Supporting Information

Facile access to highly functionalized hydroisoquinoline derivatives via phosphine-catalyzed sequential [3 + 3]/[3 + 3] annulation

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I. General Information

All the solvents and achiral catalysts were obtained from commercial sources and used without further purification unless otherwise stated. Dry acetonitrile were distilled over calcium hydride. Yields referred to isolated compounds were obtained through preparative TLC. NMR spectra were recorded on Varian and Brucker ARX 400 spectrometer in CDCl₃ solution and the chemical shifts were reported in parts per million (ppm) relative to internal standard TMS (0 ppm) for ¹H NMR and chloroform-d (77.0 ppm) for ¹³C NMR. Coupling constants were given in Hertz (Hz). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), brs (broad singlet) and m (multiplet). Infrared spectra (IR) spectra were recorded on a Perkin-Elmer 983G instrument. High resolution mass spectrometry (HRMS) were obtained on an IonSpec FT-ICR mass spectrometer with ESI or MALDI resource. Melting points were measured on a RY-I apparatus and reported uncorrected.

II. General Procedure of N-sulfonamido-allenoates 2

1. synthesis of δ-sulfonamido-allenoates 2

The N-sulfonyl propargylamines were prepared following the modified procedure described in the reported literature.¹

To a solution of N-Ts imine (10.0 mmol) in THF (40.0 mL) at 0 °C was added ethynylmagnesium bromide (12.0 mmol, 0.5 M in THF) and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed twice with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Recrystallization from ethyl acetate and Petroleum ether afforded N-Ts propargylamine.

The δ-sulfonamido-allenoates were prepared following the modified procedure described in the reported literature.²,³

In a Schlenk flask filled nitrogen the corresponding propargylamine (2 mmol, 1.0 equiv) and CuI (0.4 mmol, 0.2 equiv) in dry acetonitrile (5 mL) was carefully added ethyl diazoacetate (2.2 mmol, 1.2 equiv). The reaction mixture was stirring at 40 °C for 3 h. Then the residue was quenched with saturated NH₄Cl solution, extracted with ethyl acetate and dried on MgSO₄. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (ethyl acetate / Petroleum ether, 1:5) to give δ-sulfonamido-allenoates (few cases mixed with inseparable coupling products).

2. Spectroscopic Data of δ-sulfonamido-allenoates 2
**Ethyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate 2a**

Yellow oil, 0.59 g, 79% yield, dr = 1:1. Data of single diastereomeric isomer. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65 (d, \(J = 8.1\) Hz, 2H), 7.27 – 7.16 (m, 7H), 5.67 (t, \(J = 6.5\) Hz, 1H), 5.52 (dd, \(J = 10.9, 9.0\) Hz, 2H), 5.10 (t, \(J = 7.3\) Hz, 1H), 4.22 – 4.08 (m, 2H), 2.40 (s, 3H), 1.25 (t, \(J = 7.1\) Hz, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) = 211.6, 165.0, 143.5, 138.6, 137.4, 129.6, 128.6, 128.1, 127.3, 126.8, 97.5, 91.0, 61.2, 56.0, 21.6, 14.2. HRMS (ESI) m/z Calcd for [C\(_{20}\)H\(_{22}\)NO\(_4\)S, M + H]\(^+\) :372.1264, Found: 372.1262.

**Ethyl 5-((4-methylphenyl)sulfonamido)-5-(p-tolyl)penta-2,3-dienoate 2b**

Yellow oil, 0.75 g, 95% yield, dr = 1:1. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.68 (dd, \(J = 8.2, 1.5\) Hz, 4H), 7.23 (d, \(J = 8.2\) Hz, 4H), 7.15 (dd, \(J = 8.1, 1.9\) Hz, 4H), 7.06 (dd, \(J = 7.7, 4.8\) Hz, 4H), 5.74 (dd, \(J = 5.9, 5.1\) Hz, 1H), 5.68 (t, \(J = 6.5\) Hz, 1H), 5.53 (dd, \(J = 6.1, 2.8\) Hz, 2H), 5.47 (d, \(J = 8.0\) Hz, 1H), 5.25 (d, \(J = 8.1\) Hz, 1H), 5.09 (td, \(J = 8.1, 3.4\) Hz, 2H), 4.23 (s, 6H), 3.21 (d, \(J = 2.7\) Hz, 6H), 1.37 – 1.30 (t, 3H), 1.28 (t, \(J = 7.1\) Hz, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) = 211.6, 211.0, 165.2, 165.0, 143.4, 138.2, 137.9, 137.7, 137.5, 135.8, 135.7, 129.5, 129.5, 129.4, 129.2, 127.3, 127.2, 126.7, 98.3, 97.6, 92.5, 90.9, 61.2, 61.1, 55.8, 55.2, 21.5, 21.1, 14.2. HRMS (ESI) m/z Calcd for [C\(_{21}\)H\(_{24}\)NO\(_4\)S, M + H]\(^+\) :386.1421, Found: 386.1419.

**Ethyl 5-((4-bromophenyl)-5-((4-methylphenyl)sulfonamido)penta-2,3-dienoate 2c**

Yellow oil, 0.89 g, 99% yield, dr = 1:1. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60 (d, \(J = 8.2\) Hz, 2H), 7.33 (dd, \(J = 7.4, 6.0\) Hz, 2H), 7.20 (d, \(J = 8.0\) Hz, 2H), 7.11 (d, \(J = 7.5\) Hz, 2H), 5.68 (dt, \(J = 12.8, 5.9\) Hz, 1H), 5.58 – 5.48 (m, 1H), 5.46 (d, \(J = 13.2\) Hz, 1H), 5.08 (dt, \(J = 12.9, 5.9\) Hz, 1H), 4.21 – 4.05 (m, 2H), 2.41 (s, 3H), 1.32 – 1.22 (m, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) = 211.7, 211.5, 150.8, 143.5, 137.7, 137.6, 137.4, 137.3, 131.7, 131.5, 129.6, 129.5, 129.1, 128.7, 127.2, 122.3, 122.1, 100.0, 97.8, 97.2, 92.8, 91.3, 61.3, 61.3, 55.5, 54.9, 21.5, 21.1, 14.2. HRMS (ESI) m/z Calcd for [C\(_{20}\)H\(_{21}\)BrNO\(_4\)S, M + H]\(^+\) :450.0369, Found: 450.0362.

**Ethyl 5-(furan-2-yl)-5-((4-methylphenyl)sulfonamido)penta-2,3-dienoate 2d**

Yellow oil, 0.43 g, 60% yield, dr = 1:1. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.69 (dd, \(J = 8.2\) Hz, 2H), 7.33 – 7.21 (m, 6H), 6.23 – 6.17 (m, 4H), 5.78 (dt, \(J = 17.3, 6.1\) Hz, 2H), 5.65 (dd, \(J = 6.2, 2.5\) Hz, 1H), 5.60 – 5.55 (m, 1H), 5.37 (d, \(J = 8.1\) Hz, 1H), 5.26 – 5.16 (m, 3H), 4.23 – 4.13 (m, 4H), 2.41 (d, \(J = 2.2\) Hz, 6H), 1.27 (dt, \(J = 9.1, 7.1\) Hz, 6H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) = 211.7, 211.5, 164.9, 164.8, 150.8, 150.7, 143.5, 143.5, 142.8, 142.6, 137.6, 129.8, 129.6, 127.3, 127.2, 127.2, 110.4, 108.2, 107.9,
Ethyl 5-((4-methylphenyl)sulfonamido)octa-2,3-dienoate 2e

Yellow oil, 0.31 g, 46% yield. Allenoate 2e and 2e' were mixed with inseparable ethyl 5-((4-methylphenyl)sulfonamido)oct-3-ynoate 2e''. 2e:2e':2e'' = 1.5:1:1.

\[ \text{2e, 2e', 2e''} \]

1H NMR (400 MHz, CDCl$_3$) δ 7.83 – 7.71 (m, 7H), 7.33 – 7.25 (m, 7H), 5.51 (dt, \( J = 6.7, 3.4 \) Hz, 2H), 5.46 (dd, \( J = 6.2, 3.0 \) Hz, 1H), 5.34 (dd, \( J = 7.2, 6.3 \) Hz, 1H), 5.17 (d, \( J = 8.5 \) Hz, 1H), 5.00 (d, \( J = 9.2 \) Hz, 1.5H), 4.95 (d, \( J = 9.0 \) Hz, 1H), 4.24 – 4.10 (m, 7H), 4.07 (ddd, \( J = 9.0, 7.0, 2.4 \) Hz, 1H), 4.02 – 3.94 (m, 1H), 3.93 – 3.85 (m, 1H), 2.95 (d, \( J = 1.9 \) Hz, (1.5 + 1 + 1) H), 2.43 (d, \( J = 4.1 \) Hz, 10.5H), 1.68 – 1.59 (m, (1.5 + 1 + 1) H), 1.59 – 1.51 (m, (1.5 + 1 + 1) H), 1.45 (ddd, \( J = 18.3, 7.4, 3.3 \) Hz, (1.5 + 1 + 1) H), 1.39 – 1.31 (m, (1.5 + 1 + 1) H), 1.30 – 1.22 (m, (4.5 + 3 + 3) H), 0.93 – 0.80 (m, (4.5 + 3 + 3) H).

