 2.64 (qd, *J* = 13.7, 6.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 163.0, 143.4, 141.7, 139.0, 136.9, 136.8, 129.8, 128.6, 127.2, 126.5, 122.9, 52.1, 45.5, 44.6, 35.5, 21.6; FTIR (neat, cm^{-1}) υ_{max} 3284, 2951, 1732, 1556, 1454, 1323, 1203, 1157, 1091, 952, 813, 659; MS (ESI+) *m/z* 475 (MNa^+, ^{79}Br), 477 (MNa^+, ^{81}Br) HRMS calcd for $C_{19}H_{22}N_2O_4S^{79}Br$ (MH^+) 453.0484 found 453.0483, calcd for $C_{19}H_{22}N_2O_2S^{81}Br$ (MH^+) 455.0463 found 455.0467.

Methyl (R)-4-(6-bromopyridin-2-yl)-2-methylene-5-((2-nitrophenyl)sulfonamido)pentanoate **(*R*)-9b**: A solution of **(*R*)-8b** (3.24 g, 5.87 mmol), $Pd(PPh_3)_2Cl_2$ (206 mg, 0.29 mmol), and Et_3N (1.65 mL, 11.7 mmol) in MeOH (58 mL) was stirred overnight at 25°C under 1 atm of CO. The mixture was concentrated and the residue was dissolved in $CHCl_3$ then washed with water and 2M aq. HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated is vacuo. The crude product was purified by column chromatography using gradient elution with hexane:EtOAc 80:20, 60:40, 50:50 to give ester **9b** as a yellow oil (2.7 g 5.57 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.15 (s, 1H), 5.94 (t, *J* = 6.0 Hz, 1H), 5.47 (s, 1H), 3.75 (s, 3H), 3.55 – 3.38 (m, 2H), 3.26 (qd, *J* = 7.4, 4.4 Hz, 1H), 2.67 (qd, *J* = 13.8, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3,

162.4, 148.1, 142.1, 139.0, 136.9, 133.8, 133.6, 132.9, 131.1, 128.6, 126.8, 125.6, 123.0, 52.2, 46.3, 45.0, 35.9; FTIR (neat, cm^{-1}) υ_{max} 3233, 3097, 3024, 2951, 1714, 1697,1633, 1583, 1537, 1435, 1359, 1122, 952, 731, 499; MS (ESI+) *m/z* 484 (MH^+, 100), 486 (MH^+, 89); HRMS calcd for $C_{18}H_{19}{}^{79}BrN_3O_6S$ (MH^+) 484.0178; found 484.0193; $[\alpha]_D{}^{21}$ +14 (*c* 0.17, MeOH).

Methyl 5-(6-bromopyridin-2-yl)-1-tosylpiperidine-3-carboxylate (**cis-10a**): A mixture of **9a** (906 mg, 2.0 mmol) and DBU (0.15 mL, 1.0 mmol) in dioxane (20 mL) was heated to reflux for 2h and quenched with 2 mL of sat. aq. NH_4Cl. The mixture was extracted 3x with $CHCl_3$, then washed with water and brine. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give piperidine **10a** quantitatively as a mixture of diastereomers (63:37 *cis:trans*).

^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.33 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.00 – 3.92 (m, 1H), 3.67 (s, 3H), 3.02 (m, 1H), 2.88 – 2.72 (m, 1H), 2.47-2.39 (m, 6H), 2.33 – 2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 162.2, 144.0, 142.1, 139.2, 133.4, 130.0, 127.7, 126.9, 121.5, 52.2, 50.4, 47.2, 43.1, 41.3, 32.5, 21.7; FTIR (neat, cm^{-1}) υ_{max} 3498, 2096, 1635, 1435, 1344, 1165, 1089, 985 ; MS (ESI+) *m/z* 475 (MNa^+, ^{79}Br), 477 (MNa^+, ^{81}Br); HRMS calcd for $C_{19}H_{22}N_2O_4S^{79}Br$ (MH^+) 453.0484 found 453.0498, calcd for $C_{19}H_{22}N_2O_4S^{81}Br$ (MH^+) 455.0463 found 453.0482.

methyl 5-(6-bromopyridin-2-yl)-1-tosylpiperidine-3-carboxylate (**trans-10a**): To a solution of **9a** (125 mg, 0.27 mmol) in THF (3 mL) was added LiHMDS (0.27 mmol, 1 M) in THF at 0 °C and stirred for 60 h. The mixture was quenched with sat. aq. NH_4Cl, then extracted 3x with $CHCl_3$, then washed brine. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give piperidine **10a** quantitatively as a mixture of diastereomers (5:95 *cis:trans*).

