



Supporting Information

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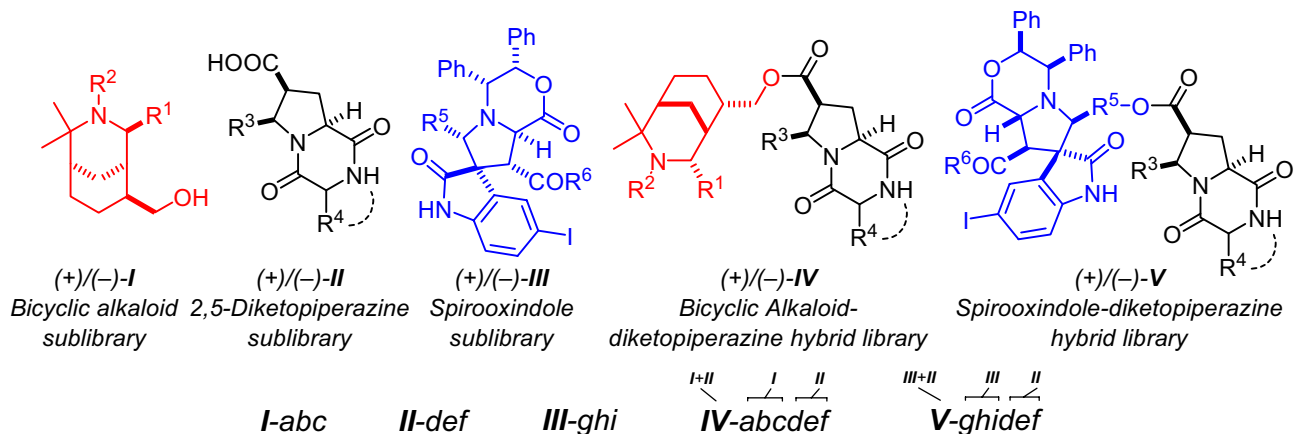
# Convergent Diversity-Oriented Synthesis of Small-Molecule Hybrids

Chuo Chen, Xiaodong Li, Christopher S. Neumann, Michael M.-C. Lo and Stuart L. Schreiber\*

**General Procedures.** All reactions with air and moisture-sensitive materials were performed in flame-dried glassware under a positive pressure of argon. Flash column chromatography was performed as described by Still et al.<sup>[1]</sup> employing E. Merck silica gel 60 (230–400 mesh ASTM). TLC analyses were performed on triethylamine-deactivated 250  $\mu\text{m}$  Silica Gel 60 F<sub>254</sub> plates purchased from EM Science and visualized by quenching of UV fluorescence ( $\lambda_{\text{max}}=254$  nm) or by staining with ceric ammonium molybdate. The enantiomeric ratios of the azomethine ylide cycloaddition products were determined by HPLC using Chiralpak AS column or Chiralcel OD column with 1 mL/min flow rate and monitored by UV fluorescence at 230 nm and 205 nm after released from the solid support.<sup>[2]</sup> Diastereomeric ratios of the sublibrary coupling products were determined by <sup>1</sup>H NMR spectroscopy. Quality assessment of the library was performed by LC/MS on a Micromass Platform LCZ mass spectrometer in ESI mode attached to a Waters 2690 HPLC system. The LC/MS chromatography was performed on a Waters Symmetry C18 3.5 WM, 2.1 mm  $\times$  50 mm column using a flow rate of 0.4 ml/min and a 10 min gradient of 15 $\rightarrow$ 100% CH<sub>3</sub>CN in H<sub>2</sub>O, constant 0.1% formic acid with 200–450 nm detection on a Waters 996 photodiode array detector.

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Anhydrous solvents were dispensed from a delivery system which passes the solvents through packed columns (tetrahydrofuran, methylene chloride, acetonitrile: dry neutral alumina; benzene: dry neutral alumina and Q5 reactant; *N,N*-dimethylformamide: activated molecular sieves). Chloroform, methanol Hünig's base, triethylamine and 2,6-lutidine were distilled under nitrogen from calcium hydride. *tert*-Butyl acrylate was distilled under vacuum (ca. 30 mmHg) from calcium hydride. (+)- $\beta$ -Pinene is no longer commercially available after 2003 and can be prepared from (+)- $\alpha$ -pinene according to the literature procedure.<sup>[3]</sup> 3-Indoleacetonitrile was purchased from ACROS Organics and purified by HPFC Biotage system with a pre-packed flash silica gel column.

## Sublibrary and Library Nomenclature; Structures of Demonstration Compounds



a — pinene: (+) = 1; (-) = 2

b — nitrile ( $R^1$ ): Me = 1; *i*-Bu = 2; (MeO)<sub>3</sub>PhCH<sub>2</sub> = 3

c — amine cap ( $R^2$ ): 4-BrPhN<sub>2</sub> = 1; 4-(NO<sub>2</sub>)PhN<sub>2</sub> = 2; Me = 3; (MeO)<sub>3</sub>PhCH<sub>2</sub> = 4

d — QUINAP: (*R*) = 1; (*S*) = 2

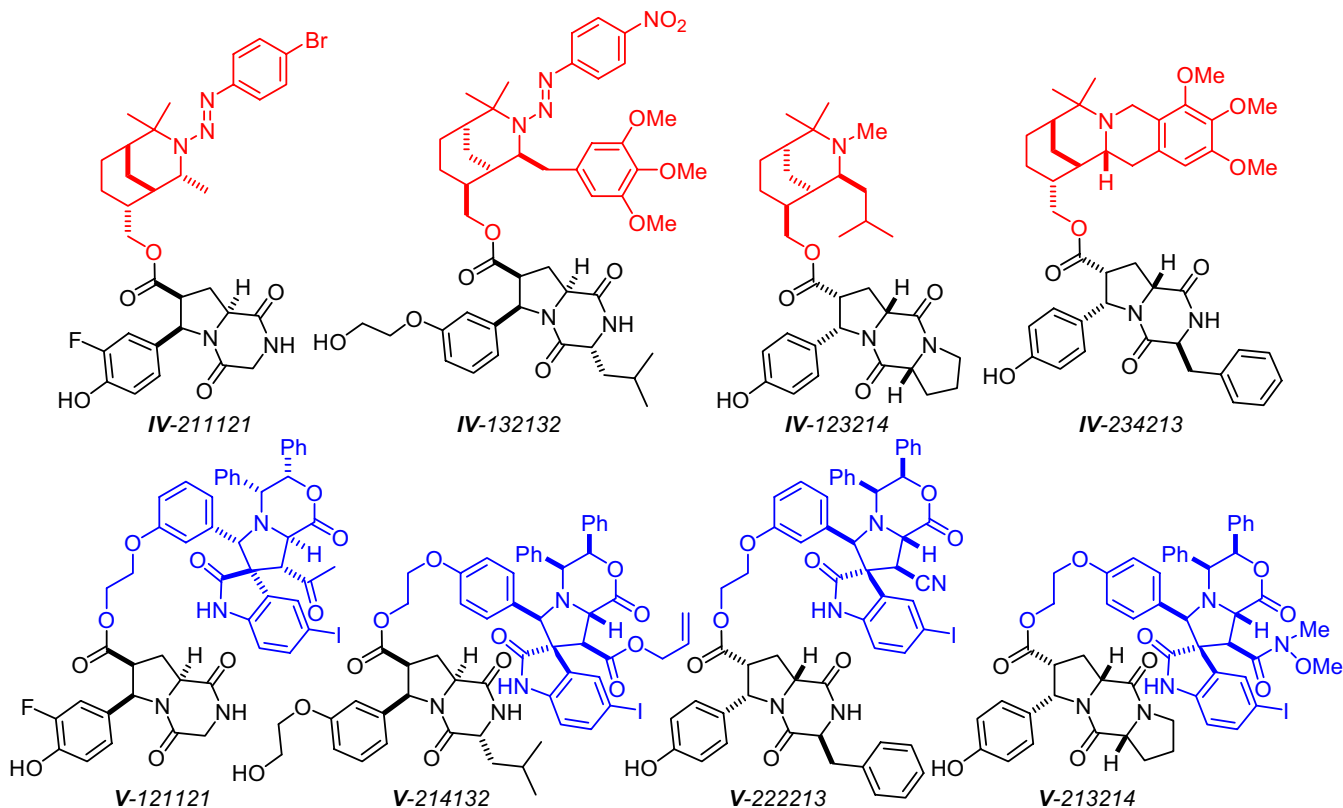
e — phenolic aldehyde ( $R^3$ ): 4-(HO)Ph = 1; 3-F-4-(HO)Ph = 2; 3-(HOCH<sub>2</sub>CH<sub>2</sub>O)Ph = 3

f — amino acid ( $R^4$ ): H (Gly) = 1; (*R*)-*i*-Bu (D-Leu) = 2; (*S*)-Bn (L-Phe) = 3; (*R*)-(CH<sub>2</sub>)<sub>3</sub> (D-Pro) = 4