13C NMR (101 MHz, CDCl$_3$) δ 211.1, 210.8, 167.8, 165.3, 165.2, 143.5, 143.3, 137.9, 137.8, 137.5, 129.7, 129.4, 127.5, 127.2, 127.1, 97.9, 97.0, 91.6, 90.1, 81.5, 61.6, 61.1, 61.1, 52.3, 51.3, 45.7, 38.6, 37.7, 25.7, 21.5, 21.5, 18.6, 18.5, 18.4, 14.1, 14.1, 13.5, 13.5, 13.4.

HRMS (ESI) m/z Calcd for [C$_{18}$H$_{19}$NNaO$_5$S, M + Na]$^+$: 384.0876, Found: 384.0878.

Isopropyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate 2f

Yellow oil, 0.44 g, 57% yield, dr = 1:1.

1H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, \( J = 8.2 \) Hz, 4H), 7.26 – 7.18 (m, 14H), 5.72 (dd, \( J = 6.1, 4.7 \) Hz, 1H), 5.69 – 5.63 (m, 1H), 5.53 – 5.47 (m, 2H), 5.38 (d, \( J = 8.0 \) Hz, 1H), 5.19 – 5.08 (m, 3H), 5.02 (ddd, \( J = 18.7, 12.5, 6.2 \) Hz, 2H), 2.40 (s, 6H), 1.28 (d, \( J = 6.3 \) Hz, 6H), 1.23 (d, \( J = 6.3 \) Hz, 6H).

13C NMR (101 MHz, CDCl$_3$) δ 211.5, 210.8, 164.7, 143.4, 138.7, 138.6, 137.6, 129.8, 129.6, 129.5, 128.7, 128.5, 128.3, 128.1, 127.3, 127.2, 126.8, 98.1, 97.5, 93.1, 91.4, 68.8, 68.7, 56.1, 55.4, 21.9, 21.9, 21.8, 21.5. HRMS (ESI) m/z Calcd for [C$_{21}$H$_{24}$NO$_4$S, M + H]$^+$: 386.1421, Found: 386.1421.

Tert-butyl 5-((4-methylphenyl)sulfonamido)-5-phenylpenta-2,3-dienoate 2g

Yellow oil, 0.60 g, 75% yield, dr = 1:1. Data of single diastereomeric isomer.

1H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, \( J = 8.1 \) Hz, 2H), 7.45 (s, 1H), 7.35 – 7.18 (m, 6H), 5.68 (t, \( J = 5.5 \) Hz, 1H), 5.43 (dd, \( J = 6.0, 3.3 \) Hz, 1H), 5.15 – 5.06 (m, 1H), 4.98 (s, 1H), 2.40 (s, 3H), 1.49 (s, 9H).

13C NMR (101 MHz, CDCl$_3$) δ 210.3, 164.2, 143.4, 138.9, 137.7, 129.5, 129.8, 128.7, 128.5, 128.3, 128.1, 127.3, 127.2, 126.8, 98.1, 97.5, 93.1, 91.4, 68.8, 68.7, 56.1, 55.4, 21.9, 21.9, 21.8, 21.5. HRMS (ESI) m/z Calcd for [C$_{22}$H$_{29}$N$_2$O$_4$S, M + NH$_4$]$^+$: 417.1843, Found: 417.1841.
III. Optimization of the Reaction Conditions

2-(1,3-diarylallylidene)malononitrile (1, 0.1 mmol) with δ-sulfonamido-allenoates (2, 0.2 mmol), additive (1 equiv) and solvent (1.0 mL) were added to a dry flask filled with Ar. Then catalyst (40 mol %) was added. This mixture was stirred at the corresponding temperature until the complete consumption of the starting materials monitored by TLC. After the removal of the solvent, the residue was purified by preparative TLC (petroleum ether: ethyl acetate = 5:1~3:1) to afford product 3.

Table S1. Optimization of the sequential [3 + 3]/[3 + 3] annulations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>cat. (40 mol %)</th>
<th>solvent</th>
<th>temp</th>
<th>additive</th>
<th>time</th>
<th>yield 3aa</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>-</td>
<td>2d</td>
<td>70%</td>
<td>4:3:1</td>
</tr>
<tr>
<td>2</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>40 °C</td>
<td>-</td>
<td>2d</td>
<td>38%</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>25 °C</td>
<td>-</td>
<td>2d</td>
<td>33%</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>80 °C</td>
<td>-</td>
<td>2d</td>
<td>28%</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>PBu₃</td>
<td>CH₃Cl₂</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>22%</td>
<td>4:5:1</td>
</tr>
<tr>
<td>6</td>
<td>PBu₃</td>
<td>(CH₂Cl)₂</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>9%</td>
<td>4:1</td>
</tr>
<tr>
<td>7</td>
<td>PBu₃</td>
<td>EA</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>18%</td>
<td>5:1</td>
</tr>
<tr>
<td>8</td>
<td>PBu₃</td>
<td>THF</td>
<td>60 °C</td>
<td>-</td>
<td>2d</td>
<td>13%</td>
<td>4:1</td>
</tr>
<tr>
<td>9</td>
<td>PBu₃</td>
<td>CH₃CN</td>
<td>60 °C</td>
<td>-</td>
<td>2d</td>
<td>26%</td>
<td>4:1</td>
</tr>
<tr>
<td>10</td>
<td>PBu₃</td>
<td>1,4-Dioxane</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>7%</td>
<td>4:1</td>
</tr>
<tr>
<td>11</td>
<td>PBu₃</td>
<td>tol</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>28%</td>
<td>2:1:1</td>
</tr>
<tr>
<td>12</td>
<td>PBu₃</td>
<td>DMSO</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>PBu₃</td>
<td>O</td>
<td>60 °C</td>
<td>-</td>
<td>3d</td>
<td>14%</td>
<td>2.5:1</td>
</tr>
<tr>
<td>14</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>MS, 4A</td>
<td>2d</td>
<td>69%</td>
<td>6.7:1</td>
</tr>
<tr>
<td>15</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>CH₂CO₂Na, 1eq</td>
<td>2d</td>
<td>62%</td>
<td>5.9:1</td>
</tr>
<tr>
<td>16</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>NH₂Ts, 1eq</td>
<td>2d</td>
<td>50%</td>
<td>6.1:1</td>
</tr>
<tr>
<td>17</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>CH₂COOH, 1eq</td>
<td>4d</td>
<td>59%</td>
<td>5.6:1</td>
</tr>
<tr>
<td>18</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>PhCOOH, 1eq</td>
<td>4d</td>
<td>77%</td>
<td>6:1</td>
</tr>
<tr>
<td>19</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>4d</td>
<td>79%</td>
<td>6.2:1</td>
</tr>
<tr>
<td>20</td>
<td>LBBA-Et</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>6d</td>
<td>33%</td>
<td>2:1</td>
</tr>
<tr>
<td>21</td>
<td>LBBA-Me</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>4d</td>
<td>45%</td>
<td>2.7:1</td>
</tr>
<tr>
<td>22</td>
<td>P(4-MeOC₆H₄)₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>4d</td>
<td>48%</td>
<td>4.7:1</td>
</tr>
<tr>
<td>23</td>
<td>PBu₃ (20 mol %)</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>4d</td>
<td>78%</td>
<td>4:1:1</td>
</tr>
<tr>
<td>24</td>
<td>PBu₃</td>
<td>CHCl₃</td>
<td>60 °C</td>
<td>Buffer</td>
<td>4d</td>
<td>61%</td>
<td>3:1:1</td>
</tr>
</tbody>
</table>

(84%°)
IV. Reaction on gram Scale

2-(1,3-diarylallylidene)malononitrile 1f (1.8 mmol, 0.60 g) with δ-sulfonamido-allenoates 2a (3.6 mmol, 1.34 g), AcONa (1.8 mmol, 147.6 mg), AcOH (1.8mmol, 103 µL) and CHCl₃ (18 mL) were added to a dry flask filled with Ar. Then PBu₃ (0.72 mmol, 153.3 mg) was added. This mixture was stirred for 4 days at 60 °C until the complete consumption of the starting materials monitored by TLC. The reaction was quenched by the addition of water and the aqueous layer was extracted with ethyl acetate and dried on MgSO₄. After removal of the solvent, the crude product was purified by column chromatography (Petroleum ether/ ethyl acetate = 10:1 to 5:1) to give product 3fa (1.13 g, 89% yield) with dr of 3.7:1.

