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<td><strong>Author(s)</strong></td>
<td>Barát, Viktor; Csókás, Dániel; Bates, Roderick Wayland</td>
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A Synthesis of (-)-Cytisine using a 6-endo aza-Michael Addition

Viktor Barát, Dániel Csókás and Roderick W. Bates*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371.

E-mail: roderick@ntu.edu.sg

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. The chemistry of cytisine 1 has also been the subject of two reviews, and a further synthesis has appeared since then.

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. This particular disconnection appears underexploited. 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.

![FIGURE 1. Cytisine](image)

**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). Alkylation of the corresponding enolate with 1-bromo-2-iodo-2-propene 4 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. 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 and decompose the by-product by treatment
with trifluoroacetic acid. We also prepared the corresponding o-nitrobenzene sulfonamide
8b. 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. We then
attempted the base catalysed cyclisation (Table 1) of acrylate 9a. While no reaction was
observed using i-Pr2NEt, 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**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>base</th>
<th>solvent</th>
<th>temperature/°C</th>
<th>trans: cis ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>DBU(^a)</td>
<td>THF</td>
<td>60</td>
<td>38:62</td>
</tr>
<tr>
<td>2</td>
<td>9a</td>
<td>DBU(^a)</td>
<td>dioxane</td>
<td>100</td>
<td>27:73(^c)</td>
</tr>
<tr>
<td>3</td>
<td>9b</td>
<td>DBU(^a)</td>
<td>dioxane</td>
<td>100</td>
<td>37:63(^c)</td>
</tr>
<tr>
<td>4</td>
<td>9a</td>
<td>Cs(_2)CO(_3)(^b)</td>
<td>THF</td>
<td>RT</td>
<td>43:57</td>
</tr>
<tr>
<td>5</td>
<td>9a</td>
<td>Cs(_2)CO(_3)(^b)</td>
<td>THF</td>
<td>-5</td>
<td>91:9</td>
</tr>
<tr>
<td>6</td>
<td>9a</td>
<td>LiHMDS(^b)</td>
<td>THF</td>
<td>0</td>
<td>95:5(^c)</td>
</tr>
<tr>
<td>7</td>
<td>9b</td>
<td>LiHMDS(^b)</td>
<td>THF</td>
<td>0</td>
<td>95:5(^c)</td>
</tr>
</tbody>
</table>