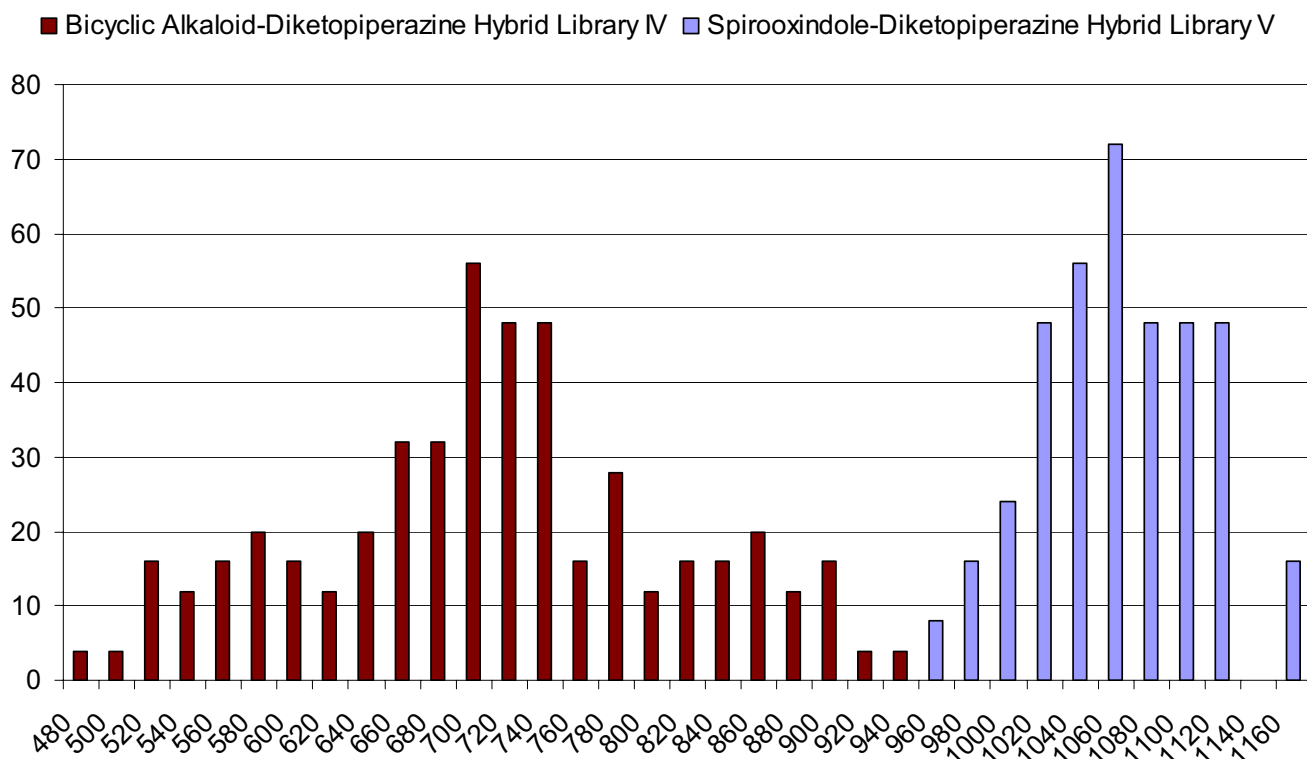
g — auxiliary: (+) = 1; (-) = 2

h — (2-hydroxyethoxy)phenyl ( $R^5$ ): *p* = 1; *m* = 2

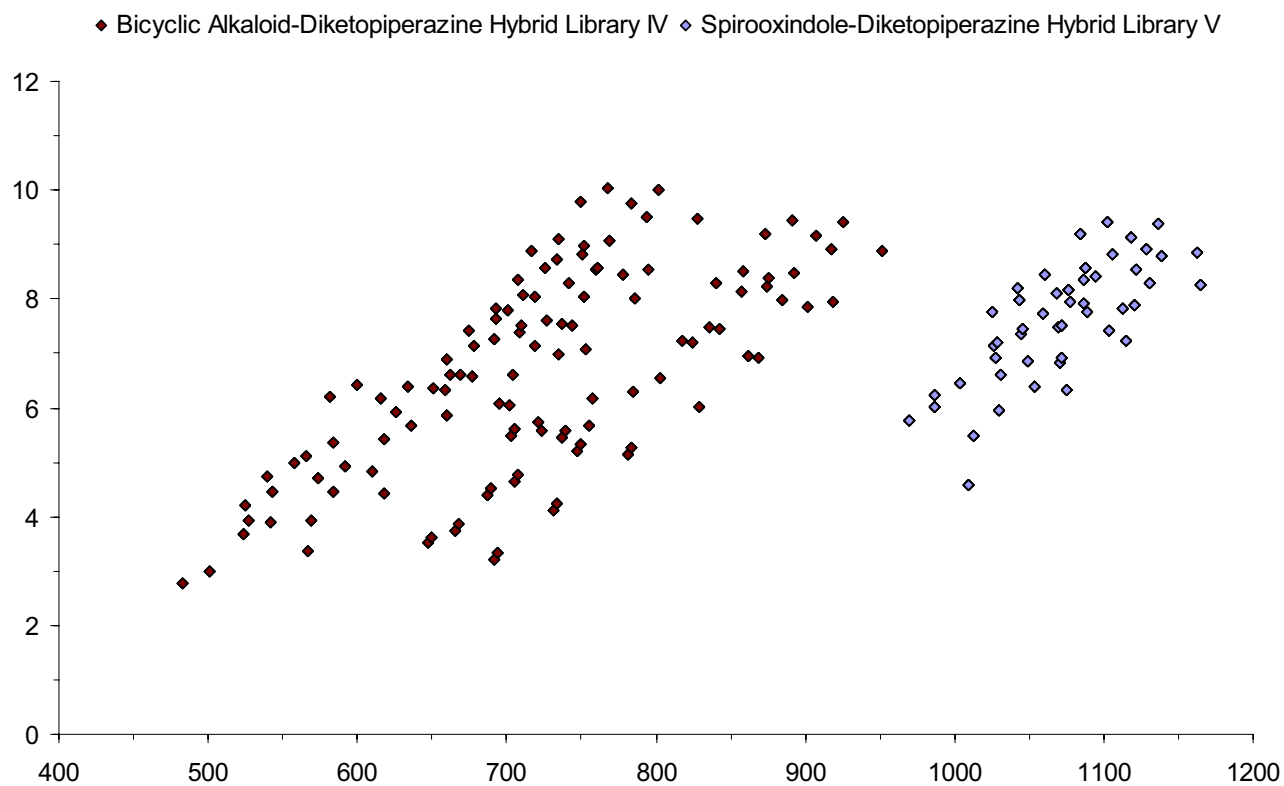
i — dipolarophile ( $R^6$ ): C(O)Me = 1; CN = 2; C(O)NMe(OMe) = 3, COOAllyl = 4



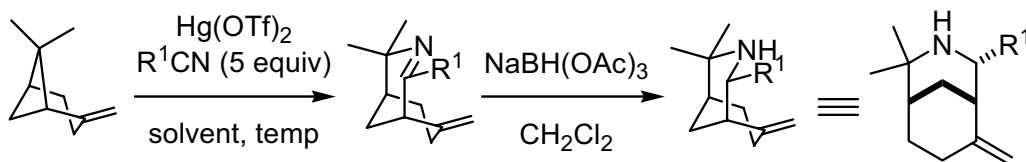
## Library Molecular Weight Distribution



## Library Calculated Log P versus Molecular Weight



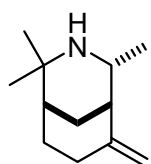
## Synthesis of Sublibrary I



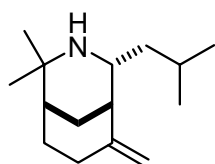
R <sup>1</sup>	Hg(OTf) <sub>2</sub> (equiv)	solvent (concentration) <sup>a</sup>	temp	time	yield (over two steps)
	0.5	CH <sub>2</sub> Cl <sub>2</sub> (0.375 M)	-78 °C	3 h	73%
	0.5	CH <sub>2</sub> Cl <sub>2</sub> (0.375 M)	-78 °C	14 h	61%
	1.0	CHCl <sub>3</sub> (0.2 M)	-45 °C	3 h	35–58%
	1.0	CHCl <sub>3</sub> (0.4 M)	-55 °C	2 h	46% <sup>b</sup> (77%) <sup>c</sup>

<sup>a</sup> Concentration of pinene. <sup>b</sup> ca. 95% purity. cf. (i) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564–568. (ii) Dobler, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 2025–2032. <sup>c</sup> Based on recovered starting material.

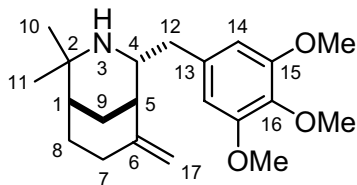
**General procedure for the mercury(II) catalyzed Ritter reaction.** To a suspension of mercury(II) trifluoromethanesulfonate and the nitrile (5.0 equiv) in methylene chloride or chloroform cooled at the indicated temperature was added (+)- or (-)-β-pinene (1.0 equiv). After stirred for the indicated period of time, the reaction was quenched by 1 M sodium carbonate, extracted with methylene chloride and washed again with 1 M sodium carbonate. The crude imine was dried over sodium sulfate, concentrated and dissolved in methylene chloride. Sodium triacetoxyborohydride (2.5 equiv) was added and the solution was stirred for 3 h. The reaction was quenched with 1 M sodium carbonate, extracted with methylene chloride, washed again with 1 M sodium carbonate, dried over sodium sulfate and concentrated. The crude amine was dissolved in diethyl ether and extracted with 1 N hydrogen chloride (10 equiv). The acidic aqueous solution was washed twice with diethyl ether followed by basified with 1 N sodium hydroxide (20 equiv) and extracted with methylene chloride for three times. The combined methylene chloride extracts were then dried over sodium sulfate and concentrated to give the corresponding amine as analytically pure material.



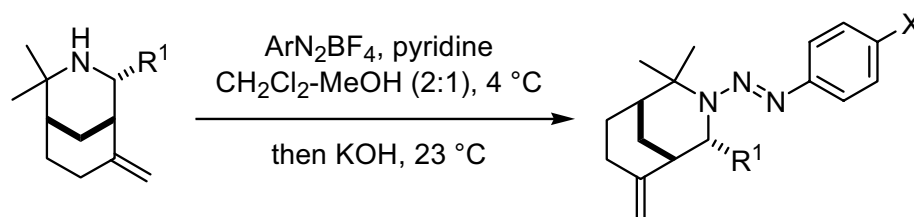
**(1R,4R,5S)-2,2,4-trimethyl-6-methylene-3-azabicyclo[3.3.1]nonane.**  $[\alpha]_D^{27} +114.0^\circ$  (*c* 1.43, CHCl<sub>3</sub>);  $R_f = 0.55$  (25% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>) 3333, 3059, 3025, 3001, 2919, 2869, 1605, 1494, 1458, 1415, 1090, 1035, 1021, 745, 697; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.71 (dd,  $J = 2.4, 2.4$  Hz, 1H), 4.53 (dd,  $J = 2.4, 2.4$  Hz, 1H), 3.19 (qd,  $J = 6.4, 2.8$  Hz, 1H), 2.73 (dddd,  $J = 14.3, 14.3, 6.5, 3.4, 2.4$  Hz, 1H), 2.19-2.13 (m, 2H), 2.07-2.02 (m, 2H), 1.61 (ddd,  $J = 12.7, 3.4, 2.9$  Hz, 1H), 1.50 (dddd,  $J = 13.7, 13.7, 6.5, 3.9$  Hz, 1H), 1.41-1.39 (m, 1H), 1.22 (s, 3H), 1.13 (s, 3H), 0.93 (d,  $J = 6.4$  Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  149.6, 108.9, 53.0, 49.6, 44.6, 35.9, 33.0, 31.7, 29.8, 28.9, 27.5, 21.1; HRMS(ES<sup>+</sup>) calcd for C<sub>12</sub>H<sub>22</sub>N (M+H)<sup>+</sup> 180.1752, found 180.1751.