V. Table S2. Chiral phosphine catalysts catalyzed sequential [3 + 3]/[3 + 3] annulation

<table>
<thead>
<tr>
<th>entry</th>
<th>Cat. (40 mol %)</th>
<th>conditions</th>
<th>yield &amp; dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNHTsPPh₂</td>
<td>25 °C, 6d</td>
<td>31%, dr = 4.3:1</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>PhNHTsPPh₂</td>
<td>25 °C, 4d</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Conditions</td>
<td>Yield</td>
<td>Dr</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>3</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>25 °C, 4d</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>PhCOOH, 1eq 25 °C, 10d</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td><img src="structure5.png" alt="Structure" /></td>
<td>PhCOOH, 1eq 25 °C, 10d</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td><img src="structure6.png" alt="Structure" /></td>
<td>AcONa/AcOH=1eq:1eq 25 °C, 4d</td>
<td>nd</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td><img src="structure7.png" alt="Structure" /></td>
<td>AcONa/AcOH=1eq:1eq 60 °C, 4d</td>
<td>80%, dr = 4.8:1</td>
<td>12%</td>
</tr>
<tr>
<td>8</td>
<td><img src="structure8.png" alt="Structure" /></td>
<td>AcONa/AcOH=1eq:1eq 60 °C, 6d</td>
<td>72%, dr = 5.2:1</td>
<td>-14%</td>
</tr>
</tbody>
</table>

Reaction condition: **1a** (0.1 mmol), **2a** (0.2 mmol), cat. (40 mol %) in solvent (1 mL). Dr was determined through $^1$H NMR spectroscopy. 1eq = 1 equiv.

**VI. Discussion about the mechanism**

There are triple additions of δ-sulfonamido-allenoates to 2-(1,3-Diarylallylidene)malononitrile **1** during the proposed mechanism cycle, which is quite different from any reaction mode of phosphine-catalyzed allenoates reported yet. Fortunately, the structure of side product **4aa** gave us a clue of possible pathway of how the addition initiates, as shown in Figure 3 in main text. It is still mysterious how intermediate **B** is formed through intermediate **α-A**. In 2013, Tong and coworkers reported an isomerization of 5-hydroxyl-2,3-dienoate catalyzed by PPh$_3$, leading to 5-oxohex-2(3)-enoate.$^3$ They proposed a convincing mechanism that consisted of continuous proton shifts and keto-enol tautomerism (Figure S1, a).

**Figure S1**. Possible pathway from **2** to intermediate **B**
However, in our case, none of such isomerization product was detected. In our opinion, this is the reason why δ-sulfonamido-allenoates could participate in this \([3 + 3]/[3 + 3]\) domino annulation. We speculated that there is a similar process when it comes to δ-sulfonamido-allenoates (Figure S1, b), given that the enamine structure of side product 4aa is analogous to T5. Generally, \(\alpha\)-A can be transformed into S-int 2 after continuous H-shifts with the help of -NHTs. Next, intermediate S-int 3, which is a resonance form of S-int 2, undergoes 1,2-H-shift to afford key intermediate B, which attacks the electrophilic diene to initiate the whole annulation. [D]-3fa with incorporation of deuterium at the C1 position may imply the possibility of appearance of S-int 3. The fact that no deuterium was found at the amine position is confusing. We speculated that the imine-enamine tautomerism takes place fast and hydrogen atoms of the amine stem from starting substrates. The structure of cyano-enamine is relatively stable that excludes the possibility of hydrogen-exchanging with D\(_2\)O after the reaction completes.
VII. Spectroscopic Data and HPLC Chromatogram

Combined yields are given. Diastereomeric isomers could not be separated by flash column chromatography. Major isomers (syn-) were obtained after recrystallization in CH$_2$Cl$_2$/n-Hexane 2 or 3 times. NMR and other data only for major isomers (syn-) is given below. Pure minor isomers (anti-) were not available after recrystallization. The NMR data of isomers mixture is not included because it is quite complicated. Side product 4aa was isolated as mixture of 3 pairs of diastereomeric isomers and its analytic data is not included in this text. Fortunately, the structure of 4aa was determined by analogy (4ba CCDC 1942509).

**Ethyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3aa)**

Combined Yield: 84% (54.0 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 207-208 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 2.5$ Hz, 1H), 7.60 – 7.56 (m, 2H), 7.55 – 7.44 (m, 3H), 7.33 – 7.25 (m, 3H), 7.20 (d, $J = 7.1$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 7.0$ Hz, 4H), 6.79 (d, $J = 8.2$ Hz, 2H), 5.22 (s, 2H), 3.92 (dq, $J = 10.9$, 7.1 Hz, 1H), 3.77 (dq, $J = 10.9$, 7.1 Hz, 1H), 3.08 (ddd, $J = 11.8$, 4.3, 2.6 Hz, 1H), 2.34 (dd, $J = 13.1$, 4.5 Hz, 1H), 2.30 (s, 3H), 2.03 – 1.92 (m, 1H), 0.80 (t, $J = 7.0$ Hz, 3H).
7.1 Hz, 3H).

^{13}C \text{ NMR} (101 MHz, CDCl_3) \delta 166.9, 162.7, 160.2, 151.7, 146.5, 144.9, 139.7, 139.7, 135.5, 135.1, 133.6, 133.4, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.4, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 13.6.

^{19}F \text{ NMR} (376 MHz, CDCl_3) \delta -116.54.

IR (KBr, cm^{-1}): 3483, 2923, 2850, 2188, 1710, 1638, 1510, 1366, 1250, 1170, 1102, 1086, 1014, 838, 698, 663, 583.

HRMS (ESI) m/z Calcd for [C_{38}H_{31}FN_{3}O_{4}S, M - H]^{-} :644.2025, Found: 644.2022.

Ethyl (4aR,6R)-3-amino-4-cyano-1,4a,6-triphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ba)

Combined Yield: 83% (52.1 mg), dr = 3.3:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. >220 °C

^{1}H \text{ NMR} (400 MHz, CDCl_3) \delta 7.63 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 2H), 7.49 - 7.45 (m, 1H), 7.35 – 7.24 (m, 3H), 7.21 (d, J = 7.2 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 7.1 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 5.21 (s, 2H), 3.90 (tt, J = 14.2, 7.1 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.08 (d, J = 10.9 Hz, 1H), 2.37 (dd, J = 13.1, 4.3 Hz, 1H), 2.30 (s, 3H), 2.01 (t, J = 12.5 Hz, 1H), 0.73 (t, J = 7.1 Hz, 3H).

^{13}C \text{ NMR} (101 MHz, CDCl_3) \delta 166.9, 162.8, 160.2, 151.7, 146.5, 144.9, 139.7, 139.7, 135.5, 135.1, 133.6, 133.4, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.4, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 13.6.

IR (KBr, cm^{-1}): 3468, 3392, 2188, 1711, 1637, 1393, 1251, 1169, 1086, 1029, 1012, 754, 699, 662, 608, 563.

HRMS (ESI) m/z Calcd for [C_{38}H_{32}FN_{3}O_{4}S, M - H]^{-} :626.2119, Found: 626.2116.

Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(p-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ca)

Combined Yield: 86% (55.4 mg), dr = 4:1;

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 153-155 °C

^{1}H \text{ NMR} (400 MHz, CDCl_3) \delta 7.60 (dd, J = 11.4, 4.7 Hz, 3H), 7.58 (d, J = 7.3 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.35 – 7.24 (m, 3H), 7.25 (d, J = 7.2 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 7.1 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 5.21 (s, 2H), 3.90 (tt, J = 10.7, 7.1 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.08 (d, J = 10.9 Hz, 1H), 2.37 (dd, J = 13.1, 4.3 Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 1.99 (t, J = 12.5 Hz, 1H), 0.79 (t, J = 7.1 Hz, 3H).