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.50 (m, 1H), 7.38 – 7.29 (m, 4H), 3.76-3.68 (m, 4H), 3.54 – 3.39 (m, 1H), 3.30 (dq, *J* = 13.0, 4.3 Hz, 1H), 3.10 – 2.90 (m, 2H), 2.80 – 2.69 (m, 1H), 2.44 (s, 3H), 2.20 – 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 162.2, 143.9, 141.8, 139.1, 133.0, 129.9, 127.8, 126.5, 122.0, 52.3, 49.9, 47.6, 39.8, 38.5, 30.1, 21.6; FTIR (neat, cm^{-1}) υ_{max} 3495, 2096, 1645, 1435, 1344, 1165, 1089, 912 ; MS (ESI+) *m/z* 475 (MNa^+, ^{79}Br), 477 (MNa^+, ^{81}Br); HRMS calcd for calcd for $C_{19}H_{22}N_2O_4S^{79}Br$ (MH^+) 453.0484 found 453.0491, calcd for $C_{19}H_{22}N_2O_4S^{81}Br$ (MH^+) 455.0463 found 455.0473.

Methyl (3S,5R)-5-(6-bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxylate (**cis-(*R*,*S*)-10b**): A mixture of **(*R*)-9b** (1.0 g, 2.06 mmol) and DBU (0.154 mL, 1.03 mmol) in dioxane (20 mL) was heated to reflux for 2h and quenched with 2 mL of sat. aq. NH_4Cl. The mixture was extracted 3x with $CHCl_3$, then washed with water and brine. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give piperidine **10b** quantitatively as a mixture of diastereomers (63:37 *cis:trans*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 1H), 7.77 – 7.67 (m, 2H), 7.68 – 7.61 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 4.21 – 4.14 (m, 1H), 4.07 – 4.01 (m, 1H), 3.70 (s, 3H), 3.09 – 2.98 (m, 2H), 2.98 – 2.88 (m, 1H), 2.80 (tt, *J* = 12.1, 3.8 Hz, 1H), 2.43 – 2.31 (m, 1H), 1.93 (dd, *J* = 25.2, 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 162.0, 148.3, 142.2, 139.2, 134.0, 132.3, 132.0, 131.1, 127.0, 124.5, 121.6, 52.3, 50.0, 47.0, 43.2, 41.4, 32.9; MS (ESI+) *m/z* 484 (MH^+, 100), 486 (MH^+, 80); HRMS calcd for $C_{18}H_{19}BrN_3O_6S$ (MH^+, ^{79}Br) 484.0178; found 484.0181.

Methyl (3R,5R)-5-(6-bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxylate (***trans*-(*R*,*R*)-10b**): To a solution of **(*R*)-9b** (600 mg, 1.24 mmol) in THF (12 mL) was added LiHMDS (1.24 mmol, 1 M) in THF at 0 °C and stirred for 40 h. The mixture was quenched with sat. aq. NH_4Cl, then extracted 3x with $CHCl_3$, then washed brine. The combined organic

layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give piperidine 10b quantitatively as a mixture of diastereomers (5:95 *cis:trans*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 1H), 7.77 – 7.67 (m, 2H), 7.67 – 7.60 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 4.09 (dd, *J* = 12.6, 3.5 Hz, 1H), 3.82 (dd, *J* = 12.1, 3.7 Hz, 1H), 3.67 (s, 3H), 3.44 – 3.19 (m, 3H), 2.93 – 2.77 (m, 1H), 2.31 (dt, *J* = 13.7, 4.0 Hz, 1H), 2.21 – 2.07 (m, 1H).