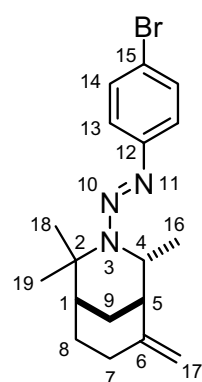
**(1R,4R,5S)-2,2-dimethyl-4-(2-methylpropyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $[\alpha]_D^{28} +129.4^\circ$  (*c* 1.18, CHCl<sub>3</sub>);  $R_f = 0.69$  (25% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>) 3064, 2954, 2921, 2867, 1638, 1455, 1436, 1377, 1363, 1260, 1239, 1144, 1125, 882, 655, 636; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.69 (dd,  $J = 2.4, 2.4$  Hz, 1H), 4.53 (dd,  $J = 2.4, 2.4$  Hz, 1H), 3.08 (td,  $J = 6.8, 2.4$  Hz, 1H), 2.78 (dddd,  $J = 14.2, 14.2, 6.3, 2.5, 2.4$  Hz, 1H), 2.16-2.13 (m, 3H), 2.06-2.02 (m, 1H), 1.66-1.57 (m, 2H), 1.48 (dddd,  $J = 13.7, 13.7, 6.3, 4.4$  Hz, 1H), 1.41-1.39 (m, 1H), 1.22 (s, 3H), 1.16-1.11 (m, 1H), 1.13 (s, 3H), 1.08-1.03 (m, 1H), 0.88 (d,  $J = 6.3$  Hz, 3H), 0.85 (d,  $J = 6.8$  Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  150.3, 108.4, 53.0, 51.8, 44.3, 42.9, 36.5, 33.2, 31.9, 29.9, 29.1, 27.4, 24.1, 22.9, 22.8; HRMS(ES<sup>+</sup>) calcd for C<sub>15</sub>H<sub>28</sub>N (M+H)<sup>+</sup> 222.2222, found 222.2225.



**(1R,4R,5S)-2,2-dimethyl-6-methylene-4-(3,4,5-trimethoxybenzyl)-3-azabicyclo[3.3.1]nonane.**  $[\alpha]_D^{27} +111.1^\circ$  (*c* CHCl<sub>3</sub>);  $R_f = 0.18$  (20% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>) 2930, 2833, 1587, 1506, 1458, 1420, 1330, 1239, 1123, 1011, 806; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.42 (s, 2H, H<sub>14</sub>), 4.77 (dd,  $J = 2.4, 2.4$  Hz, 1H, H<sub>17</sub>), 4.58 (dd,  $J = 2.4, 2.4$  Hz, 1H, H<sub>17'</sub>), 3.87, (s, 3H, OCH<sub>3</sub>), 3.84, (s, 6H, OCH<sub>3</sub>), 3.31 (ddd,  $J = 7.8, 5.9, 2.9$  Hz, 1H, H<sub>4</sub>), 3.02, (dddd,  $J = 13.7, 13.6, 6.3, 2.5, 2.4$  Hz, 1H, H<sub>7</sub>), 2.55 (dd,  $J = 13.7, 5.9$  Hz, 1H, H<sub>12</sub>), 2.40 (dd,  $J = 13.7, 7.8$  Hz, 1H, H<sub>12'</sub>), 2.21-2.04 (m, 4H, H<sub>5,7,9,8</sub>), 1.59 (ddd,  $J = 12.7, 3.4, 2.9$  Hz, 1H, H<sub>9'</sub>), 1.49 (dddd,  $J = 13.6, 13.5, 6.0, 4.1$  Hz, 1H, H<sub>8'</sub>), 1.42-1.40 (m, 1H, H<sub>1</sub>), 1.18 (s, 3H, H<sub>10</sub> or H<sub>11</sub>), 1.11 (s, 3H, H<sub>10</sub> or H<sub>11</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  152.9, 150.6, 136.0, 135.5, 108.7, 106.0, 60.8, 56.0, 55.7, 53.0, 43.0, 42.1, 36.5, 33.2, 31.9, 29.7, 29.2, 27.1; HRMS(ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>32</sub>NO<sub>3</sub> (M+H)<sup>+</sup> 346.2382, found 346.2385.



**General procedure for the triazene formation.** To a solution of aryldiazonium tetrafluoroborate (1.0 equiv) in methanol (0.2–0.5 M) cooled at 4 °C was added a solution of the amine (1.0 equiv) in methylene chloride (0.1–0.25 M) followed by pyridine (3.0 equiv). This solution was stirred at 4 °C for 30 min before a solution of potassium hydroxide (1.0 M in water, 2.0 equiv) was added. After warmed to room temperature, brine was added and the solution was extracted three times with methylene chloride. The organic extracts were dried over sodium sulfate and concentrated to give the corresponding triazene with >90% purity by  $^1\text{H}$  NMR. The crude triazenes were used directly for the subsequent hydroboration reactions.



**(1R,4R,5S)-3-[2-(4-bromophenyl)-1-azeryl]-2,2,4-trimethyl-6-methylene-3-**

**azabicyclo[3.3.1]nonane.**  $R_f$  = 0.67 (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ )

2976, 2927, 2865, 1643, 1477, 1454, 1436, 1260, 1231, 1103, 1069, 1003, 892, 832;

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (d,  $J$  = 8.8 Hz, 2H,  $\text{H}_{13}$  or  $14$ ), 7.31 (d,  $J$  = 8.8 Hz,

2H,  $\text{H}_{13}$  or  $14$ ), 4.75 (dd,  $J$  = 2.0, 2.0 Hz, 1H,  $\text{H}_{17}$ ), 4.66 (dd,  $J$  = 2.0, 2.0 Hz, 1H,  $\text{H}_{17'}$ ),

3.94 (qd,  $J$  = 5.9, 5.9 Hz, 1H,  $\text{H}_4$ ), 2.52-2.49 (m, 1H,  $\text{H}_5$ ), 2.40 (dddd,  $J$  = 14.2, 14.2,

5.0, 2.0 Hz, 1H,  $\text{H}_7$ ), 2.27-2.24 (m, 1H,  $\text{H}_8$ ), 2.20-2.16 (m, 2H,  $\text{H}_{7,9}$ ), 1.79-1.77 (m,

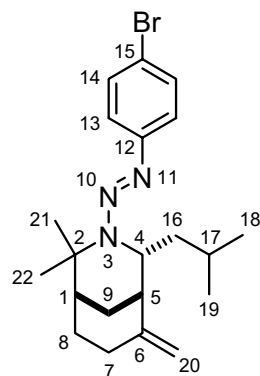
1H,  $\text{H}_1$ ), 1.72 (s, 3H,  $\text{H}_{18}$  or  $19$ ), 1.70 (ddd,  $J$  = 12.7, 3.4, 3.4 Hz, 1H,  $\text{H}_9$ ), 1.53 (dddd,  $J$  = 13.7, 13.7, 5.0,

4.4 Hz, 1H,  $\text{H}_8$ ), 1.37 (d,  $J$  = 5.9 Hz, 3H,  $\text{H}_{16}$ ), 1.34 (s, 3H,  $\text{H}_{18}$  or  $19$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$

150.1 ( $\text{C}_{12}$  or  $15$ ), 149.8 ( $\text{C}_{12}$  or  $15$ ), 131.8 ( $\text{C}_{13}$  or  $14$ ), 122.3 ( $\text{C}_{13}$  or  $14$ ), 118.8 ( $\text{C}_6$ ), 109.6 ( $\text{C}_{17}$ ), 63.3 ( $\text{C}_2$ ),

54.5 ( $\text{C}_4$ ), 45.7 ( $\text{C}_5$ ), 39.5 ( $\text{C}_1$ ), 30.7, 30.0 ( $\text{C}_{18}$  or  $19$ ), 29.7, 29.5, 27.7 ( $\text{C}_{18}$  or  $19$ ), 19.1 ( $\text{C}_{16}$ ); HRMS( $\text{ES}^+$ )

calcd for  $\text{C}_{18}\text{H}_{25}\text{BrN}_3$  ( $\text{M}+\text{H}$ ) $^+$  362.1232, found 262.1241.



**(1R,4R,5S)-3-[2-(4-bromophenyl)-1-azeryl]-2,2-dimethyl-4-(2-methylpropyl)-**

**6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f$  = 0.65 (20% ethyl acetate-hexanes);

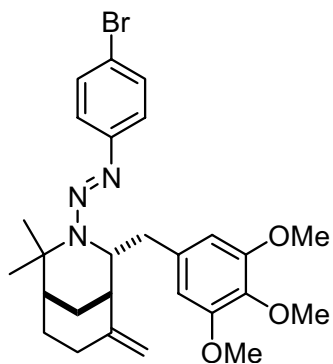
FTIR (neat,  $\text{cm}^{-1}$ ) 3067, 2953, 2933, 1888, 1643, 1476, 1454, 1431, 1231, 1156,

889, 828;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 (d,  $J$  = 8.8 Hz, 2H,  $\text{H}_{13}$  or  $14$ ), 7.31

(d,  $J$  = 8.8 Hz, 2H,  $\text{H}_{13}$  or  $14$ ), 4.78 (dd,  $J$  = 2.0, 2.0 Hz, 1H,  $\text{H}_{20}$ ), 4.67 (dd,  $J$  = 2.0,

2.0 Hz, 1H,  $\text{H}_{20'}$ ), 3.97 (ddd,  $J$  = 8.3, 8.3, 2.0 Hz, 1H,  $\text{H}_4$ ), 2.82-2.78 (m, 1H,  $\text{H}_5$ ),

2.33 (ddd,  $J = 13.7, 13.7, 4.9$  Hz, 1H, H<sub>7</sub>), 2.27-2.23 (m, 1H, H<sub>7'</sub>), 2.20 (dd,  $J = 13.7, 4.9$  Hz, 1H, H<sub>8</sub>), 2.11 (ddd,  $J = 13.2, 5.4, 2.9$  Hz, 1H, H<sub>9</sub>), 1.94 (ddd,  $J = 13.2, 8.3, 2.0$  Hz, 1H, H<sub>16</sub>), 1.87-1.78 (m, 2H, H<sub>17,1</sub>), 1.72-1.68 (m, 1H, H<sub>9'</sub>), 1.69 (s, 3H, H<sub>21 or 22</sub>), 1.52 (dddd,  $J = 13.7, 13.7, 4.9, 4.4$  Hz, 1H, H<sub>8'</sub>), 1.38 (s, 3H, H<sub>21 or 22</sub>), 1.13 (ddd,  $J = 13.2, 8.3, 4.9$  Hz, 1H, H<sub>16'</sub>), 1.01 (d,  $J = 6.3$  Hz, 3H, H<sub>18 or 19</sub>), 0.83 (d,  $J = 6.3$  Hz, 3H, H<sub>18 or 19</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 150.5 (C<sub>12 or 15</sub>), 150.0 (C<sub>12 or 15</sub>), 131.8 (C<sub>13 or 14</sub>), 122.2 (C<sub>13 or 14</sub>), 118.6 (C<sub>6</sub>), 109.7 (C<sub>20</sub>), 63.6 (C<sub>2</sub>), 57.9 (C<sub>4</sub>), 42.0 (C<sub>5</sub>), 39.1 (C<sub>1</sub>), 38.0 (C<sub>16</sub>), 31.6 (C<sub>21 or 22</sub>), 30.0 (C<sub>9</sub>), 30.2 (C<sub>7</sub>), 29.7 (C<sub>8</sub>), 27.8 (C<sub>21 or 22</sub>), 26.1 (C<sub>17</sub>), 23.6 (C<sub>18 or 19</sub>), 22.1 (C<sub>18 or 19</sub>); HRMS(ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>31</sub>BrN<sub>3</sub> (M+H)<sup>+</sup> 404.1701, found 404.1711.