^{13}C \text{ NMR} (101 MHz, CDCl_3) \delta 167.1, 151.7, 146.7, 144.8, 140.9, 139.3, 136.2, 135.8, 135.2, 133.6, 132.9, 129.9, 129.4, 129.2, 129.1, 128.7, 128.5, 127.9, 121.0, 126.8, 125.9, 125.7, 119.1, 115.1, 60.3, 47.4,
Ethyl (4aR,6R)-3-amino-4-cyano-6-(4-methoxyphenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3da)

Combined Yield: 69% (45.4 mg), dr = 3.7:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 162-163 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 – 7.56 (m, 3H), 7.49 (dt, $J = 22.2$, 7.1 Hz, 3H), 7.31 (dd, $J = 14.2$, 7.2 Hz, 2H), 7.26 (d, $J = 4.3$ Hz, 1H), 7.20 (d, $J = 7.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 4H), 6.80 (dd, $J = 10.8$, 8.5 Hz, 4H), 6.70 (d, $J = 8.6$ Hz, 2H), 5.20 (s, 2H), 3.92 (dq, $J = 14.3$, 7.1 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.72 (s, 3H), 3.04 (d, $J = 10.4$ Hz, 1H), 2.34 (dd, $J = 13.2$, 4.5 Hz, 1H), 2.30 (s, 3H), 1.98 (t, $J = 12.5$ Hz, 1H), 0.80 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.2, 158.1, 151.7, 146.6, 144.9, 139.3, 136.3, 136.0, 135.2, 133.6, 132.7, 129.9, 129.4, 129.3, 128.7, 128.5, 128.1, 127.9, 126.8, 125.9, 125.6, 119.1, 113.8, 60.3, 55.3, 47.3, 40.7, 38.5, 21.6, 13.7.

IR (KBr, cm$^{-1}$): 3465, 2918, 2187, 1712, 1639, 1395, 1326, 1259, 119.0, 60.4, 47.1, 40.5, 39.3, 21.7, 13.5.

Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ea)

Combined Yield: 89% (62.1 mg), dr = 3.4:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 145-147 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (s, 1H), 7.61 (d, $J = 7.0$ Hz, 2H), 7.58 – 7.50 (m, 3H), 7.45 (d, $J = 7.9$ Hz, 2H), 7.39 – 7.28 (m, 4H), 7.23 (d, $J = 7.2$ Hz, 1H), 7.11 – 7.02 (m, 4H), 5.27 (s, 2H), 3.95 (dq, $J = 14.1$, 6.9 Hz, 1H), 3.78 (dq, $J = 14.4$, 7.1 Hz, 1H), 3.18 (d, $J = 10.6$ Hz, 1H), 2.37 (dd, $J = 13.3$, 4.1 Hz, 1H), 2.33 (s, 3H), 2.00 (t, $J = 12.4$ Hz, 1H), 0.78 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.5, 151.7, 148.4, 146.4, 145.0, 140.2, 135.0, 134.3, 134.2, 133.5, 129.9, 129.5, 129.4, 128.8, 128.6, 127.9, 127.4, 127.0, 125.8, 125.4, 125.2, 119.0, 60.4, 47.1, 40.5, 39.3, 21.7, 13.5.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.28, -62.30.

IR (KBr, cm$^{-1}$): 3465, 2189, 1712, 1639, 1395, 1326, 1255, 1169, 1112, 1017, 751, 699, 663, 563.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{36}$N$_3$O$_4$S, M + H]$^+$: 656.2225, Found: 656.2222.

Ethyl (4aR,6R)-3-amino-6-(4-(trifluoromethyl)phenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ea)

Combined Yield: 89% (62.1 mg), dr = 3.4:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 145-147 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (s, 1H), 7.61 (d, $J = 7.0$ Hz, 2H), 7.58 – 7.50 (m, 3H), 7.45 (d, $J = 7.9$ Hz, 2H), 7.39 – 7.28 (m, 4H), 7.23 (d, $J = 7.2$ Hz, 1H), 7.11 – 7.02 (m, 4H), 5.27 (s, 2H), 3.95 (dq, $J = 14.1$, 6.9 Hz, 1H), 3.78 (dq, $J = 14.4$, 7.1 Hz, 1H), 3.18 (d, $J = 10.6$ Hz, 1H), 2.37 (dd, $J = 13.3$, 4.1 Hz, 1H), 2.33 (s, 3H), 2.00 (t, $J = 12.4$ Hz, 1H), 0.78 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.5, 151.7, 148.4, 146.4, 145.0, 140.2, 135.0, 134.3, 134.2, 133.5, 129.9, 129.5, 129.4, 128.8, 128.6, 127.9, 127.4, 127.0, 125.8, 125.4, 125.2, 119.0, 60.4, 47.1, 40.5, 39.3, 21.7, 13.5.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -62.28, -62.30.

IR (KBr, cm$^{-1}$): 3465, 2189, 1712, 1639, 1395, 1326, 1255, 1169, 1112, 1017, 751, 699, 663, 563.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{36}$N$_3$O$_4$S, M + H]$^+$: 656.2225, Found: 656.2222.

Ethyl (4aR,6R)-3-amino-6-(4-(bromophenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydro-
isoquinoline-7-carboxylate (3fa)

Combined Yield: 97% (68.9 mg), dr = 3.7:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 166-167 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, $J = 2.2$ Hz, 1H), 7.61 (d, $J = 7.2$ Hz, 2H), 7.54 (dd, $J = 14.1$, 6.6 Hz, 3H), 7.33 (dd, $J = 15.4$, 6.9 Hz, 5H), 7.23 (d, $J = 7.3$ Hz, 2H), 7.08 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 8.1$ Hz, 4H), 5.24 (s, 2H), 3.96 (dq, $J = 14.3$, 7.1 Hz, 1H), 3.82 (dq, $J = 14.3$, 7.1 Hz, 1H), 3.09 (d, $J = 11.3$ Hz, 1H), 2.41 – 2.34 (m, 1H), 2.33 (s, 3H), 1.98 (t, $J = 12.5$ Hz, 1H), 0.85 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.7, 151.7, 146.4, 144.9, 143.2, 139.9, 135.1, 134.9, 133.7, 133.5, 131.5, 129.9, 129.4, 128.9, 128.8, 128.5, 127.9, 127.0, 125.3, 120.0, 119.0, 60.4, 47.2, 40.5, 38.9, 21.7, 13.7.

IR (KBr, cm$^{-1}$): 3461, 2188, 1708, 1637, 1394, 1250, 1169, 1186, 1012, 233, 753, 699, 663, 544.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{31}$BrN$_3$O$_4$S, M - H]: 704.1224, Found: 704.1221.

Ethyl (4aR,6R)-3-amino-6-(4-chlorophenyl)-4-cyano-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ga)

Combined Yield: 80% (52.8 mg), dr = 4.1:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 159-160 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, $J = 2.4$ Hz, 1H), 7.58 (d, $J = 7.0$ Hz, 2H), 7.52 (t, $J = 7.2$ Hz, 2H), 7.47 (d, $J = 7.1$ Hz, 1H), 7.30 (dd, $J = 14.7$, 7.3 Hz, 3H), 7.20 (d, $J = 7.3$ Hz, 2H), 7.14 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 8.2$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.1$ Hz, 2H), 5.24 (s, 2H), 3.93 (dq, $J = 14.3$, 7.1 Hz, 1H), 3.84 – 3.73 (m, 1H), 3.07 (dd, $J = 8.0$, 2.5 Hz, 1H), 2.33 (dd, $J = 13.2$, 4.4 Hz, 1H), 2.29 (s, 3H), 1.96 (t, $J = 12.5$ Hz, 1H), 0.81 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.7, 151.8, 146.5, 144.9, 142.7, 139.9, 135.1, 135.0, 133.7, 133.5, 132.0, 129.9, 129.4, 128.8, 128.6, 128.5, 128.5, 127.9, 127.0, 125.9, 125.4, 119.0, 60.4, 47.2, 40.6, 38.9, 21.6, 13.6.

IR (KBr, cm$^{-1}$): 3463, 2188, 1709, 1637, 1491, 1394, 1252, 1169, 1087, 1015, 754, 699, 663, 564.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{31}$ClN$_3$O$_4$S, M - H]: 660.1729, Found: 660.1726.

Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(m-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ha)

Combined Yield: 87% (55.6 mg), dr = 4:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. >220 °C
\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.58 (dd, \( J = 8.7, 4.8 \) Hz, 3H), 7.50 (t, \( J = 7.3 \) Hz, 2H), 7.44 (t, \( J = 7.2 \) Hz, 1H), 7.33 – 7.25 (m, 3H), 7.20 (d, \( J = 6.9 \) Hz, 2H), 7.06 (d, \( J = 8.3 \) Hz, 2H), 6.99 – 6.93 (m, 3H), 6.77 (d, \( J = 8.1 \) Hz, 3H), 5.18 (s, 2H), 3.91 – 3.81 (m, 1H), 3.76 – 3.65 (m, 1H), 3.28 (d, \( J = 10.9 \) Hz, 1H), 2.28 (s, 3H), 2.26 – 2.21 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 (s, 3H), 0.69 (t, \( J = 7.1 \) Hz, 3H).

\( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 167.1, 151.7, 146.5, 144.9, 142.1, 139.2, 136.7, 135.2, 135.0, 133.6, 132.8, 130.1, 129.9, 129.3, 129.2, 128.7, 128.5, 127.9, 126.9, 126.3, 126.1, 125.8, 125.6, 125.5, 119.1, 60.2, 46.0, 40.8, 34.4, 21.6, 18.7, 13.4.

IR (KBr, cm\(^{-1}\)): 3465, 3365, 2919, 2188, 1711, 1637, 1367, 1250, 1169, 1086, 1033, 1013, 751, 699, 663, 567.

HRMS (ESI) m/z Calcd for \([\text{C}_{39}\text{H}_{36}\text{N}_3\text{O}_4\text{S}, \text{M} + \text{H}]^+\) : 642.2421, Found: 642.2424.

**Ethyl (4aR,6R)-3-amino-4-cyano-1,4a-diphenyl-6-(o-tolyl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ia)**

\[ \begin{array}{c}
\text{EtO}_2 \\
\text{Ph} \\
\text{NTs} \\
\text{Ph} \\
\text{CN} \\
\text{NH}_2 \\
\end{array} \]

Combined Yield: 61% (39.2 mg), dr = 3.6:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 216-218 °C
\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.60 (dd, \( J = 8.5, 4.8 \) Hz, 3H), 7.52 (t, \( J = 7.3 \) Hz, 2H), 7.49 – 7.44 (m, 1H), 7.29 (dd, \( J = 16.2, 8.5 \) Hz, 3H), 7.22 (d, \( J = 7.2 \) Hz, 2H), 7.08 (d, \( J = 8.1 \) Hz, 2H), 6.99 (s, 3H), 6.78 (d, \( J = 7.9 \) Hz, 3H), 5.22 (s, 2H), 3.87 (dt, \( J = 14.2, 7.1 \) Hz, 1H), 3.74 (d, \( J = 7.1 \) Hz, 1H), 3.31 (d, \( J = 11.3 \) Hz, 1H), 2.30 (s, 3H), 2.28 – 2.22 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 (s, 3H), 0.71 (t, \( J = 7.1 \) Hz, 3H).

\( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 166.4, 151.7, 145.8, 145.0, 140.4, 140.1, 135.0, 134.4, 134.1, 133.9.

IR (KBr, cm\(^{-1}\)): 3466, 3367, 2188, 1711, 1637, 1250, 1169, 1086, 1033, 751, 699, 663, 567, 543.

HRMS (ESI) m/z Calcd for \([\text{C}_{39}\text{H}_{36}\text{N}_3\text{O}_4\text{S}, \text{M} + \text{H}]^+\) : 642.2421, Found: 642.2425.

**Ethyl (4aR,6S)-3-amino-4-cyano-6-(2,4-dichlorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ja)**

\[ \begin{array}{c}
\text{EtO}_2 \\
\text{Ph} \\
\text{NTs} \\
\text{Ph} \\
\text{CN} \\
\text{NH}_2 \\
\end{array} \]

Combined Yield: 88% (61.4 mg), dr = 5.5:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 184-185 °C
\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.71 (d, \( J = 2.3 \) Hz, 1H), 7.59 (d, \( J = 7.1 \) Hz, 2H), 7.50 (dt, \( J = 20.5, 7.0 \) Hz, 3H), 7.36 – 7.25 (m, 4H), 7.20 (d, \( J = 7.1 \) Hz, 2H), 7.07 (d, \( J = 8.2 \) Hz, 3H), 6.80 (dd, \( J = 12.5, 8.4 \) Hz, 3H), 5.24 (s, 2H), 4.00 – 3.88 (m, 1H), 3.85 – 3.75 (m, 1H), 3.66 (d, \( J = 10.9 \) Hz, 1H), 2.38 (dd, \( J = 12.9, 4.2 \) Hz, 1H), 2.29 (s, 3H), 1.81 (t, \( J = 12.4 \) Hz, 1H), 0.83 (t, \( J = 7.1 \) Hz, 3H).

\( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 166.4, 151.7, 145.8, 145.0, 140.4, 140.1, 135.0, 134.4, 134.1, 133.9.
Ethyl (4aR,6R)-3-amino-4-cyano-6-(naphthalen-2-yl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ka)

Combined Yield: 94% (63.9 mg), dr = 3.2:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 174-175 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 2.4$ Hz, 1H), 7.65 – 7.59 (m, 3H), 7.57 – 7.46 (m, 3H), 7.37 (dd, $J = 14.3, 6.8$ Hz, 4H), 7.29 (t, $J = 7.0$ Hz, 5H), 7.11 (d, $J = 8.2$ Hz, 2H), 7.04 (d, $J = 7.4$ Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 2H), 5.20 (s, 2H), 4.01 (d, $J = 11.1$ Hz, 1H), 3.80 (td, $J = 14.1, 7.0$ Hz, 1H), 2.54 (dd, $J = 13.3, 4.1$ Hz, 1H), 2.31 (s, 3H), 2.07 (t, $J = 12.5$ Hz, 1H), 0.42 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.2, 151.8, 146.4, 144.9, 140.5, 139.4, 136.6, 135.2, 133.8, 133.6, 133.1, 131.1, 129.9, 129.4, 129.3, 128.9, 128.6, 128.0, 127.1, 126.8, 126.0, 125.9, 125.6, 125.4, 125.4, 123.1, 119.0, 60.1, 46.6, 40.9, 33.5, 21.7, 13.3.

IR (KBr, cm$^{-1}$): 3677, 3656, 2924, 2188, 1712, 1638, 1394, 1251, 1169, 1085, 1013, 676, 569, 542.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{30}$Cl$_2$N$_3$O$_4$S, M - H]: 694.1340, Found: 694.1338.

Ethyl (4aR,6S)-3-amino-4-cyano-1,4a-diphenyl-6-(thiophen-2-yl)-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3la)

Combined Yield: 85% (54.0 mg), dr = 4.5:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 217-218 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.55 (d, $J = 7.0$ Hz, 3H), 7.52 – 7.41 (m, 3H), 7.28 (dd, $J = 14.9, 7.2$ Hz, 3H), 7.18 (d, $J = 7.1$ Hz, 2H), 7.07 – 6.96 (m, 3H), 6.77 (d, $J = 7.7$ Hz, 3H), 6.61 (s, 1H), 5.20 (s, 2H), 4.02 – 3.90 (m, 1H), 3.87 – 3.75 (m, 1H), 3.41 (d, $J = 10.8$ Hz, 1H), 2.46 (dd, $J = 12.8, 3.6$ Hz, 1H), 2.28 (s, 3H), 2.11 (t, $J = 12.4$ Hz, 1H), 0.86 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.8, 151.7, 146.6, 146.3, 144.9, 139.8, 135.4, 135.1, 133.6, 132.6, 129.9, 129.4, 128.8, 128.5, 127.9, 127.0, 126.6, 125.9, 125.2, 124.2, 123.0, 119.0, 60.4, 47.6, 40.6, 34.4, 21.6, 13.7.

IR (KBr, cm$^{-1}$): 3750, 3112, 2931, 2187, 1712, 1638, 1394, 1249, 1169, 1085, 1013, 699, 663, 559, 543, 518, 456.

HRMS (ESI) m/z Calcd for [C$_{36}$H$_{30}$N$_3$O$_4$S$_2$, M - H]: 676.2276, Found: 676.2273.
Ethyl (4aR,6S)-3-amino-4-cyano-6-(furan-2-yl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ma)

Combined Yield: 49% (30.5 mg), dr = 3.8:1;
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 214-215 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 – 7.45 (m, 6H), 7.36 – 7.27 (m, 3H), 7.23 – 7.16 (m, 3H), 7.07 (d, $J$ = 8.2 Hz, 2H), 6.81 (d, $J$ = 8.1 Hz, 2H), 6.22 (s, 1H), 5.88 (d, $J$ = 3.0 Hz, 1H), 5.25 (s, 2H), 4.04 (tt, $J$ = 14.2, 7.1 Hz, 1H), 3.95 – 3.84 (m, 1H), 3.32 – 3.24 (m, 1H), 2.37 (dd, $J$ = 13.0, 4.3 Hz, 1H), 2.32 (s, 3H), 2.19 (t, $J$ = 12.5 Hz, 1H), 0.99 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.6, 155.8, 151.7, 146.3, 144.9, 140.5, 139.9, 135.1, 133.5, 133.2, 129.9, 129.4, 128.8, 128.5, 127.9, 127.0, 125.9, 125.2, 119.0, 110.4, 105.1, 60.5, 44.1, 40.4, 32.8, 21.6, 13.8.