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

The esters 10 were found to be unstable during column chromatography on silica gel. The corresponding alcohols in the tosyl series, 11a, obtained by LiAlH₄ 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
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). 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 KOt-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.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>temperature/°C</th>
<th>time/h</th>
<th>conversion/%</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-60</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-60</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>KOt-Bu</td>
<td>THF</td>
<td>-78</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>NaOt-Bu</td>
<td>THF</td>
<td>-60</td>
<td>20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78 to 25</td>
<td>20</td>
<td>100</td>
<td>dec.</td>
</tr>
<tr>
<td>6</td>
<td>KOt-Bu</td>
<td>PhMe/THF</td>
<td>-40</td>
<td>20</td>
<td>33</td>
<td>58:44</td>
</tr>
<tr>
<td>7</td>
<td>KHMDS</td>
<td>THF</td>
<td>-40</td>
<td>20</td>
<td>78</td>
<td>67:33</td>
</tr>
<tr>
<td>8</td>
<td>KOt-Bu</td>
<td>THF</td>
<td>-40</td>
<td>20</td>
<td>70</td>
<td>67:33</td>
</tr>
<tr>
<td>9</td>
<td>NaHMDS</td>
<td>DME/THF</td>
<td>-40</td>
<td>17</td>
<td>55</td>
<td>69:31</td>
</tr>
<tr>
<td>10</td>
<td>KOt-Bu</td>
<td>Pyr/THF</td>
<td>-40</td>
<td>20</td>
<td>88</td>
<td>70:30</td>
</tr>
</tbody>
</table>
### 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\(^\text{13}\) 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\(^\text{18}\). In the present case, a second, better donor is present: the pyridine nitrogen\(^\text{19}\). 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.\textsuperscript{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 16\textsubscript{a} 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 $\geq$95\% e.e. by formation of Mosher’s esters.\textsuperscript{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.\textsuperscript{22} 154.5-155.5 °C) and optical rotation (-72 (c 0.5, CHCl\textsubscript{3}); lit.\textsuperscript{23} -76 (c 1.0, CHCl\textsubscript{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$_2$Cl$_2$ 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$_2$CO$_3$ (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$_3$) $\delta$ 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$_3$) $\delta$ 163.8, 151.2, 138.9, 116.9, 105.1, 54.2, 53.2, 49.9, 35.8; FTIR (neat, cm$^{-1}$) $\nu_{max}$ 3279, 1643, 1537, 1155; MS (ESI+) m/z 191 (MH$^+$), 403 (2MNa$^+$, 88); HRMS calcd for C$_{11}$H$_{15}$N$_2$O (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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 170.1, 155.8, 141.6, 139.0, 126.7, 123.0, 61.3, 43.4, 14.3; FTIR (neat, cm$^{-1}$) $\nu_{max}$ 3084, 2983, 1732, 1581, 1556, 1435, 1176, 1118, 1028; MS (ESI+) m/z 244 (MH$^+$, 100), 246 (MH$^+$, 97); HRMS calcd for C$_9$H$_{11}^{79}$BrNO$_2$ (MH$^+$) 243.9973; found 243.9982. HRMS calcd for C$_9$H$_{11}^{81}$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 (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. NH₄Cl (20 mL) and extracted with 3x15 mL EtOAc. The combined organic layers were dried over anhydrous MgSO₄ 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, CDCl₃) 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, CDCl₃) 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) \(\nu_{max}\) 2981, 1643, 1556 1435, 1242, 1126, 1018, 900, 769; MS (ESI+) \(m/z\) 410 (MH⁺, 79Br, 100), 412 (MH⁺, 95); HRMS calcd for C₁₂H₁₄⁷⁹BrINO₂ 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 LiAlH₄ (2.1 g, 55 mmol) portionwise over 2 h at 0°C under a stream of N₂. The mixture was quenched by dropwise addition of sat. aq. NaSO₄ 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, CDCl₃) 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, CDCl₃) δ 163.6, 141.7,
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), PPh₃ (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 CH₂Cl₂ (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 CH₂Cl₂. It was washed with sat. aq. Na₂CO₃, then the organic layer was dried over anhydrous MgSO₄, 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, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₂₁⁷⁷BrIN₂O₄S (MH⁺) 578.9450; found 578.9447; HRMS calcd for C₁₅H₂₁⁶¹BrIN₂O₄S (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), PPh₃ (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$_2$Cl$_2$ (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$_2$Cl$_2$. 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
calc'd for C$_{18}$H$_{18}$N$_3$O$_6$S$^{79}$BrI (MH$^+$) 609.9144 found 609.9135, HRMS calc'd for
C$_{18}$H$_{18}$N$_3$O$_6$S$^{81}$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$_2$CO$_3$ (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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 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$^{-1}$) $\upsilon_{\text{max}}$ 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$_{19}$BrIN$_2$O$_2$S (MH$^+$) 520.9392; found 520.9395; HRMS calcd for C$_{17}$H$_{19}$BrIN$_2$O$_2$S 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$_2$CO$_3$ (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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_{16}$BrIN$_2$O$_2$S (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$_3$)$_2$Cl$_2$ (188 mg, 0.26 mmol), and Et$_3$N (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 CHCl₃ then washed with water. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated in 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%).

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) v max 3284, 2951, 1732, 1556, 1454, 1323, 1203, 1157, 1091, 952, 813, 659; MS (ESI+) m/z 475 (MNa+, Br), 477 (MNa+, Br) HRMS calcd for C₁₉H₂₂N₂O₄S₇9Br (MH⁺) 453.0484 found 453.0483, calcd for C₁₉H₂₂N₂O₂S₈₁Br (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(PPh₃)₂Cl₂ (206 mg, 0.29 mmol), and Et₃N (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 CHCl₃ then washed with water and 2M aq. HCl. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated in 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%).

¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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\(^{-1}\)) \(\nu_{\text{max}}\) 3233, 3097, 3024, 2951, 1714, 1697, 1633, 1583, 1537, 1359, 1122, 952, 731, 499; MS (ESI+) \(m/z\) 484 (MH\(^+\), 100), 486 (MH\(^+\), 89); HRMS calcd for C\(_{18}\)H\(_{19}\)BrN\(_3\)O\(_6\)S (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\(_4\)Cl. 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).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(^{-1}\)) \(\nu_{\text{max}}\) 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\(_2\)O\(_4\)S\(^{79}\)Br (MH\(^+\)) 453.0484 found 453.0498, calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_4\)S\(^{81}\)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\(_4\)Cl, 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 172.8, 162.2, 143.9, 141.8, 139.1, 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\(^{-1}\)) \(\nu_{\text{max}}\) 3495, 2096, 1645, 1435, 1344, 1165, 1089, 912; MS (ESI+) \(m/z\) 475 (MNa\(^+\), 79 Br), 477 (MNa\(^+\), 81 Br); HRMS calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_4\)S\(_79\)Br (MH\(^+\)) 453.0484 found 453.0491, calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_4\)S\(_{81}\)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\(_4\)Cl. 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_3\)O\(_6\)S (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\(_4\)Cl, then extracted 3x with CHCl\(_3\), then washed with brine. The combined organic
layers were dried over anhydrous MgSO₄, filtered and concentrated to give piperidine 10b quantitatively as a mixture of diastereomers (5:95 cis:trans).