**(1R,4R,5S)-3-[2-(4-bromophenyl)-1-azeryl]-2,2-dimethyl-4-(3,4,5-**

**trimethoxybenzyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.39$

(20% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>) 2936, 2836, 1647, 1588,

1506, 1458, 1417, 1238, 1126, 1099, 1005, 828; <sup>1</sup>H NMR (500 MHz,

CDCl<sub>3</sub>) δ 7.47 (d,  $J = 8.8$  Hz, 2H), 7.35 (d,  $J = 8.8$  Hz, 2H), 6.77 (s, 2H),

4.93 (s, 1H), 4.69 (s, 1H), 4.18 (dd,  $J = 6.8, 6.8$  Hz, 1H), 3.86 (s, 6H), 3.85-

3.83 (m, 1H), 3.84 (s, 3H), 3.69 (d,  $J = 13.2$  Hz, 1H), 2.72-2.69 (m, 1H),

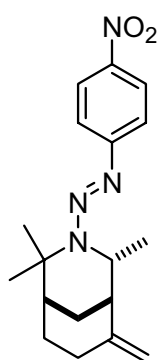
2.42 (ddd,  $J = 13.7, 13.7, 5.4$  Hz, 1H), 2.34-2.30 (m, 1H), 2.28 (dd,  $J = 13.7, 9.3$  Hz, 1H), 2.08 (ddd,  $J$

$= 13.2, 5.4, 2.4$  Hz, 1H), 1.86-1.83 (m, 1H), 1.84 (s, 3H), 1.69 (ddd,  $J = 13.2, 3.4, 3.4$  Hz, 1H), 1.57

(dddd,  $J = 13.7, 13.7, 4.4, 4.4$  Hz, 1H), 1.40 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 152.8, 150.7,

149.9, 136.3, 136.1, 131.9, 122.3, 119.1, 110.7, 106.3, 64.1, 60.9, 56.1, 41.0, 39.2, 34.7, 31.8, 30.6,

30.3, 29.9, 27.6; HRMS(ES<sup>+</sup>) calcd for C<sub>27</sub>H<sub>35</sub>BrN<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 528.1862, found 528.1870.



**(1R,4R,5S)-3-[2-(4-nitrophenyl)-1-azeryl]-2,2,4-trimethyl-6-methylene-3-**

**azabicyclo[3.3.1]nonane.**  $R_f = 0.55$  (20% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>)

2976, 2935, 2865, 1645, 1599, 1588, 1508, 1429, 1335, 1267, 1228, 1103, 853; <sup>1</sup>H NMR

(500 MHz, CDCl<sub>3</sub>) δ 8.20 (d,  $J = 8.8$  Hz, 2H), 7.48 (d,  $J = 8.8$  Hz, 2H), 4.78 (dd,  $J = 2.0,$

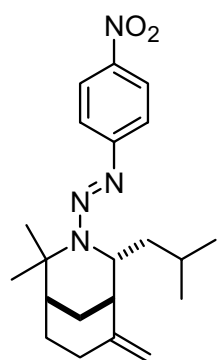
2.0 Hz, 1H), 4.60 (dd,  $J = 2.0, 2.0$  Hz, 1H), 4.09 (qd,  $J = 6.3, 5.9$  Hz, 1H), 2.58-2.56 (m,

1H), 2.36-2.17 (m, 4H), 1.85-1.82 (m, 1H), 1.76-1.72 (m, 1H), 1.74 (s, 3H), 1.59-1.52 (m,

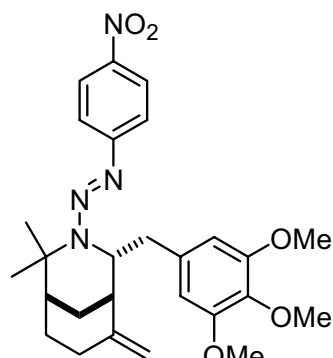
1H), 1.42 (s, 3H), 1.40 (d,  $J = 6.3$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 156.0, 149.1,

144.8, 124.9, 120.7, 110.1, 64.5, 55.6, 45.2, 39.2, 30.4, 29.5, 29.4, 27.7, 18.7; HRMS(ES<sup>+</sup>) calcd for

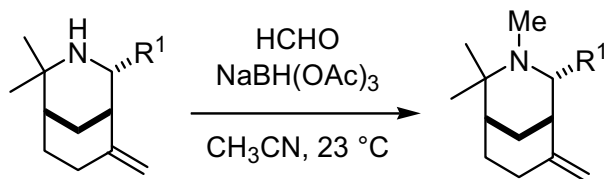
C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 329.1977, found 329.1969.



**(1R,4R,5S)-3-[2-(4-nitrophenyl)-1-azeny]-2,2-dimethyl-4-(2-methylpropyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.58$  (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 2953, 2927, 1599, 1588, 1513, 1333, 1226, 1108, 857;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (d,  $J = 8.8$  Hz, 2H), 7.47 (d,  $J = 8.8$  Hz, 2H), 4.81 (s, 1H), 4.70 (s, 1H), 4.14 (dd,  $J = 6.8, 6.8$  Hz, 1H), 2.88-2.84 (m, 1H), 2.27-2.22 (m, 3H), 2.13-2.08 (m, 1H), 1.93 (ddd,  $J = 13.2, 8.8, 2.0$  Hz, 1H), 1.89-1.86 (m, 1H), 1.86-1.81 (m, 1H), 1.75 (ddd,  $J = 13.2, 3.9, 3.4$  Hz, 1H), 1.71 (s, 3H), 1.61-1.52 (m, 1H), 1.46 (s, 3H), 1.19-1.14 (m, 1H), 1.02 (d,  $J = 6.8$  Hz, 3H), 0.84 (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 149.7, 144.7, 124.9, 120.5, 118.9, 110.3, 64.8, 58.8, 41.7, 38.8, 37.9, 30.2, 30.0, 29.6, 27.8, 26.2, 23.5, 22.0; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{21}\text{H}_{31}\text{N}_4\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$  371.2447, found 371.2438.

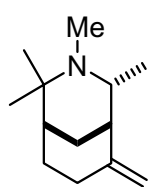


**(1R,4R,5S)-3-[2-(4-nitrophenyl)-1-azeny]-2,2-dimethyl-4-(3,4,5-trimethoxybenzyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.29$  (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 2936, 1588, 1504, 1456, 1335, 1235, 1126, 1101, 855;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (d,  $J = 9.0$  Hz, 2H), 7.53 (d,  $J = 9.0$  Hz, 2H), 6.75 (s, 2H), 4.95 (s, 1H), 4.70 (s, 1H), 4.34 (dd,  $J = 7.4, 7.4$  Hz, 1H), 3.89-3.82 (m, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.69 (d,  $J = 13.2$  Hz, 1H), 2.77-2.55 (m, 1H), 2.37-2.30 (m, 3H), 2.09 (dd,  $J = 13.2, 2.0$  Hz, 1H), 1.93-1.90 (m, 1H), 1.79 (s, 3H), 1.74 (ddd,  $J = 13.2, 3.4, 3.4$  Hz, 1H), 1.63-1.56 (m, 1H), 1.51 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  155.7, 152.8, 149.8, 145.0, 136.3, 135.8, 125.0, 120.8, 111.3, 106.3, 65.3, 61.0, 56.1, 40.7, 38.9, 34.6, 32.7, 30.3, 30.1, 29.8, 27.6; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{27}\text{H}_{35}\text{N}_4\text{O}_5$  ( $\text{M}+\text{H}$ ) $^+$  495.2607, found 495.2613.

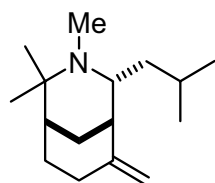


**General procedure for the reductive methylation of amines.** To a solution of the amine (1.0 equiv) in acetonitrile (0.1–0.2 M) was added a solution of formaldehyde (36% in water, 2.0 equiv) followed by sodium triacetoxyborohydride (1.5 equiv). After stirred at room temperature for 3 h, brine was added and the solution was extracted three times with methylene chloride. The organic layer was dried over sodium sulfate and concentrated to give the corresponding tertiary amine. The  $^1\text{H}$  NMR spectra of

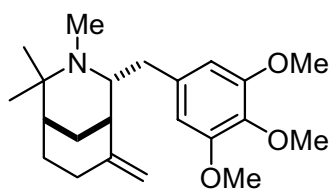
the crude tertiary amines showed >95% purity. The crude amines were used directly for the subsequent hydroboration reactions.



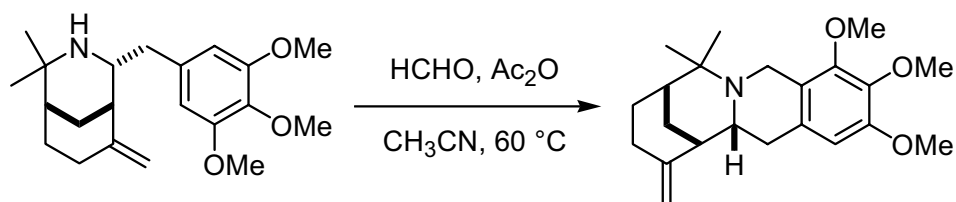
**(1R,4R,5S)-2,2,3,4-tetramethyl-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.74$  (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3064, 2976, 2927, 2896, 2771, 1768, 1640, 1456, 1374, 1358, 1253, 1094, 880;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.64 (dd,  $J = 2.4, 2.4$  Hz, 1H), 4.49 (dd,  $J = 2.4, 2.4$  Hz, 1H), 3.09-3.00 (m, 1H), 2.62 (qd,  $J = 6.3, 2.9$  Hz, 1H), 2.15-2.13 (m, 1H), 2.12-2.04 (m, 3H), 2.09 (s, 3H), 1.50 (ddd,  $J = 12.2, 2.9, 2.9$  Hz, 1H), 1.45-1.37 (m, 2H), 1.20 (s, 3H), 1.02 (s, 3H), 0.92 (d,  $J = 6.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.3, 107.4, 58.8, 56.1, 47.4, 40.7, 34.1, 32.9, 31.7, 29.5, 28.9, 20.4, 17.4; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  194.1909, found 194.1905.