IR (KBr, cm$^{-1}$): 3742, 3468, 2188, 1711, 1369, 1366, 1251, 1170, 1086, 1016, 748, 699, 663, 569.

HRMS (ESI) m/z Calcd for [C$_{36}$H$_{32}$N$_3$O$_5$S, M + H]$^+$: 618.2057, Found: 618.2052.

Ethyl (4aR,6R)-3-amino-4a-(4-bromophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3na)

Combined Yield: 86% (61.0 mg), dr = 4:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 209-209 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J$ = 2.4 Hz, 1H), 7.52 (dt, $J$ = 21.3, 7.0 Hz, 5H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.20 – 7.09 (m, 5H), 7.02 (d, $J$ = 8.4 Hz, 2H), 6.90 (t, $J$ = 7.5 Hz, 4H), 5.38 (s, 2H), 3.90 (dq, $J$ = 10.9, 7.1 Hz, 1H), 3.74 (dq, $J$ = 10.8, 7.1 Hz, 1H), 3.06 (dd, $J$ = 7.9, 2.5 Hz, 1H), 2.40 (s, 3H), 2.26 (dd, $J$ = 13.2, 4.4 Hz, 1H), 1.99 (t, $J$ = 12.5 Hz, 1H), 0.73 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.0, 152.0, 146.1, 145.5, 143.6, 139.7, 136.1, 135.2, 133.6, 133.4, 133.0, 131.6, 129.8, 129.4, 129.3, 128.6, 128.5, 127.9, 127.7, 127.1, 126.5, 125.4, 121.1, 118.9, 60.3, 47.0, 40.4, 39.3, 21.7, 13.5.

IR (KBr, cm$^{-1}$): 3465, 3374, 2188, 1711, 1636, 1598, 1399, 1253, 1170, 1086, 1006, 825, 752, 700, 662, 538.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{31}$BrN$_3$O$_4$S, M - H]$^-$: 704.1224, Found: 704.1220.

Ethyl (4aR,6R)-3-amino-4a-(4-chlorophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3oa)

Combined Yield: 86% (61.0 mg), dr = 4:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 209-209 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J$ = 2.4 Hz, 1H), 7.52 (dt, $J$ = 21.3, 7.0 Hz, 5H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.20 – 7.09 (m, 5H), 7.02 (d, $J$ = 8.4 Hz, 2H), 6.90 (t, $J$ = 7.5 Hz, 4H), 5.38 (s, 2H), 3.90 (dq, $J$ = 10.9, 7.1 Hz, 1H), 3.74 (dq, $J$ = 10.8, 7.1 Hz, 1H), 3.06 (dd, $J$ = 7.9, 2.5 Hz, 1H), 2.40 (s, 3H), 2.26 (dd, $J$ = 13.2, 4.4 Hz, 1H), 1.99 (t, $J$ = 12.5 Hz, 1H), 0.73 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.0, 152.0, 146.1, 145.5, 143.6, 139.7, 136.1, 135.2, 133.6, 133.4, 133.0, 131.6, 129.8, 129.4, 129.3, 128.6, 128.5, 127.9, 127.7, 127.1, 126.5, 125.4, 121.1, 118.9, 60.3, 47.0, 40.4, 39.3, 21.7, 13.5.

IR (KBr, cm$^{-1}$): 3465, 3374, 2188, 1711, 1636, 1598, 1399, 1253, 1170, 1086, 1006, 825, 752, 700, 662, 538.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{31}$BrN$_3$O$_4$S, M - H]$^-$: 704.1224, Found: 704.1220.
Ethyl (4aR,6R)-3-amino-4-cyano-4a-(4-fluorophenyl)-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3pa)

Combined Yield: 90% (59.8 mg), dr = 3.4:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 201-202 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, $J = 2.5$ Hz, 1H), 7.58 – 7.44 (m, 5H), 7.20 – 7.11 (m, 7H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 7.9$ Hz, 4H), 5.39 (s, 2H), 3.90 (dq, $J = 10.9, 7.1$ Hz, 1H), 3.74 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.11 – 3.01 (m, 1H), 2.38 (s, 3H), 2.27 (dd, $J = 13.2, 4.4$ Hz, 1H), 1.99 (t, $J = 12.5$ Hz, 1H), 0.73 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.9, 152.1, 145.6, 145.5, 143.7, 139.7, 136.1, 135.2, 133.7, 133.0, 132.8, 129.8, 129.4, 129.3, 128.7, 128.6, 128.5, 127.9, 127.7, 127.3, 127.1, 126.5, 125.6, 118.9, 60.3, 47.1, 40.3, 39.4, 21.7, 13.5.

IR (KBr, cm$^{-1}$): 3462, 3363, 2188, 1712, 1636, 1599, 1492, 1400, 1253, 1171, 1089, 1010, 752, 701, 663, 536.

HRMS (ESI) m/z Calcd for [C$_{38}$H$_{31}$ClN$_3$O$_4$S, M - H]$: 660.1729, Found: 660.1727.

Ethyl (4aR,6R)-3-amino-4a-(4-(benzyloxy)phenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3qa)

Combined Yield: 68% (43.8 mg), dr = 3.8:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 218-219 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, $J = 2.2$ Hz, 1H), 7.51 (dt, $J = 13.0, 7.0$ Hz, 5H), 7.20 – 7.07 (m, 7H), 6.89 (dd, $J = 10.5, 5.5$ Hz, 6H), 5.33 (s, 2H), 3.90 (tt, $J = 14.3, 7.1$ Hz, 1H), 3.74 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.06 (d, $J = 1.1$ Hz, 1H), 2.34 (s, 3H), 2.30 (dd, $J = 13.2, 4.2$ Hz, 1H), 1.99 (t, $J = 12.5$ Hz, 1H), 0.73 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.0, 163.0, 160.5, 152.0, 145.3, 143.7, 142.6, 139.6, 136.1, 135.2, 133.9, 133.0, 129.8, 129.3, 128.5, 128.5, 127.9, 127.5, 127.4, 127.1, 126.5, 125.9, 118.9, 115.5, 115.3, 60.3, 47.3, 40.2, 39.4, 21.6, 13.5.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -115.36.

IR (KBr, cm$^{-1}$): 3462, 2188, 1711, 1637, 1600, 1505, 1393, 1254, 1188, 1086, 1012, 806, 751, 701, 663, 591, 561.


Ethyl (4aR,6R)-3-amino-4a-(4-(benzyloxy)phenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3qa)
Combined Yield: 53% (38.6 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 192-193 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.62 (d, \(J = 2.5\) Hz, 1H), 7.54 (dt, \(J = 13.4, 7.3\) Hz, 6H), 7.46 (t, \(J = 7.4\) Hz, 3H), 7.38 (t, \(J = 7.2\) Hz, 1H), 7.12 (ddd, \(J = 14.5, 11.1, 6.4\) Hz, 7H), 6.89 (dd, \(J = 14.7, 7.8\) Hz, 4H), 6.79 (d, \(J = 8.2\) Hz, 2H), 5.22 (s, 2H), 5.13 (s, 2H), 3.90 (ddd, \(J = 14.3, 9.0, 5.4\) Hz, 1H), 3.74 (dq, \(J = 11.9, 7.1\) Hz, 1H), 3.15 – 3.07 (m, 1H), 2.34 (d, \(J = 4.4\) Hz, 1H), 2.31 (s, 3H), 1.97 (t, \(J = 12.5\) Hz, 1H), 0.74 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.1, 157.8, 151.6, 144.9, 144.0, 139.3, 138.9, 136.8, 135.9, 135.2, 133.7, 133.1, 129.9, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 127.7, 127.1, 127.0, 126.3, 125.9, 119.1, 114.8, 70.2, 60.2, 47.3, 40.1, 39.4, 21.7, 13.5.

IR (KBr, cm\(^{-1}\)): 3455, 3378, 2925, 2187, 1709, 1637, 1602, 1507, 1391, 1351, 1246, 1170, 1085, 1026, 735, 699, 662, 560.