(5-(6-Bromopyridin-2-yl)-1-tosylpiperidin-3-yl)methanol (**cis/trans-11a**): A mixture of ***cis*/*trans*-10a** (0.45 g, 1.0 mmol) was cooled to 0 °C in THF (10 mL) and $LiAlH_4$ (76 mg, 2 mmol) was added portion wise. The mixure was quenched by careful addition of sat. aq. Na_2SO_4 solution and concentrated *in vacuo*. The crude product was purified by column chromatography eluting with hexane:EtOAc 1:4 to give piperidine **11a** as a white foam (286 mg, 0.67 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 4H), 7.46 (dd, *J* = 15.0, 7.5 Hz, 2H), 7.30 (dt, *J* = 7.4, 3.6 Hz, 8H), 7.11 (d, *J* = 7.6 Hz, 1H), 3.97 (ddd, *J* = 15.4, 14.4, 6.0 Hz, 1H), 3.79 (dd, *J* = 10.7, 8.4 Hz, 1H), 3.64 (dd, *J* = 10.9, 5.6 Hz, 2H), 3.61 – 3.38 (m, 3H), 3.38 – 3.24 (m, 1H), 3.24 – 3.09 (m, 2H), 3.09 – 2.93 (m, 2H), 2.88 (dd, *J* = 11.4, 2.9 Hz, 1H), 2.65 (s, 1H), 2.41 (s, 4H), 2.40 (s, 2H), 2.11 – 1.84 (m, 5H), 1.84 – 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.17, 163.06, 143.88, 143.78, 141.98, 141.78, 139.19, 139.14, 133.27, 133.14, 129.94, 129.93, 127.78, 127.73, 126.63, 126.45, 121.59, 121.54, 65.26, 63.13, 50.82, 50.13, 49.02, 47.57, 43.47, 39.39, 38.74, 35.19, 32.57, 30.93, 21.68, 21.67; FTIR (neat, cm^{-1}) υ_{max} 3489, 2088, 1637, 1435, 1338, 1163, 985MS (ESI+) *m/z* 447 (MNa^+, ^{79}Br), 449 (MNa^+, ^{81}Br); HRMS calcd for $C_{18}H_{22}N_2O_3S^{79}Br$ (MH^+) 425.0535 found 425.0569, calcd for $C_{18}H_{22}N_2O_3S^{81}Br$ (MH^+) 427.0514 found 427.0538.

((3S,5R)-5-(6-Bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)methanol ***cis*/*trans*-11b**: A solution of ***cis*/*trans*-10b** (*dr* 1:1) (1.06 g, 2.19 mmol) in THF (22 mL) was

cooled to 0 °C and $LiAlH_4$ (0.166 g, 4.38 mmol) was added portion wise over 1 h. The mixture was quenched by careful addition of sat. aq. Na_2SO_4 solution and concentrated *in vacuo*. The residue was purified by column chromatography eluting with CH_2Cl_2:MeOH:NH_3(aq) 95:5:1 to give piperidine **11b** as a yellow oil (696 mg, 1.52 mmol, *dr 1:1*, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.93 (m, 2H), 7.75 – 7.66 (m, 4H), 7.66 – 7.60 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 3.6 Hz, 1H), 7.33 (d, *J* = 3.5 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 4.05 (m, 2H), 3.95 – 3.75 (m, 3H), 3.65 (ddd, *J* = 18.7, 10.6, 5.2 Hz, 2H), 3.59 – 3.47 (m, 1H), 3.30 (dd, *J* = 12.5, 10.1 Hz, 1H), 3.17 (ddd, *J* = 16.4, 9.7, 4.4 Hz, 2H), 3.10 – 2.91 (m, 2H), 2.61 (t, *J* = 11.9 Hz, 1H), 2.07 (m, 5H), 1.95 – 1.76 (m, 1H), 1.59 – 1.42 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.8, 142.1, 142.0, 141.1, 139.2, 133.9, 133.8, 132.9, 132.2, 131.9, 131.2, 131.1, 131.0, 126.8, 126.7, 124.4, 124.3, 121.6. 65.2, 62.4, 50.4, 50.3, 48.8, 46.8, 43.6, 39.5, 38.9, 35.5, 33.0, 31.1; MS (ESI+) *m/z* 456 (MH^+, 100), 458 (MH^+, 92); HRMS calcd for $C_{17}H_{19}{}^{79}BrN_3O_5S$ (MH^+) 456.0229; found 456.0220.

N-Tosyl cytisine (**12a**): A solution of ***cis*/*trans*-11a** (0.37 g, 0.87 mmol) and Et_3N (0.25 mL, 1.7 mmol) in DCM (16mL) was cooled to 0°C and mesyl chloride (0.1 mL, 1.2 mmol) was added slowly. After stirring the mixture for 1 h, water was added and extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. A white foamy material was obtained (0.42 g, quantitative). The obtained mixture of mesylates in $CHCl_3$ (25 mL) was heated at reflux for 4 h then cooled to room temperature. Sat. aq. Na_2CO_3 (10 mL) was added and the mixture stirred for 0.5 h at 23°C. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue

was purified by column chromatography eluting with EtOAc to give *N*-tosyl cytisine **12a** as a tan solid (115 mg, 0.34 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 3H), 6.43 (d, *J* = 9.1 Hz, 1H), 5.97 (d, *J* = 6.7 Hz, 1H), 3.89 (dt, *J* = 15.7, 11.0 Hz, 2H), 3.82 – 3.70 (m, 2H), 3.04 (s, 1H), 2.74 (t, *J* = 13.2 Hz, 2H), 2.51 (s, 3H), 2.40 (s, 2H), 2.27 – 2.01 (m, 1H), 1.91 (d, *J* = 13.1 Hz, 1H), 1.72 (d, *J* = 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 148.5, 144.0, 138.8, 133.6, 129.9, 127.5, 117.8, 105.3, 52.7, 52.0, 49.0, 34.3, 27.2, 25.3, 21.7; FTIR (neat, cm^{-1}) υ_{max} 3419, 2115, 1633, 1377, 1165, 1008, 948; MS (ESI+) *m/z* 455 (MH), 467 (MNa^+); HRMS calcd for $C_{18}H_{21}N_2O_3S$ 345.1273 found 345.1294; mp: 201-203°C.

The unreacted *trans* mesylate was recovered from the column (61 mg, 0.12 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.35 (dd, *J* = 8.0, 4.1 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 1H), 4.46 – 4.25 (m, 1H), 3.71 – 3.61 (m, 1H), 3.58 – 3.46 (m, 1H), 2.45 (s, 2H), 2.38 – 2.23 (m, 1H), 2.05 (ddd, *J* = 15.3, 10.8, 4.8 Hz, 1H), 1.91 – 1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 144.2, 142.0, 139.3, 133.0, 130.1, 127.8, 126.8, 121.8, 70.0, 50.4, 47.0, 39.2, 37.5, 32.8, 30.4, 21.7; FTIR (neat, cm^{-1}) υ_{max} 3419, 2088, 1643, 1454, 1377, 999; MS (ESI+) *m/z* 525 (MNa^+, ^{79}Br), 527 (MNa^+, ^{81}Br); HRMS calcd for $C_{19}H_{24}N_2O_5S_2{}^{79}Br$ (MH^+) 503.0310 found 503.0316, calcd for $C_{19}H_{24}N_2O_5S_2{}^{81}Br$ (MH^+) 505.0290 found 505.0304; mp: 140-141°C.

N-Nosyl (-)-cytisine **(*R*,*R*)-12b***:* A 1:1 diastereomeric mixture of ***cis*/*trans*-11b** (0.392 g, 0.86 mmol) and Et_3N (0.18 mL, 1.3 mmol) in CH_2Cl_2 (15mL) was cooled to 0°C and mesyl chloride (0.08 mL, 1.03 mmol) was added slowly. After stirring the mixture for 1 h, water was added and extracted three times with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. A white foamy material was obtained (0.308 g, 0.61 mmol, 77%). The obtained mixture of mesylates in $CHCl_3$ (12 mL) was heated at reflux for 6.5 h then cooled to room temperature. Sat. aq. Na_2CO_3 (10 mL) was

added and the mixture stirred for 9 h at 23°C. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography eluting with $CHCl_3$:MeOH:NH_3(aq) 95:5:1 to give *N*-nosyl cytisine **(S)-12b** as an orange oil (76 mg, 0.2 mmol, 33% (66% from the *cis* mesylate).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 2H), 7.61 – 7.51 (m, 2H), 7.21 (dd, *J* = 9.1, 6.8 Hz, 1H), 6.33 (d, *J* = 9.1 Hz, 1H), 6.02 (d, *J* = 6.9 Hz, 1H), 4.10 (d, *J* = 15.8 Hz, 1H), 3.97 (dddd, *J* = 12.4, 4.8, 3.7, 2.0 Hz, 1H), 3.84 (ddd, *J* = 15.7, 6.6, 1.0 Hz, 1H), 3.20 (dd, *J* = 12.3, 2.1 Hz, 1H), 3.18 – 3.08 (m, 2H), 2.56 (brs, 1H), 2.09 – 1.97 (m, 1H), 1.95 – 1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 147.9, 138.6, 133.8, 131.8, 131.6, 130.3, 124.0, 117.9, 105.5, 53.0, 51.8, 48.6, 34.4, 27.2, 25.3; FTIR (neat, cm^{-1}) υ_{max} 3439, 2292, 1645, 1454, 1373, 1056, 956; MS (ESI+) 376 (MH^+, 52), 751 ($2MH^+$, 100)*;* HRMS calcd for $C_{17}H_{18}N_3O_5S$ (MH^+) 376.0967; found 376.0982; $[\alpha]_D^{22}$ -184 (c 0.95 $CHCl_3$).