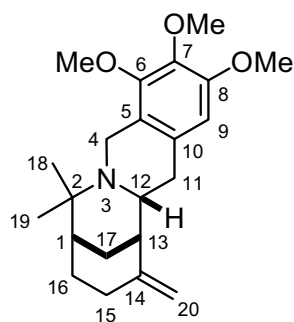
**(1R,4R,5S)-2,2,3-trimethyl-4-(2-methylpropyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.71$  (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3068, 2953, 2777, 1638, 1458, 1374, 1360, 1090, 883;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.67 (dd,  $J = 2.4, 2.4$  Hz, 1H), 4.52 (dd,  $J = 2.4, 2.4$  Hz, 1H), 3.08-3.00 (m, 1H), 2.48 (ddd,  $J = 8.8, 3.4, 3.4$  Hz, 1H), 2.32-2.30 (m, 1H), 2.12-2.02 (m, 3H), 2.11 (s, 3H), 1.68-1.62 (m, 1H), 1.51 (ddd,  $J = 12.7, 2.9, 2.9$  Hz, 1H), 1.44-1.36 (m, 2H), 1.30 (ddd,  $J = 13.2, 9.3, 3.9$  Hz, 1H), 1.20 (s, 3H), 1.13 (ddd,  $J = 13.7, 8.8, 4.9$  Hz, 1H), 1.03 (s, 3H), 0.85 (d,  $J = 6.8$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.1, 107.5, 59.4, 57.2, 43.2, 41.0, 40.5, 34.3, 32.9, 32.0, 29.8, 29.3, 25.3, 24.3, 22.0, 17.7; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{16}\text{H}_{30}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  236.2378, found 236.2375.



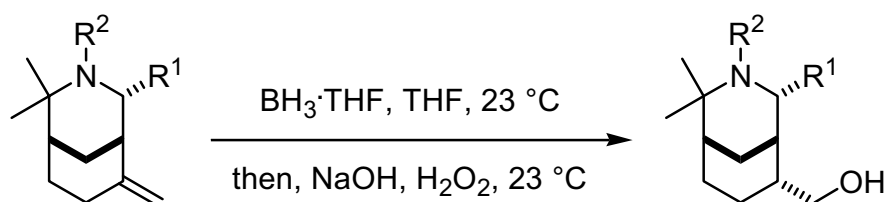
**(1R,4R,5S)-2,2,3-trimethyl-4-(3,4,5-trimethoxybenzyl)-6-methylene-3-azabicyclo[3.3.1]nonane.**  $R_f = 0.42$  (20% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 2930, 1640, 1597, 1492, 1456, 1413, 1381, 1340, 1238, 1124, 1106, 1040, 880;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.42 (s, 2H), 4.76 (dd,  $J = 2.4, 2.4$  Hz, 1H), 4.47 (dd,  $J = 2.4, 2.4$  Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.16-3.10 (m, 1H), 3.00 (dd,  $J = 13.7, 3.7$  Hz, 1H), 2.80 (ddd,  $J = 9.7, 3.7, 3.4$  Hz, 1H), 2.31 (dd,  $J = 13.7, 9.7$  Hz, 1H), 2.25 (s, 3H), 2.19-2.18 (m, 1H), 2.15-2.04 (m, 3H), 1.47-1.37 (m, 3H), 1.25 (s, 3H), 1.08 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.7, 151.9, 136.7, 135.9, 108.8, 106.6, 63.6, 60.9, 57.5, 56.1, 42.4, 40.5, 38.2, 35.0, 33.1, 32.1, 29.9, 29.1, 17.8; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{22}\text{H}_{34}\text{NO}_3$  ( $\text{M}+\text{H}$ ) $^+$  360.2539, found 360.2548.



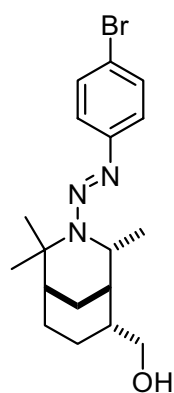
**Procedure for the tetracyclic core formation via Pictet-Spengler reaction.** To a solution of 2,2-dimethyl-6-methylene-4-(3,4,5-trimethoxybenzyl)-3-azabicyclo[3.3.1]nonane in acetonitrile (0.1 M) was added a solution of formaldehyde (36% in water, 2.0 equiv) followed by acetic anhydride (10.0 equiv). This solution was stirred at 60 °C for 18 h. After cooled to room temperature, saturated sodium bicarbonate was added and the solution was extracted three times with methylene chloride. The organic extracts were dried over sodium sulfate and concentrated. The crude amine was dissolved in diethyl ether and extracted with 1 N hydrogen chloride (10 equiv). The acidic aqueous solution was washed twice with diethyl ether followed by basified with 1 N sodium hydroxide (20 equiv) and extracted with methylene chloride for three times. The combined organic extracts were dried over sodium sulfate and concentrated to give the corresponding tetracyclic amine with >90% purity by <sup>1</sup>H NMR. The crude amine was used directly for the subsequent hydroboration reaction.



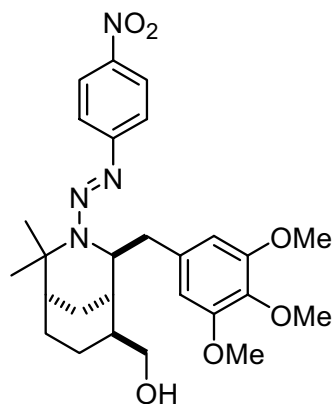
**(1R,12R,13S)-2,2-dimethyl-6,7,8-trimethoxy-14-methylene-benzo[*e*]-3-azatricyclo[7.3.1.0<sup>5,10</sup>]tridecane.**  $R_f = 0.59$  (40% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 2930, 1638, 1599, 1495, 1456, 1415, 1383, 1345, 1240, 1126, 1106, 1040, 883; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.37 (s, 1H, H<sub>9</sub>), 4.70 (dd,  $J = 2.4, 2.4$  Hz, 1H, H<sub>20</sub>), 4.59 (dd,  $J = 2.4, 2.4$  Hz, 1H, H<sub>20'</sub>), 4.04 (d,  $J = 15.6$  Hz, 1H, H<sub>4</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.33 (d,  $J = 15.6$  Hz, 1H, H<sub>4'</sub>), 2.94 (ddd,  $J = 13.7, 13.2, 5.9, 2.4$  Hz, 1H, H<sub>15</sub>), 2.88 (ddd,  $J = 11.2, 3.9, 3.4$  Hz, 1H, H<sub>12</sub>), 2.77 (dd,  $J = 16.6, 11.2$  Hz, 1H, H<sub>11</sub>), 2.37 (dd,  $J = 16.6, 3.4$  Hz, 1H, H<sub>11'</sub>), 2.35-2.32 (m, 1H, H<sub>13</sub>), 2.21 (ddd,  $J = 12.7, 5.9, 2.9$  Hz, 1H, H<sub>17</sub>), 2.14 (dd,  $J = 13.2, 4.4$  Hz, 1H, H<sub>15'</sub>), 2.07 (dd,  $J = 13.8, 5.9$ , 1H, H<sub>16</sub>), 1.60 (ddd,  $J = 12.7, 3.4, 2.9$  Hz, 1H, H<sub>17'</sub>), 1.56-1.53 (m, 1H, H<sub>1</sub>), 1.46 (dddd,  $J = 13.8, 13.7, 5.6, 4.4$  Hz, 1H, H<sub>16'</sub>), 1.35 (s, 3H, H<sub>18</sub> or 19), 1.22 (s, 3H<sub>18</sub> or 19); <sup>13</sup>C NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  152.1, 151.7, 149.6, 139.6, 130.5, 121.5, 108.0, 106.5, 60.9, 60.6, 56.8, 56.0, 54.6, 45.0, 43.5, 41.4, 35.0, 31.9, 31.7, 29.4, 28.2, 19.6; HRMS(ES<sup>+</sup>) calcd for C<sub>22</sub>H<sub>32</sub>NO<sub>3</sub> (M+H)<sup>+</sup> 358.2382, found 358.2375.



**General procedure for the hydroboration-oxidation of olefins.** To a solution of the alkene (1.0 equiv) in tetrahydrofuran (0.2 M) was added a solution of boran-tetrahydroborane complex (1.0 M in tetrahydroboran, 1.5 equiv). This solution was stirred at room temperature for 3.5 h before a solution of hydrogen peroxide (30% in water, 1.2 equiv) and sodium hydroxide (3.0 M in water, 4.5 equiv) was added. After another 2h stirring, brine was added and the solution was extracted three times with methylene chloride. The organic layer was dried over sodium sulfate and concentrated to give the corresponding alcohol with >90% purity by  $^1\text{H}$  NMR. The crude alcohols were used directly for the subsequent sublibrary coupling reactions. A portion of **I-123**, **I-211**, **I-132** and **I-234** was purified by triethylamine-deactivated silica gel column chromatography with 2% triethylamine in ethyl acetate-hexanes as the eluent for analytical purposes.

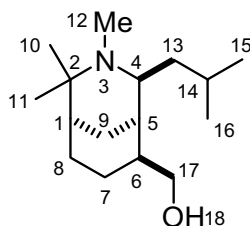


**(1R,4R,5S,6R)-3-[2-(4-bromophenyl)-1-azanyl]-6-hydroxymethyl-2,2,4-trimethyl-3-azabicyclo[3.3.1]nonane (I-211).**  $[\alpha]_{\text{D}}^{28} +55.7^\circ$  ( $c$  1.18,  $\text{CHCl}_3$ );  $R_f = 0.29$  (50% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3346 (br), 2927, 1477, 1456, 1436, 1392, 1379, 1360, 1231, 1153, 1140, 1103, 1065, 1003, 828;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (d,  $J = 8.8$  Hz, 2H), 7.27 (d,  $J = 8.8$  Hz, 2H), 4.08 (dq,  $J = 6.8, 6.3$  Hz, 1H), 3.79 (dd,  $J = 10.3, 5.9$  Hz, 1H), 3.74 (dd,  $J = 10.3, 8.8$  Hz, 1H), 2.26 (ddd,  $J = 13.7, 2.4, 2.4$  Hz, 1H), 2.21-2.16 (m, 2H), 1.90 (dddd,  $J = 8.8, 8.3, 7.8, 5.9$  Hz, 1H), 1.72 (s, 3H), 1.70-1.66 (m, 3H), 1.62 (ddd,  $J = 14.2, 3.9, 3.4$  Hz, 1H), 1.55 (d,  $J = 6.3$  Hz, 3H), 1.54-1.48 (m, 2H), 1.37 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.3, 131.8, 122.2, 118.5, 67.7, 63.8, 57.8, 47.7, 41.0, 37.8, 32.8, 28.7, 28.0, 27.0, 23.2, 19.5; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{18}\text{H}_{27}\text{BrN}_3\text{O}$  ( $\text{M}+\text{H}^+$ ) 380.1337, found 380.1335.