¹H NMR (400 MHz, CDCl₃) 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 LiAlH₄ (76 mg, 2 mmol) was added portion wise. The mixture was quenched by careful addition of sat. aq. Na₂SO₄ 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%).

¹H NMR (400 MHz, CDCl₃) 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 (dd, 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); ¹³C NMR (100 MHz, CDCl₃) 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) νmax 3489, 2088, 1637, 1435, 1338, 1163, 985MS (ESI+) m/z 447 (MNa⁺, ⁷⁹Br), 449 (MNa⁺, ⁸¹Br); HRMS calcd for C₁₈H₂₂N₂O₃S⁷⁹Br (MH⁺) 425.0535 found 425.0569, calcd for C₁₈H₂₂N₂O₃S⁸¹Br (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 LiAlH₄ (0.166 g, 4.38 mmol) was added portion wise over 1 h. The mixture was quenched by careful addition of sat. aq. Na₂SO₄ solution and concentrated in vacuo. The residue was purified by column chromatography eluting with CH₂Cl₂:MeOH:NH₃(aq) 95:5:1 to give piperidine 11b as a yellow oil (696 mg, 1.52 mmol, dr 1:1, 70%).

¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (400 MHz, CDCl₃) 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 C₁₇H₁₉BrN₃O₅S (MH⁺) 456.0229; found 456.0220.

N-Tosyl cytisine (12a): A solution of cis/trans-11a (0.37 g, 0.87 mmol) and Et₃N (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 CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. A white foamy material was obtained (0.42 g, quantitative). The obtained mixture of mesylates in CHCl₃ (25 mL) was heated at reflux for 4 h then cooled to room temperature. Sat. aq. Na₂CO₃ (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 MgSO₄, 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%).

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.46 (d, J = 8.1 \text{ Hz}, 2H), 7.24 (d, J = 7.9 \text{ Hz}, 3H), 6.43 (d, J = 9.1 \text{ Hz}, 1H), 5.97 (d, J = 6.7 \text{ Hz}, 1H), 3.89 (dt, J = 15.7, 11.0 \text{ Hz}, 2H), 3.82 – 3.70 (m, 2H), 3.04 (s, 1H), 2.74 (t, J = 13.2 \text{ Hz}, 2H), 2.51 (s, 3H), 2.40 (s, 2H), 2.27 – 2.01 (m, 1H), 1.91 (d, J = 13.1 \text{ Hz}, 1H), 1.72 (d, J = 13.1 \text{ Hz}, 1H); \]^13C NMR (100 MHz, CDCl3) 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\(^{-1}\)) \( \nu_{\text{max}} \) 3419, 2115, 1633, 1377, 1165, 1008, 948; MS (ESI+) \( m/z \) 455 (MH), 467 (MNa\(^{+}\)); HRMS calcd for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_3\)S 345.1273 found 345.1294; mp: 201-203°C.