The unreacted *trans* mesylate was recovered from the column (147 mg, 0.29 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 1H), 7.77 – 7.68 (m, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 4.46 – 4.29 (m, 2H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.77 (d, *J* = 13.0 Hz, 1H), 3.30 – 3.15 (m, 3H), 2.39 (tt, *J* = 7.5, 3.9 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.01 – 1.90 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 148.5, 142.1, 139.3, 134.1, 132.0, 131.5, 131.1, 126.9, 124.4, 121.8; FTIR (neat, cm^{-1}) υ_{max} 2852, 2358, 1581, 1519, 1155, 1060, 964, 723; MS (ESI+) *m/z* 534 (MH^+, 100), 536 (MH^+, 90); 556 (MNa^+, 24), 558 (MNa^+, 25); HRMS calcd for $C_{18}H_{21}N_3O_7S_2{}^{79}Br$ (MH^+) 534.0004; found 534.9998; $[\alpha]_D^{22}$ -37 (c 1.08 $CHCl_3$).

2-(6-Bromopyridin-2-yl)acetic acid **13***:* **3** (47.15 g, 194 mmol) and LiOH•H_2O (8.15 g, 194 mmol) was stirred in a 1:1 mixture of dioxane/H_2O (250 mL) for 40 min at 25°C. Trifluoroacetic acid (14.85 mL, 194 mmol) was added and the mixture was stirred for another

30 min. The solvent was evaporated then H_2O (100 ml) was added and extracted with 3x50 ml CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, then filtered and concentrated *in vacuo*. The crude product was ground to fine powder under hexane then filtered, washed with disopropyl ether and hexane. The obtained yellow solid was dried with suction (35.4 g, 164 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 155.1, 141.2, 139.6, 127.2, 123.1, 42.5; FTIR (nujol, cm^{-1}) υ_{max} 3433, 2100, 1643, 1454, 1384, 634; MS (ESI+) *m/z* 216 (MH^+, 68), 218 (MH^+, 100); mp 84-86°C.[24]

(R)-4-Benzyl-3-(2-(6-bromopyridin-2-yl)acetyl)oxazolidin-2-one (**15**): **13** (4.3 g, 20 mmol) and CDI (3.24 g, 20 mmol) in THF (50 mL) was stirred for 1.5 h at 25°C. In another flask (*R*)-4-benzyloxazolidin-2-one (3.54 g, 20 mmol) was cooled to 0°C in THF (100 mL) and KO*t*-Bu[25] (20 mmol, 1M in THF) was added slowly and stirred for 1.5 h at 0°C. The solution of the activated acid was cannulated to the oxazolidinone salt solution at 0°C and warmed up to 25°C overnight. The mixture was quenched with sat. aq. NH_4Cl (100 mL), extracted with 4x50 mL EtOAc and washed with brine (50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, than filtered and concentrated *in vauo*. The crude product was diluted with EtOAc and the unreacted acid residue was filtered off. The filtrate was concentrated and purified by column chromatography using an eluent gradient of hexane:EtOAc 85:15 to 73:30. Further elution with 50:50 hexane:EtOAc allowed the recovery of unreacted oxazolidinone. Oxazolidinone **15** was obtained as a yellow solid (4.95 g, 13.2 mmol, 66%).

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.54 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.17 (m, 6H), 4.71 (ddd, *J* = 10.5, 6.7, 3.2 Hz, 1H), 4.46 (dd, *J* = 22.6, 16.6 Hz, 2H), 4.28 – 4.17 (m, 2H), 3.37 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.8 Hz, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 169.3, 155.7, 153.5, 141.7, 139.0, 135.4, 129.6 (2C), 129.1 (2C), 127.5, 126.7, 123.5, 66.6, 55.6, 44.4, 38.0 ; FTIR (neat, cm^{-1}) υ_{max} 2922, 2850, 1645, 1663, 1454, 1377, 530; MS (ESI+) *m/z* 375 (MH^+, 100), 377 (MH^+, 96); 397 (MNa^+, 32), 399 (MNa^+, 29); HRMS calcd for $C_{17}H_{16}{}^{79}BrN_2O_3$ (MH^+) 375.0344; found 375.0340. HRMS calcd for $C_{17}H_{16}{}^{81}BrN_2O_3$ (MH^+) 377.0324; found 374.0326; mp 100-102 °C; $[\alpha]_D{}^{21}$ -179 (*c* 0.11, MeOH).