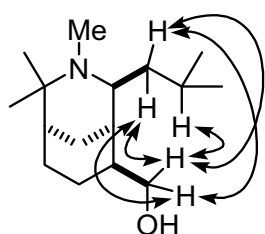


**(1R,4S,5R,6S)-6-hydroxymethyl-3-[2-(4-nitrophenyl)-1-azanyl]-2,2-dimethyl-4-(3,4,5-trimethoxybenzyl)-3-azabicyclo[3.3.1]nonane (I-132).**  $[\alpha]_{\text{D}}^{28} +429.0^\circ$  ( $c$  0.33,  $\text{CHCl}_3$ );  $R_f = 0.38$  (100% ethyl acetate); FTIR (neat,  $\text{cm}^{-1}$ ) 3482 (br), 2930, 1584, 1506, 1456, 1424, 1331, 1231, 1126, 1103, 1005, 855, 735;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 9.0$  Hz, 2H),

7.26 (d,  $J = 9.0$  Hz, 2H), 6.42 (s, 2H), 4.47 (dd,  $J = 6.3, 6.0$  Hz, 1H), 4.02 (dd,  $J = 10.3, 7.7$  Hz, 1H), 3.97 (dd,  $J = 7.7, 7.7$  Hz, 1H), 3.87-3.81 (m, 2H), 3.78 (s, 3H), 3.71 (s, 6H), 3.19 (dd,  $J = 14.9, 6.0$  Hz, 1H), 2.38-2.31 (m, 2H), 2.13 (d,  $J = 12.2$  Hz, 1H), 2.06-2.00 (m, 1H), 1.75-1.71 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59-1.43 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  156.2, 153.1, 144.4, 136.1, 124.9, 120.2, 105.3, 66.8, 66.5, 64.9, 60.9, 56.0, 44.6, 41.1, 38.8, 36.9, 35.2, 27.9, 27.8, 21.6; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{27}\text{H}_{37}\text{N}_4\text{O}_6$  ( $\text{M}+\text{H}$ ) $^+$  513.2713, found 513.2711.



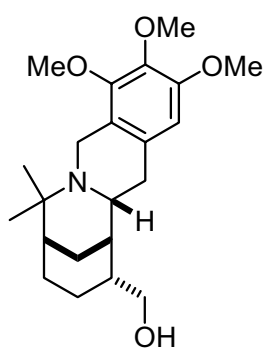
selected NOE data



**(1S,4S,5R,6S)-6-hydroxymethyl-2,2,3-trimethyl-4-(2-methylpropyl)-3-azabicyclo[3.3.1]nonane (I-123).**  $[\alpha]_{\text{D}}^{30} -2.5^\circ$  ( $c$  0.82,  $\text{CHCl}_3$ );  $R_f = 0.21$  (25% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3320 (br), 2953, 2865, 2777, 1461,

1376, 1365, 1247, 1165, 1024, 994, 933, 735;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.74 (dd,  $J = 9.8, 5.4$  Hz, 1H,  $\text{H}_{17}$ ), 3.62 (dd,  $J = 9.8, 8.8$  Hz, 1H,  $\text{H}_{17'}$ ), 2.65 (dd,  $J = 5.4, 5.4$  Hz, 1H,  $\text{H}_4$ ), 2.28 (ddd,  $J = 25.1, 12.2, 4.6$  Hz, 1H,  $\text{H}_7$ ), 2.14-2.08 (m, 2H,  $\text{H}_{8,9}$ ), 2.06 (s, 3H,  $\text{H}_{12}$ ), 1.86-1.79 (m, 2H,  $\text{H}_{6,5}$ ), 1.60 (qq,  $J = 6.8, 6.3$  Hz, 1H,  $\text{H}_{14}$ ), 1.54-1.35 (m, 6H,  $\text{H}_{18,7,9,13,8,1}$ ), 1.19-1.14 (m, 1H,  $\text{H}_{13'}$ ), 1.18 (s, 3H,  $\text{H}_{10 \text{ or } 11}$ ), 0.98 (s, 3H,  $\text{H}_{10 \text{ or } 11}$ ), 0.88 (d,  $J = 6.3$  Hz, 3H,  $\text{H}_{15 \text{ or } 16}$ ), 0.85 (d,  $J = 6.8$  Hz, 3H,  $\text{H}_{15 \text{ or } 16}$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  67.7 ( $\text{C}_{17}$ ), 61.0 ( $\text{C}_4$ ), 57.8

( $\text{C}_2$ ), 47.5 ( $\text{C}_6$ ), 43.1 ( $\text{C}_{13}$ ), 40.9 ( $\text{C}_1$ ), 36.6 ( $\text{C}_5$ ), 35.1 ( $\text{C}_9$ ), 34.0 ( $\text{C}_{12}$ ), 29.0 ( $\text{C}_6$ ), 28.8 ( $\text{C}_{10 \text{ or } 11}$ ), 27.2 ( $\text{C}_{14}$ ), 25.0 ( $\text{C}_7$ ), 23.3 ( $\text{C}_{15 \text{ or } 16}$ ), 22.9 ( $\text{C}_{15 \text{ or } 16}$ ), 17.0 ( $\text{C}_{10 \text{ or } 11}$ ); HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{16}\text{H}_{32}\text{NO}$  ( $\text{M}+\text{H}$ ) $^+$  254.2484, found 254.2478.

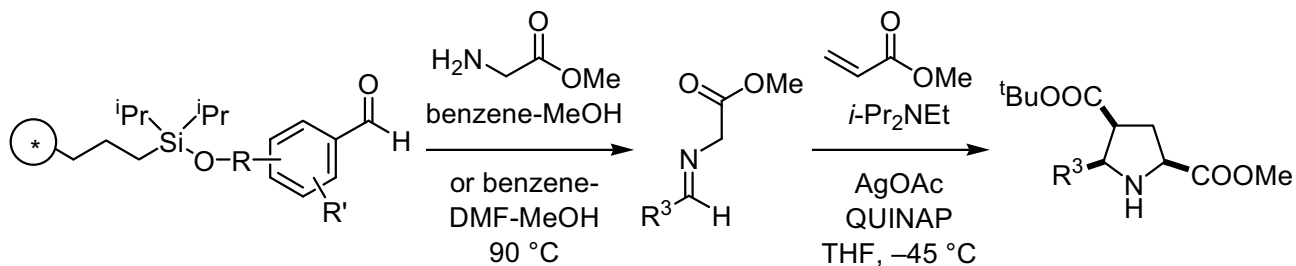


**(1R,12R,13S,14R)-14-hydroxymethyl-2,2-dimethyl-6,7,8-trimethoxybenzo[e]-3-azatricyclo[7.3.1.0<sup>5,10</sup>]tridecane (I-234).**  $[\alpha]_{\text{D}}^{27} +50.3^\circ$  ( $c$  0.26,  $\text{CHCl}_3$ );  $R_f = 0.18$  (50% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3385 (br),

2930, 1597, 1495, 1458, 1415, 1383, 1335, 1242, 1108, 1035, 944;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.37 (s, 1H), 3.98 (d,  $J = 15.4$  Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78-3.71 (m, 2H), 3.36 (d,  $J = 15.4$  Hz, 1H), 3.05 (ddd,  $J = 10.0, 3.9, 3.4$  Hz, 1H), 2.91 (dd,  $J = 15.4, 10.0$  Hz, 1H), 2.55 (dd,  $J = 15.4, 3.9$  Hz,

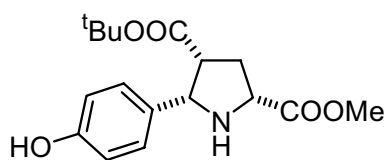
1H), 2.21-2.16 (m, 3H), 2.05-1.98 (m, 1H), 1.91-1.83 (m, 1H), 1.55-1.40 (m, 4H), 1.32 (s, 3H), 1.16 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.6, 149.5, 139.8, 131.1, 122.1, 106.2, 68.4, 60.9, 60.6, 57.4, 57.1, 56.0, 48.5, 43.0, 41.6, 37.2, 35.0, 34.0, 28.7, 28.0, 25.0, 19.8; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{22}\text{H}_{34}\text{NO}_4$  ( $\text{M}+\text{H}$ ) $^+$  376.2488, found 376.2482.

## Synthesis of Sublibrary II



**General procedure for the [3+2] cycloaddition reactions.** To a suspension of [(4-methoxyphenyl)di-*iso*-propylsilyl]propyl functionalized 500-600  $\mu\text{m}$  polystyrene beads (ca. 1.4 mmol/g, incubated with 2.5% v/v trimethylsilyl chloride in methylene chloride for 1 h and then washed with dry methylene chloride (3 $\times$ ) before use) in methylene chloride was added a solution of trifluoromethanesulfonic acid (3% v/v in methylene chloride, 6.0 equiv). After 30 min, the resulting orange [di-*iso*-propyl(trifluoromethane-sulfonyl)silyl]propyl polystyrene were washed with dry methylene chloride (3 $\times$ ). A solution of hydroxyl aldehyde (3.0 equiv) in methylene chloride was then introduced and the suspension was tumbled at room temperature for 16 h to give the polystyrene-bound aromatic aldehyde after washed with methylene chloride (3 $\times$ ), tetrahydrofuran (3 $\times$ ) and again methylene chloride (3 $\times$ ) and then dried under vacuum for 24 h. To this polystyrene-bound aromatic aldehyde (1.0 equiv) was added a solution of methyl glycinate (5.0 equiv) (from the solution after treatment of glycine methyl ester hydrochloride benzene solution with potassium hydroxide pellets (10.0 equiv)) in benzene-*N,N*-dimethylformamide-methanol (8:1:1, 0.1 M). This suspension was heated at 90  $^{\circ}\text{C}$  for 16 h. The clear solution was filtered off and the beads were washed sequentially with methylene chloride (3 $\times$ ), tetrahydrofuran (3 $\times$ ) and methylene chloride (3 $\times$ ), dried under vacuum for 24 h to afford the desired iminoester as pale yellow beads. To a suspension of the polystyrene-bound iminoester obtained above (1.0 equiv) in tetrahydrofuran was added the silver(I) acetate/(*S*)-QUINAP catalyst solution (1:1.2, 0.01 M in tetrahydrofuran, 0.1 equiv). This solution was cooled to  $-45$   $^{\circ}\text{C}$  followed by addition of *tert*-butyl acrylate (10 equiv) and Hünig's base (0.2 equiv). After stirred for 72 h, the colorless solution was filtered off and the pale orange beads were washed sequentially with tetrahydrofuran (3 $\times$ ), triphenylphosphine in tetrahydrofuran (0.05 M, 3 $\times$ ), tetrahydrofuran (3 $\times$ ) and methylene chloride (3 $\times$ ), and dried, affording the polystyrene-bound pyrrolidine as pale yellow beads. A portion of the polystyrene-bound pyrrolidine obtained above (ca. 100 beads) was treated with a solution of hydrogen fluoride-pyridine/pyridine in tetrahydrofuran (5%-5% v-v/v, 0.01 mL/bead) for 2 h followed by quenched with ethoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methylene chloride (3 $\times$ ). The filtrate was collected, concentrated and purified by silica

gel column chromatography with ethyl acetate-hexanes as the eluent to give pure pyrrolidines for analytical purposes.