HRMS (ESI) m/z Calcd for [C\(_{45}\)H\(_{38}\)N\(_3\)O\(_5\)S, \(M - H\)]: 732.2538, Found: 732.2535.

Ethyl (4aR,6R)-3-amino-4a-(3-bromophenyl)-4-cyano-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydro-isoquinoline-7-carboxylate (3ra)

Combined Yield: 84% (59.4 mg), dr = 3.6:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 182-183 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.59 (s, 2H), 7.45 (d, \(J = 4.4\) Hz, 1H), 7.37 (t, \(J = 7.2\) Hz, 1H), 7.33 (d, \(J = 14.2\) Hz, 2H), 5.35 (s, 2H), 3.90 (tt, \(J = 14.3, 7.1\) Hz, 1H), 3.07 (t, \(J = 10.6\) Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 1.97 (t, \(J = 12.6\) Hz, 1H), 0.73 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.9, 152.0, 149.5, 145.4, 143.6, 139.8, 136.0, 135.1, 133.5, 132.9, 130.1, 129.8, 129.2, 129.1, 128.6, 128.5, 127.9, 127.1, 126.5, 125.2, 124.5, 123.2, 118.7, 60.3, 47.1, 40.5, 39.3, 21.8, 13.5.

IR (KBr, cm\(^{-1}\)): 3462, 3378, 2187, 1711, 1636, 1598, 1395, 1368, 1251, 1170, 1085, 1029, 778, 700, 663, 608, 563, 538.

HRMS (ESI) m/z Calcd for [C\(_{38}\)H\(_{31}\)BrN\(_3\)O\(_4\)S, \(M - H\)]: 704.1224, Found: 704.1221.

Ethyl (4aR,6R)-3-amino-4-cyano-4a-(3-methoxyphenyl)-1,6-diphenyl-2-tosyl-2,4a,5,6-tetrahydro-isoquinoline-7-carboxylate (3sa)
**Ethyl (4aR,6R)-3-amino-4a,6-bis(4-bromophenyl)-4-cyano-1-phenyl-2-tosyl-2,4a,5,6-tetrahydro-isoquinoline-7-carboxylate (3ta)**

Combined Yield: 69% (45.6 mg), dr = 3.9:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 191-193 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 2.4$ Hz, 1H), 7.57 (d, $J = 7.1$ Hz, 2H), 7.54 – 7.43 (m, 3H), 7.15 (dd, $J = 19.7$, 15.1, 8.0 Hz, 6H), 6.91 (d, $J = 6.9$ Hz, 2H), 6.84 (d, $J = 8.0$ Hz, 4H), 6.65 (s, 1H), 5.25 (s, 2H), 3.90 (dq, $J = 10.8$, 7.1 Hz, 1H), 3.77 (s, 3H), 3.76 – 3.69 (m, 1H), 3.14 (dd, $J = 7.9$, 2.6 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.32 (s, 3H), 2.00 (dd, $J = 24.7$, 12.3 Hz, 1H), 0.73 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.1, 159.7, 151.7, 148.4, 144.9, 144.0, 139.4, 135.9, 135.2, 133.6, 133.1, 129.9, 129.5, 129.3, 128.5, 128.4, 128.0, 127.2, 126.3, 125.7, 119.0, 118.3, 112.6, 111.3, 77.6, 77.4, 71.1, 76.7, 60.3, 55.0, 47.1, 40.8, 39.5, 21.6, 13.5.

IR (KBr, cm$^{-1}$): 3462, 3378, 2188, 1711, 1637, 1599, 1492, 1394, 1253, 1169, 1086, 1017, 766, 751, 700, 663, 573, 537.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{34}$N$_3$O$_5$S, M - H]$^-$: 656.2225, Found: 656.2221.

**Ethyl (4aR,6R)-3-amino-4a,6-bis(4-bromophenyl)-4-cyano-1-phenyl-2-tosyl-2,4a,5,6-tetrahydro-isoquinoline-7-carboxylate (3ta)**

Combined Yield: 92% (72.4 mg), dr = 5.2:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 203-204 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 2.2$ Hz, 1H), 7.53 (d, $J = 6.7$ Hz, 5H), 7.31 (dd, $J = 12.9$, 8.5 Hz, 4H), 7.15 (d, $J = 8.3$ Hz, 2H), 7.00 (d, $J = 8.5$ Hz, 2H), 6.91 (d, $J = 8.2$ Hz, 2H), 6.79 (d, $J = 8.3$ Hz, 2H), 5.39 (d, $J = 3.5$ Hz, 2H), 3.98 – 3.87 (m, 1H), 3.78 (dd, $J = 10.8$, 7.1 Hz, 1H), 3.04 (dd, $J = 7.9$, 2.6 Hz, 1H), 2.40 (s, 3H), 2.23 (dd, $J = 13.2$, 4.4 Hz, 1H), 1.94 (t, $J = 12.5$ Hz, 1H), 0.81 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.6, 152.0, 145.9, 145.6, 142.8, 140.1, 135.1, 133.5, 131.7, 131.6, 129.8, 129.5, 129.4, 128.9, 128.6, 127.9, 127.6, 125.2, 121.2, 120.2, 118.8, 60.5, 46.9, 40.2, 38.8, 21.7, 13.6.

IR (KBr, cm$^{-1}$): 3466, 3437, 3365, 2188, 1711, 1636, 1598, 1488, 1399, 1247, 1170, 1085, 1008, 814, 777, 739, 700, 663, 579, 563, 537.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{34}$Br$_2$N$_3$O$_6$S, M - H]$^-$: 784.0307, Found: 784.0309.

**Ethyl (4aR,6R)-3-amino-4-cyano-1-phenyl-4a-(m-tolyl)-6-(o-tolyl)-2-tosyl-2,4a,5,6-tetrahydro-isoquinoline-7-carboxylate (3ua)**
Ethyl 3-amino-1-(4-bromophenyl)-4-cyano-6-(4-fluorophenyl)-4a-phenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fc)

Combined Yield: 88% (58.4 mg), dr = 3.7:1

Data for major diastereomer (syn-): White solid with slight yellow; m.p. 136-138 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, $J = 2.6$ Hz, 1H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 7.8$ Hz, 3H), 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 7.0$ Hz, 4H), 6.78 (d, $J = 8.1$ Hz, 2H), 5.22 (s, 2H), 3.92 (dq, $J = 10.8$, 7.1 Hz, 1H), 3.77 (dq, $J = 10.8$, 7.1 Hz, 1H), 3.07 (ddd, $J = 11.8$, 4.4, 2.6 Hz, 1H), 2.44 (s, 3H), 2.36 – 2.31 (m, 1H), 2.30 (s, 3H), 1.96 (dd, $J = 12.9$, 12.1 Hz, 1H), 0.79 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.0, 162.6, 160.2, 151.8, 146.6, 144.8, 139.9, 139.9, 139.9, 139.4, 135.0, 133.7, 133.6, 132.2, 129.7, 129.3, 129.3, 128.8, 128.6, 128.5, 127.9, 126.9, 125.9, 125.0, 119.1, 115.3, 115.1, 60.3, 47.4, 40.6, 38.7, 21.6, 21.5, 13.6.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -116.68, -116.70, -116.72.

IR (KBr, cm$^{-1}$): 3464, 3375, 2188, 1710, 1637, 1600, 1509, 1394, 1250, 1170, 1102, 1086, 1015, 830, 764, 741, 699, 663, 583, 560, 535.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{33}$FN$_3$O$_4$S, M - H]: 658.2181, Found: 658.2178.
Combined Yield: 74% (58.2 mg), dr = 2.9:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 157-159 °C

**1H NMR** (400 MHz, CDCl₃) δ 7.57 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.20 (dd, J = 15.3, 7.4 Hz, 5H), 7.09 (d, J = 7.4 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 6.71 (dd, J = 7.7, 3.8 Hz, 4H), 5.17 (s, 2H), 3.94 – 3.81 (m, 1H), 3.79 – 3.65 (m, 1H), 2.97 (d, J = 11.0 Hz, 1H), 2.27 (d, J = 4.2 Hz, 1H), 2.23 (s, 3H), 1.87 (s, 1H), 0.75 (t, J = 7.1 Hz, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 166.6, 151.5, 146.3, 145.1, 142.0, 138.5, 135.6, 134.1, 133.3, 133.0, 131.9, 131.6, 129.5, 128.8, 127.9, 127.0, 125.8, 125.7, 123.6, 120.1, 118.9, 60.5, 47.1, 40.6, 39.0, 21.7, 13.7.