(R)-4-Benzyl-3-((S)-2-(6-bromopyridin-2-yl)-4-iodopent-4-enoyl)oxazolidin-2-one **16a**: To a solution of **15** (3.25 g, 8.66 mmol) in anhydrous DMF (40 mL) was added KO*t*-Bu (8.66 mmol, 1M in DMF) at -40°C and the mixture was stirred for 30 min. A solution of 3-bromo-2-iodoprop-1-ene **4** (2.12 g, 8.66 mmol) in anhydrous DMF (10 mL) was added slowly and the mixture was stirred at -40°C for 16 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL), extracted with EtOAc (4x40 mL), washed with H_2O (40 mL) and brine (40 mL). The combined organic layers were dried over anhydrous $MgSO_4$, then filtered and concentrated *in vacuo*. The residue (*dr* 81:19 syn:anti) was purified by column chromatography eluting with hexane:EtOAc 95:5 to 90:10.

Major diastereomer (**16a**; *S,R*): pale yellow crystals (3.06 g, 5.65 mmol, 65%).

^1H NMR (396 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.21 (m, 3H), 7.16 (d, *J* = 6.4 Hz, 2H), 6.01 (d, *J* = 1.2 Hz, 1H), 5.73 (d, *J* = 1.3 Hz, 1H), 5.30 (t, *J* = 7.1 Hz, 1H), 4.78 (ddt, *J* = 9.8, 7.9, 3.2 Hz, 1H), 4.22 (t, *J* = 8.5 Hz, 1H), 4.13 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.43 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.31 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.90 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.69 (dd, *J* = 13.7, 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.7, 153.0, 141.5, 138.9, 135.6, 129.6 (2C), 129.3, 129.0 (2C), 127.4, 126.9, 124.1, 107.4, 66.4, 55.4, 51.2, 47.5, 37.6; FTIR (neat, cm^{-1}) υ_{max} 2954, 2924, 2063, 1643, 1633, 1359, 1124, 1020, 914; MS (ESI+) *m/z* 541 (MH^+, 87), 543 (MH^+, 100); 563 (MNa^+, 58), 565 (MNa^+, 52); HRMS calcd for $C_{20}H_{19}{}^{79}BrIN_2O_3$ (MH^+) 540.9624; found 540.9620. HRMS

calcd for $C_{20}H_{19}{}^{81}BrIN_2O_3$ (MH^+) 542.9603; found 542.9609; mp 117-118 °C; $[\alpha]_D{}^{21}$ -42 (*c* 0.11, MeOH)

Minor diastereomer **16b** (anti alkylated; *R*,*R*): yellow oil, (466 mg, 0.86 mmol, 10%).

^{1}H NMR (396 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.7 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.31 – 7.20 (m, 3H), 6.05 (d, *J* = 1.3 Hz, 1H), 5.74 (d, *J* = 1.5 Hz, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 4.72 (dtd, *J* = 8.5, 5.0, 3.4 Hz, 1H), 4.14 (d, *J* = 5.0 Hz, 2H), 3.42 – 3.30 (m, 2H), 2.95 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.83 (dd, *J* = 13.4, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.1, 153.1, 141.7, 138.9, 135.6, 129.7 (2C), 129.3, 129.2 (2C), 127.5, 127.1, 124.0, 107.2, 66.4, 56.0, 51.0, 47.6, 38.0; FTIR (neat, cm^{-1}) υ_{max} 2850, 2104, 1643, 1633, 1462, 1373, 1053, 526; MS (ESI+) *m/z* 541 (MH^+, 100), 543 (MH^+, 93); 563 (MNa^+, 23), 565 (MNa^+, 21); HRMS calcd for $C_{20}H_{19}{}^{79}BrIN_2O_3$ (MH^+) 540.9624; found 540.9620; HRMS calcd for $C_{20}H_{19}{}^{81}BrIN_2O_3$ (MH^+) 542.9603; found 542.9613; $[\alpha]_D{}^{21}$ -108 (*c* 0.09, MeOH).

Supporting Information

Spectroscopic data for compounds **1**, **3**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **15**, **16**, Mosher's esters of **6** and *o*-$NsNHCO_2Me$ and X-ray structures of compounds ***cis*-11a** and **16a**; cif files for the X-ray data; details of the DFT calculations; CV measurements of model compounds. The Supporting Information is available free of charge on the ACS Publications website.

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