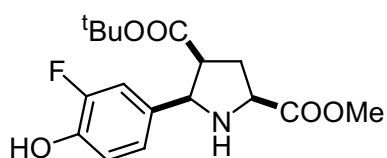
*tert*-butyl

**(2*R*,4*R*,5*S*)-5-(4-hydroxyphenyl)-2-**

**methoxycarbonylpyrrolidin-4-carboxylate.** Error! Bookmark not

defined. 90% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes;

$t_{R(\text{minor})} = 16.7$  min,  $t_{R(\text{major})} = 20.4$  min);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.18 (d,  $J = 8.8$  Hz, 2H), 6.74 (d,  $J = 8.8$  Hz, 2H), 4.42 (d,  $J = 8.0$  Hz, 1H), 3.93 (t,  $J = 8.5$  Hz, 1H), 3.81 (s, 3H), 3.22 (td,  $J = 7.9, 6.3$  Hz, 1H), 2.46-2.40 (m, 1H), 2.34-2.28 (m, 1H), 1.08 (s, 9H).



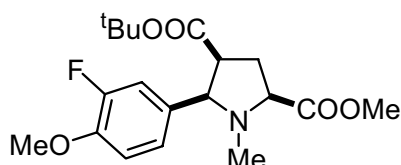
*tert*-butyl

**(2*S*,4*S*,5*R*)-5-(3-fluoro-4-hydroxyphenyl)-2-**

**methoxycarbonylpyrrolidin-4-carboxylate.**  $[\alpha]_{\text{D}}^{27} +12.0^\circ$  (90% ee,  $c$

0.64,  $\text{CH}_3\text{OH}-\text{CHCl}_3$  (1:1));  $R_f = 0.46$  (ethyl acetate); FTIR (neat,  $\text{cm}^{-1}$ )

3001, 2973, 2953, 2927, 1738, 1704, 1522, 1433, 1383, 1363, 1279, 1217, 1147;  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{OD}-\text{CDCl}_3$  (1:1))  $\delta$  7.00 (dd,  $J = 12.0, 1.7$  Hz, 1H), 6.91 (dd,  $J = 8.3, 2.0$  Hz, 1H), 6.85 (dd,  $J = 8.8, 8.3$  Hz, 1H), 4.32 (d,  $J = 7.3$  Hz, 1H), 3.88 (dd,  $J = 8.3, 8.3$  Hz, 1H), 3.79 (s, 3H), 3.19 (ddd,  $J = 7.8, 7.8, 5.4$  Hz, 1H), 2.46-2.40 (m, 1H), 2.27-2.22 (m, 1H), 1.07 (s, 9H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CD}_3\text{OD}-\text{CDCl}_3$  (1:1))  $\delta$  174.1, 172.8, 151.8 (d,  $J = 239.3$  Hz), 144.8 (d,  $J = 12.5$  Hz), 130.5 (d,  $J = 6.0$  Hz), 123.4 (d,  $J = 3.0$  Hz), 117.9 (d,  $J = 3.0$  Hz), 115.2 (d,  $J = 19.5$  Hz), 81.7, 65.0, 59.7, 52.7, 50.6, 34.3, 27.8; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{17}\text{H}_{23}\text{FNO}_5$  ( $\text{M}+\text{H}$ ) $^+$  340.1560, found 340.1551. This compound was bis-methylated with methyl iodide (5 equiv) and potassium carbonate (10 equiv) in acetone at room temperature for 5 h to determine its enantiomeric purity.



*tert*-butyl

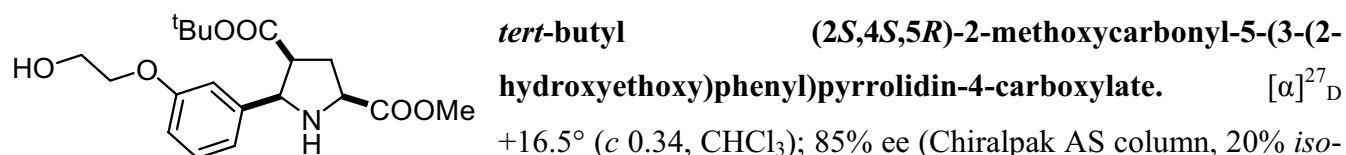
**(2*S*,4*S*,5*R*)-5-(3-fluoro-4-methoxyphenyl)-2-**

**methoxycarbonyl-1-methylpyrrolidin-4-carboxylate.**  $[\alpha]_{\text{D}}^{27} +36.5^\circ$

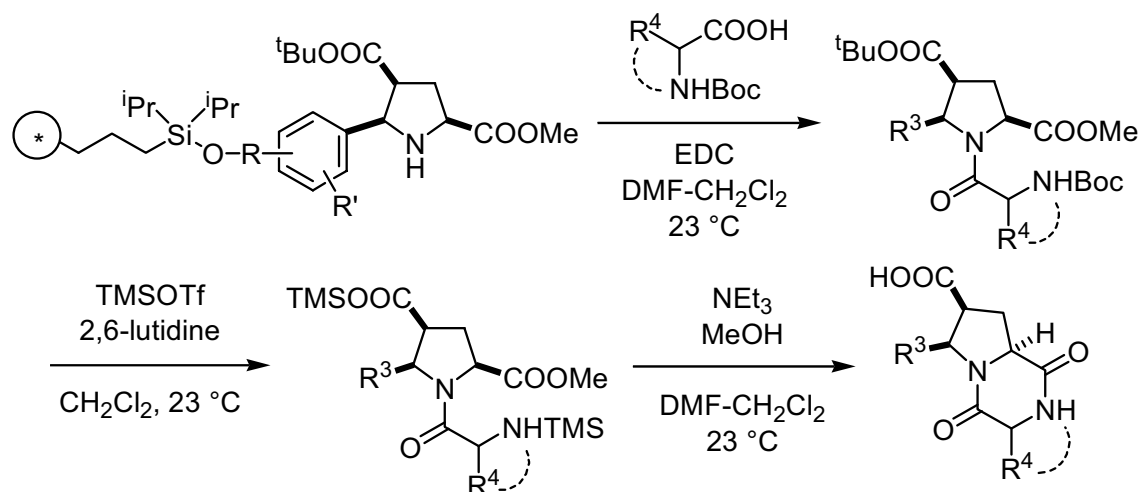
( $c$  0.51,  $\text{CHCl}_3$ ); 90% ee (Chiralcel OD column, 2% *iso*-propanol-

hexanes;  $t_{R(\text{major})} = 8.9$  min,  $t_{R(\text{minor})} = 12.4$  min);  $R_f = 0.47$  (25% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 2982, 2953, 2845, 2788, 1750, 1727, 1620, 1581, 1513, 1438, 1367, 1274, 1153, 1026, 760;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (dd,  $J = 12.7, 2.0$  Hz, 1H), 7.12 (d,  $J = 8.3$  Hz, 1H), 6.88 (dd,  $J = 8.3, 8.3$  Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.70 (d,  $J = 10.3$  Hz, 1H), 3.22 (dd,  $J = 10.3, 6.8$  Hz, 1H), 3.16 (dd,  $J = 18.6, 8.8$  Hz, 1H), 2.51 (ddd,  $J = 12.7, 10.3, 8.8$  Hz, 1H), 2.26-2.04 (m, 1H), 2.25 (s, 3H), 1.06 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.1, 170.7, 152.2 (d,  $J = 243.7$  Hz), 147.1 (d,  $J = 10.5$  Hz), 133.1 (d,

$J = 5.9$  Hz), 124.4 (d,  $J = 3.2$  Hz), 116.6 (d,  $J = 19.2$  Hz), 113.0, 80.5, 71.5, 67.2, 56.5, 52.1, 48.8, 39.7, 31.7, 28.1, 27.6; HRMS(ES<sup>+</sup>) calcd for C<sub>19</sub>H<sub>28</sub>FNO<sub>5</sub> (M+H)<sup>+</sup> 368.1873, found 368.1870.

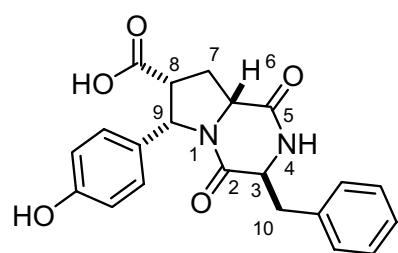


+16.5° ( $c$  0.34, CHCl<sub>3</sub>); 85% ee (Chiralpak AS column, 20% *iso*-propanol-hexanes;  $t_{R(\text{major})} = 9.6$  min,  $t_{R(\text{minor})} = 19.1$  min);  $R_f = 0.26$  (ethyl acetate); FTIR (neat, cm<sup>-1</sup>) 2976, 2950, 2933, 2868, 1734, 1602, 1581, 1442, 1367, 1253, 1215, 1151; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.20 (dd,  $J = 8.3, 8.3$  Hz, 1H), 6.94-6.93 (m, 2H), 6.78 (d,  $J = 7.3$  Hz, 1H), 4.42 (d,  $J = 7.8$  Hz, 1H), 4.05-4.04 (m, 2H), 3.94-3.89 (m, 3H), 3.79 (s, 3H), 3.22 (dd,  $J = 13.7, 7.8$  Hz, 1H), 2.67 (br, 2H), 2.44-2.38 (m, 1H), 2.31-2.26 (m, 1H), 1.04 (s, 9H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.7, 171.8, 158.6, 141.0, 129.2, 120.0, 113.6, 113.5, 80.7, 69.3, 65.4, 61.3, 59.8, 52.3, 50.1, 34.0, 27.5; HRMS(ES<sup>+</sup>) calcd for C<sub>19</sub>H<sub>28</sub>NO<sub>6</sub> (M+H)<sup>+</sup> 366.1916, found 366.1917.

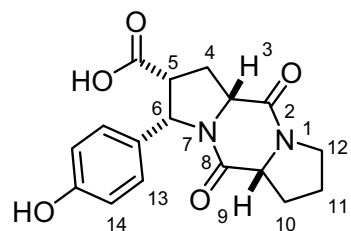


**General procedure for the 2,5-diketopiperazine formation reactions.** To the pyrrolidines obtained above was added *N*-Boc-protected amino acids (Gly, D-Leu, L-Phe and D-Pro) (5.0 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 5.0 equiv) in methylene chloride-*N,N*-dimethylformamide (95:5, 0.1 M). After agitated at room temperature for 16 h, the solution was filtered off and the beads were washed sequentially with methylene chloride (3×), tetrahydrofuran (3×), methylene chloride (3×), and dried under vacuum for 24 h. These white beads were then swelled in methylene chloride and added a equal volume of trimethylsilyl trifluoromethanesulfonate (2.0 M, 10.0 equiv) and 2,6-lutidine (3.0 M) in methylene chloride (final concentration: 1.0 M trimethylsilyl trifluoromethanesulfonate, 1.5 M 2,6-lutidine). This suspension was heated at 40 °C for 4 h followed

by washed with methylene chloride (3×), tetrahydrofuran (3×), methylene chloride (3×), and dried under vacuum for 16 h. These yellow-light orange beads were then incubated with 7.5% triethylamine-7.5 % methanol in *N,N*-dimethylformamide-methylene chloride (10 equiv, 1:1) at room temperature for 24 h followed by washed with *N,N*-dimethylformamide-methylene chloride (1:1, 3×), methylene chloride (3×) and dried under vacuum for 24 h to give the polystyrene-bound 2,5-diketopiperazine as yellow to orange beads. A portion of the polystyrene-bound diketopiperazine intermediates of the demonstration compounds (**II-213**, **II-214**, **II-121**, **II-132**) obtained above (ca. 100 beads) was treated with a solution of hydrogen fluoride-pyridine/pyridine in tetrahydrofuran (5%-5% v-v/v, 0.01 mL/bead) for 2 h followed by quenched with ethoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methanol (3×). The filtrate was collected, concentrated and purified by air- and ammonia-deactivated silica gel column chromatography with methanol-methylene chloride as the eluent to give pure 2,5-diketopiperazine for analytical purposes.