**IR** (KBr, cm⁻¹): 3466, 3366, 2188, 1711, 1637, 1598, 1489, 1398, 1366, 1255, 1171, 1085, 829, 747, 703, 663, 564, 538.

**HRMS (ESI)** m/z Calcd for [C₃₈H₃₇Br₂N₃O₄S, M - H]⁻: 784.0309, Found: 784.0308.

Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-1-(furan-2-yl)-4a-phenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fd)

Combined Yield: 87% (60.6 mg), dr = 4.2:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 146-149 °C

**1H NMR** (400 MHz, CDCl₃) δ 8.03 (d, J = 1.9 Hz, 1H), 7.65 (s, 1H), 7.30 (d, J = 8.0 Hz, 3H), 7.27 – 7.21 (m, 2H), 7.15 – 7.05 (m, 4H), 6.86 – 6.72 (m, 5H), 6.62 (s, 1H), 5.21 (s, 2H), 3.98 (td, J = 14.2, 7.1 Hz, 1H), 3.85 (td, J = 14.2, 7.1 Hz, 1H), 3.04 (d, J = 10.9 Hz, 1H), 2.33 (d, J = 4.4 Hz, 1H), 2.29 (s, 3H), 1.95 (t, J = 12.5 Hz, 1H), 0.88 (t, J = 7.1 Hz, 3H).

**13C NMR** (101 MHz, CDCl₃) δ 166.7, 151.2, 147.4, 146.1, 145.0, 143.6, 143.1, 135.6, 133.1, 132.9, 131.6, 129.5, 129.3, 128.9, 128.8, 128.2, 127.0, 126.1, 125.8, 120.1, 118.9, 113.5, 112.0, 60.5, 47.3, 40.9, 38.9, 21.6, 13.7.

**IR** (KBr, cm⁻¹): 3461, 3378, 2188, 1711, 1637, 1598, 1489, 1398, 1366, 1255, 1171, 1085, 1013, 829, 747, 703, 663, 583, 563, 537.

**HRMS (ESI)** m/z Calcd for [C₃₆H₃₉BrN₃O₅S, M - H]⁻: 694.1017, Found: 694.1014.

Ethyl (4aR,6R)-3-amino-6-(4-bromophenyl)-4-cyano-4a-phenyl-1-propyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3fe)
Combined Yield: 15% (10.2 mg), dr = 3.4:1
Data for major diastereomer (syn-): White solid with slight yellow; m.p. 208-209 °C

**1H NMR** (400 MHz, CDCl$_3$) δ 7.68 (d, $J = 2.2$ Hz, 1H), 7.23 (s, 1H), 7.19 (s, 2H), 7.13 (t, $J = 7.5$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 2H), 6.97 (d, $J = 7.5$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 6.71 (d, $J = 8.2$ Hz, 2H), 4.98 (s, 2H), 3.93 (dq, $J = 10.9$, 7.1 Hz, 1H), 3.78 (dq, $J = 10.9$, 7.1 Hz, 1H), 3.08 (ddd, $J = 14.5$, 8.6, 5.8 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.88 (d, $J = 9.4$ Hz, 1H), 2.36 (d, $J = 3.6$ Hz, 1H), 2.29 (dd, $J = 13.2$, 4.6 Hz, 1H), 1.79 (dt, $J = 14.4$, 9.6 Hz, 2H), 1.71 – 1.63 (m, 1H), 0.98 (t, $J = 7.3$ Hz, 3H), 0.83 (t, $J = 7.1$ Hz, 4H).

**13C NMR** (101 MHz, CDCl$_3$) δ 166.7, 151.8, 145.4, 144.9, 143.2, 142.3, 134.2, 133.4, 132.8, 131.5, 129.3, 128.9, 128.6, 128.0, 127.5, 126.7, 125.9, 120.0, 119.2, 60.6, 47.6, 41.0, 39.2, 33.5, 23.3, 21.6, 13.7.

**IR** (KBr, cm$^{-1}$): 3465, 2926, 2187, 1711, 1640, 1393, 1262, 1231, 1163, 1013, 753, 699, 665, 548.

**HRMS (ESI)** m/z Calcd for [C$_{35}$H$_{33}$BrN$_3$O$_4$S, M - H]: 670.1381, Found: 670.1378.

**isopropyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3af)**

Combined Yield: 64% (42.4 mg), dr = 5:1
The major isomer was not available even after recrystallization.
White solid with slight yellow; m.p. 140-142 °C

**1H NMR** (400 MHz, CDCl$_3$) δ(major) 7.60 (d, $J = 2.4$ Hz, 1H), 7.56 (d, $J = 7.1$ Hz, 2H), 7.52 – 7.42 (m, 3H), 7.32 – 7.24 (m, 2H), 7.24 (s, 1H), 7.19 (d, $J = 7.2$ Hz, 2H), 7.03 (d, $J = 8.3$ Hz, 2H), 6.84 (d, $J = 7.0$ Hz, 4H), 6.77 (d, $J = 8.1$ Hz, 2H), 5.20 (s, 2H), 4.70 (dt, $J = 12.4$, 6.2 Hz, 1H), 3.04 (dd, $J = 7.7$, 4.5 Hz, 1H), 2.32 (dd, $J = 13.2$, 4.5 Hz, 1H), 2.28 (s, 3H), 1.94 (t, $J = 12.5$ Hz, 1H), 0.96 (d, $J = 6.2$ Hz, 3H), 0.61 (d, $J = 6.2$ Hz, 3H).

**13C NMR** (101 MHz, CDCl$_3$) δ(major) 166.5, 151.8, 145.4, 144.9, 143.2, 142.3, 134.2, 133.4, 132.8, 131.5, 129.3, 128.9, 128.6, 128.0, 127.5, 126.7, 125.9, 120.0, 119.2, 60.6, 47.6, 41.0, 39.2, 33.5, 23.3, 21.6, 13.7.

**19F NMR** (376 MHz, CDCl$_3$) δ -116.73, -116.75, -116.76.
**IR** (KBr, cm$^{-1}$): 3665, 2926, 2188, 1706, 1638, 1599, 1509, 1393, 1256, 1144, 1087, 1013, 941, 839, 699, 664, 584, 560, 537.

**HRMS (ESI)** m/z Calcd for [C$_{39}$H$_{33}$FN$_3$O$_4$S, M - H]: 658.2181, Found: 658.2178.

**tert-butyl (4aR,6R)-3-amino-4-cyano-6-(4-fluorophenyl)-1,4a-diphenyl-2-tosyl-2,4a,5,6-tetrahydroisoquinoline-7-carboxylate (3ag)**
Combined Yield: 53% (35.5 mg), dr = 5.8:1

The major isomer was not available even after recrystallization.

White solid with slight yellow; m.p. 129-131 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ(major) 7.61 – 7.55 (m, 3H), 7.51 (t, $J$ = 7.3 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.32 – 7.28 (m, 2H), 7.22 (d, $J$ = 7.1 Hz, 2H), 7.06 (d, $J$ = 8.2 Hz, 2H), 6.99 (d, $J$ = 8.2 Hz, 1H), 6.86 (d, $J$ = 7.0 Hz, 4H), 6.79 (d, $J$ = 8.1 Hz, 2H), 5.22 (s, 2H), 3.01 (dd, $J$ = 7.6, 2.6 Hz, 1H), 2.36 – 2.31 (m, 1H), 2.30 (s, 3H), 1.94 (t, $J$ = 12.5 Hz, 1H), 1.04 (s, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ(major) 166.04, 162.67, 160.24, 151.79, 146.54, 144.82, 140.23, 140.20, 139.24, 136.79, 135.14, 134.07, 133.75, 132.73, 129.89, 129.37, 128.72, 128.46, 127.89, 126.81, 125.91, 119.08, 115.24, 115.03, 80.87, 47.63, 40.65, 38.87, 27.60, 21.60.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -116.80, -116.81, -116.83, (-118.77 minor).

IR (KBr, cm$^{-1}$): 3461, 3379, 2925, 2188, 1706, 1637, 1599, 1501, 1394, 1256, 1187, 1169, 1086, 1013, 838, 751, 700, 663, 583, 563, 539.

HRMS (ESI) m/z Calcd for [C$_{39}$H$_{33}$FN$_3$O$_4$S, M + H]$^+$: 674.2483, Found: 674.2487.
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VIII. References

IX. X-ray crystal structure of 3aa and 4ba

CCDC 1882908 (3aa) and CCDC 1942509 (4ba) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.