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

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.63 (d, J = 8.2 \text{ Hz}, 1H), 7.50 (t, J = 7.7 \text{ Hz}, 1H), 7.35 (dd, J = 8.0, 4.1 \text{ Hz}, 2H), 7.26 (d, J = 7.5 \text{ Hz}, 1H), 4.46 – 4.25 (m, 1H), 3.71 – 3.61 (m, 1H), 3.58 – 3.46 (m, 1H), 2.45 (s, 2H), 2.38 – 2.23 (m, 1H), 2.05 (ddd, J = 15.3, 10.8, 4.8 \text{ Hz}, 1H), 1.91 – 1.79 (m, 1H); \]^13C NMR (100 MHz, CDCl3) 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\(^{-1}\)) \( \nu_{\text{max}} \) 3419, 2088, 1643, 1454, 1377, 999; MS (ESI+) \( m/z \) 525 (MNa\(^{+}\), 79Br), 527 (MNa\(^{+}\), 81Br); HRMS calcd for C\(_{19}\)H\(_{24}\)N\(_2\)O\(_5\)S\(_2\)\(^{79}\)Br (MH\(^{+}\)) 503.0310 found 503.0316, calcd for C\(_{19}\)H\(_{24}\)N\(_2\)O\(_5\)S\(_2\)\(^{81}\)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\(_3\)N (0.18 mL, 1.3 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)CO\(_3\) (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$^{-1}$) $\nu$$_{max}$ 3439, 2292, 1645, 1454, 1373, 1056, 956; MS (ESI+) m/z 376 (MH$^+$, 52), 751 (2MH$^+$, 100); HRMS calcd for C$_{17}$H$_{18}$N$_3$O$_5$S (MH$^+$) 376.0967; found 376.0982; $\alpha$$_{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$^{-1}$) $\nu$$_{max}$ 2852, 2358, 1581, 1519, 1155, 1060, 964, 723; MS (ESI+) m/z 534 (MH$^+$, 100), 536 (MH$^+$, 90); 556 (MNa$^+$, 24), 558 (MNa$^+$, 25); HRMS calcd for C$_{18}$H$_{21}$N$_3$O$_5$S$_2$Br (MH$^+$) 534.0004; found 534.9998; $\alpha$$_{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$_2$O (8.15 g, 194 mmol) was stirred in a 1:1 mixture of dioxane/H$_2$O (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 H₂O (100 ml) was added and extracted with 3x50 ml CH₂Cl₂. The combined organic layers were washed with brine and dried over anhydrous MgSO₄, 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, CDCl₃) 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); ^1^C NMR (100 MHz, CDCl₃) δ 173.8, 155.1, 141.2, 139.6, 127.2, 123.1, 42.5; FTIR (nujol, cm⁻¹) *ν* 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 KOt-Bu²⁵ (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. NH₄Cl (100 mL), extracted with 4x50 mL EtOAc and washed with brine (50 mL). The combined organic layers were dried over anhydrous MgSO₄, then filtered and concentrated *in vacuo*. 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 a 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, CDCl₃) 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); ^1^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$^{-1}$) $\nu_{\text{max}}$ 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$_{16}$BrN$_2$O$_3$ (MH$^+$) 375.0344; found 375.0340. HRMS calcd for C$_{17}$H$_{16}$BrN$_2$O$_3$ (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 KOT-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$_4$Cl (100 mL), extracted with EtOAc (4x40 mL), washed with H$_2$O (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%).

$^1$H 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$^{-1}$) $\nu_{\text{max}}$ 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$_{19}$BrIN$_2$O$_3$ (MH$^+$) 540.9624; found 540.9620. HRMS
calcd for C_{20}H_{19}BrIN_2O_3 (MH^+) 542.9603; found 542.9609; mp 117-118 °C; [α]_D^{21} -42 (c 0.11, MeOH)

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

^1H 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); ^13C 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) ν_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}BrIN_2O_3 (MH^+) 540.9624; found 540.9620; HRMS calcd for C_{20}H_{19}BrIN_2O_3 (MH^+) 542.9603; found 542.9613; [α]_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.

Acknowledgments

We thank Professor Richard Webster and Sher Li Gan for the electrochemical study. We thank Nanyang Technological University and the Singapore Ministry of Education Academic Research Fund Tier 1 (grant RG62/10) for financial support of this work.

References


5. Under the same conditions, 2-methoxy-6-methylpyridine gave a mere 16% yield, thus we were unable to intersect with the Honda synthesis: Honda, T.; Takahashi, R.; Namiki, H. Syntheses of (+)-Cytisine, (−)-Kuraramine, (−)-Isokuraramine, and (−)-Jussiaeiine A *J. Org. Chem.* **2005**, *70*, 499-504.


11. For an example of selective carbonylation of an iodide in the presence of a bromide, see Takahashi, T.; Kusaka, S.; Doi, T.; Sunazuka, T.; Omura, S. A Combinatorial Synthesis of a
Macrophelide Library Utilizing a Palladium-Catalyzed Carbonylation on a Polymer Support


13. Details of all X-ray structure determinations have been deposited with the Cambridge Crystallographic Data Centre and may be obtained at http://www.ccdc.cam.ac.uk; CCDC deposition numbers: cis-11a 1576570; 16a 1576602.


15. In contrast, van Tamelen (ref. 1) employed a monosubstituted pyridine and used an oxidation at this point.


17. Exposure of the major isomer 16a to KOt-Bu in THF at -40°C for 1 hour resulted in formation of a 56:44 mixture of diastereoisomers. The minor isomer 16b was converted to a 13:87 mixture under the same conditions.


21. We were unable to develop a suitable set of conditions for chiral HPLC.


25. Commercial KO'Bu was dissolved in dry THF and filtered under a nitrogen atmosphere to remove KOH. The solvent was removed under a stream of nitrogen (https://chemtips.wordpress.com/tag/potassium-butoxide/).