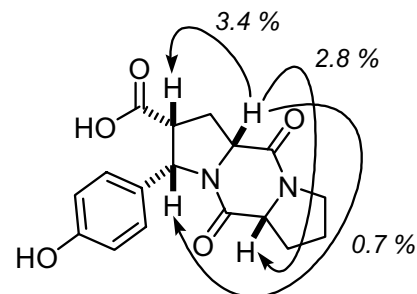


**(3*S*,6*R*,8*R*,9*S*)-3-Benzyl-9-(4-hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (**II-213**).**  $[\alpha]_D^{28} +26.0^\circ$  (*c* 0.23, CH<sub>3</sub>OH);  $R_f = 0.56$  (30% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3235 (br), 1668, 1613, 1513, 1415, 1292, 1256, 1106, 1026, 846; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.36-7.31 (m, 3H), 7.25-7.23 (m, 2H), 6.94 (d,  $J = 8.5$  Hz, 2H), 6.61 (d,  $J = 8.5$  Hz, 2H), 5.16 (d,  $J = 9.3$  Hz, 1H, H<sub>9</sub>), 4.09 (dd,  $J = 5.4, 5.4$  Hz, 1H, H<sub>3</sub>), 3.19 (dd,  $J = 13.7, 5.4$  Hz, 1H, H<sub>10</sub>), 3.05-2.97 (m, 3H, H<sub>8,6,10</sub>), 2.28 (ddd,  $J = 12.7, 12.7, 12.7$  Hz, 1H, H<sub>7</sub>), 1.99 (ddd,  $J = 12.7, 6.3, 5.9$  Hz, 1H, H<sub>7</sub>); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  176.1, 171.9, 168.4, 157.9, 137.2, 131.1, 130.3, 129.8, 129.5, 128.6, 115.7, 63.4, 60.4, 58.8, 51.1, 49.8, 40.3, 29.5; HRMS(ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 381.1450, found 381.1456.

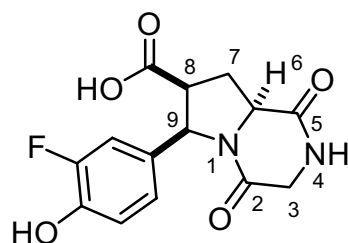


**(3*R*,5*R*,6*S*,9*R*)-6-(4-Hydroxyphenyl)-2,8-dioxo-1,7-diazatricyclo[7.3.0.0<sup>3,7</sup>]dodecan-5-carboxylate (**II-214**).**  $[\alpha]_D^{28} +154.3^\circ$  (*c* 0.16, CH<sub>3</sub>OH);  $R_f = 0.32$  (40% selected NOE data methanol-methylene chloride); FTIR

(neat, cm<sup>-1</sup>) 3201 (br), 2984, 2879, 1654, 1609, 1513, 1406, 1238, 1172, 844; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  6.89 (d,  $J = 8.5$  Hz, 2H, H<sub>13</sub>), 6.62 (d,  $J = 8.5$  Hz, 2H, H<sub>14</sub>), 5.25 (d,  $J = 8.8$  Hz, 1H, H<sub>6</sub>), 4.56 (dd,  $J = 11.2, 6.8$  Hz, 1H, H<sub>3</sub>), 4.37 (dd,  $J = 7.3, 7.3$  Hz, 1H, H<sub>9</sub>),

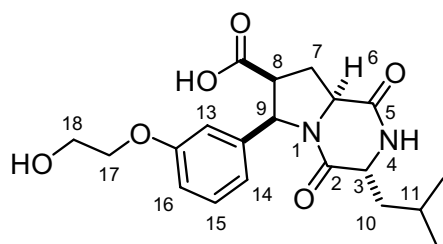


3.58-3.55 (m, 2H, H<sub>12</sub>), 3.45 (ddd,  $J = 13.2, 8.8, 6.3$  Hz, 1H, H<sub>5</sub>), 2.57 (ddd,  $J = 13.2, 13.2, 11.2$  Hz, 1H, H<sub>4</sub>), 2.28-2.20 (m, 2H, H<sub>4',10</sub>), 2.00-1.94 (m, 3H, H<sub>10',11</sub>); <sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD)  $\delta$  175.4, 169.1, 169.0, 157.9, 130.4, 129.3, 115.8, 62.7, 62.0, 61.5, 51.5, 49.8, 46.2, 28.5, 28.3, 24.4; HRMS(ES<sup>+</sup>) calcd for C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 331.1294, found 331.1298.



**(6*S*,8*S*,9*R*)-9-(3-Fluoro-4-hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (II-121).**  $[\alpha]_{\text{D}}^{27} -113.3^\circ$  (90% ee,  $c$  0.94, CH<sub>3</sub>OH);  $R_f = 0.17$  (40% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3227 (br), 1670, 1579, 1518, 1442, 1406, 1297, 1110; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD)  $\delta$  6.84 (d,  $J = 11.7$  Hz, 1H), 6.78-6.76 (m,

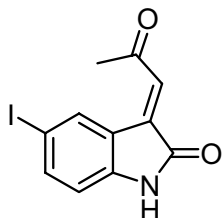
2H), 5.24 (d,  $J = 8.8$  Hz, 1H, H<sub>9</sub>), 4.47 (ddd,  $J = 11.3, 6.3, 1.1$  Hz, 1H, H<sub>6</sub>), 4.11 (dd,  $J = 16.8, 1.5$  Hz, 1H, H<sub>3</sub>), 3.68 (d,  $J = 16.8$  Hz, 1H, H<sub>3'</sub>), 3.39 (ddd,  $J = 14.1, 8.8, 5.8$  Hz, 1H, H<sub>8</sub>), 2.50 (ddd,  $J = 14.1, 13.2, 11.3$  Hz, 1H, H<sub>7</sub>), 2.27 (ddd,  $J = 13.2, 6.3, 5.8$  Hz, 1H, H<sub>7'</sub>); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  175.8, 172.8, 167.5, 152.3 (d,  $J = 238.3$  Hz), 145.4 (d,  $J = 133.3$  Hz), 131.6 (d,  $J = 5.0$  Hz), 124.2 (d,  $J = 3.2$ ), 118.1 (d,  $J = 3.2$  Hz), 116.2 (d,  $J = 19.6$  Hz), 62.6, 59.9, 51.7, 47.3, 29.1; HRMS(ES<sup>+</sup>) calcd for C<sub>14</sub>H<sub>14</sub>FN<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 309.0886, found 309.0885.



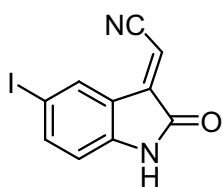
**(6*S*,8*S*,9*R*)-9-(3-(2-Hydroxyethoxy)phenyl)-3-(2-methylpropyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (II-132).**  $[\alpha]_{\text{D}}^{27} -88.8^\circ$  ( $c$  0.17, CH<sub>3</sub>OH);  $R_f = 0.17$  (40% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3309 (br), 2959, 2868, 2828, 1668, 1581, 1445, 1411, 1294, 1251, 1028,

880; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.12 (dd,  $J = 7.8, 7.8$  Hz, 1H, H<sub>15</sub>), 6.77 (dd,  $J = 8.3, 2.4$  Hz, 1H), 6.73-6.71 (m, 2H), 5.28 (d,  $J = 8.8$  Hz, 1H, H<sub>9</sub>), 4.57 (dd,  $J = 11.7, 6.3$  Hz, 1H, H<sub>6</sub>), 4.00-3.98 (m, 2H, H<sub>17</sub>), 3.84-3.78 (m, 3H, H<sub>18,3</sub>), 3.42 (ddd,  $J = 13.2, 8.8, 5.8$  Hz, 1H, H<sub>8</sub>), 2.51 (ddd,  $J = 13.2, 12.7, 11.7$  Hz, H<sub>7</sub>), 2.29 (ddd,  $J$  12.7, 6.3, 5.8 Hz, H<sub>7'</sub>), 1.82-1.73 (m, 2H, H<sub>11,10</sub>), 1.61-1.55 (m, 1H, H<sub>10'</sub>), 0.99 (d,  $J = 6.3$  Hz, 3H, H<sub>12</sub>), 0.95 (d,  $J = 6.3$  Hz, 3H, H<sub>12'</sub>); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD)  $\delta$  174.8, 172.0, 169.6, 160.0, 140.9, 130.0, 120.6, 114.70, 114.67, 70.4, 63.7, 61.7, 59.1, 57.4, 50.5, 42.2, 29.2, 25.7, 23.3, 21.8; HRMS(ES<sup>+</sup>) calcd for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup> 391.1869, found 391.1878.

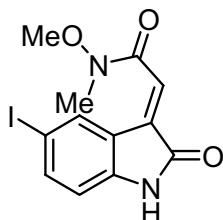
## Synthesis of Sublibrary III



**(*E*)-(5-iodo-2-oxoindolin-3-ylidene)propan-2-one.** To a solution of 1-triphenylphosphoranylidene-2-propanone (25 mmol, 1.0 equiv) in tetrahydrofuran (150 mL) was added 5-iodoisatin (25 mmol, 1.0 equiv). The reaction was stirred at room temperature for 18 h before quenched with 1.0 N hydrochloric acid (200 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, concentrated in vacuo and purified by flash column chromatography (ethyl acetate-hexanes) followed by two recrystallizations (tetrahydrofuran-hexanes) to yield (*E*)-(5-iodo-2-oxoindolin-3-ylidene)propan-2-one (4.22 g, 54%) as a red solid:  $^1\text{H-NMR}$  (500 MHz; acetone- $d_6$ )  $\delta$  9.79 (br, 1H), 8.84 (d,  $J = 1.8$  Hz, 1H), 7.71 (dd,  $J = 8.3, 1.8$  Hz, 1H), 7.14 (s, 1H), 6.81 (d,  $J = 8.3$  Hz, 1H), 2.51 (s, 3H);  $^{13}\text{C-NMR}$  (100 MHz; acetone- $d_6$ )  $\delta$  199.4, 168.7, 145.5, 142.1, 137.0, 134.9, 129.6, 123.7, 113.2, 84.4, 32.1.

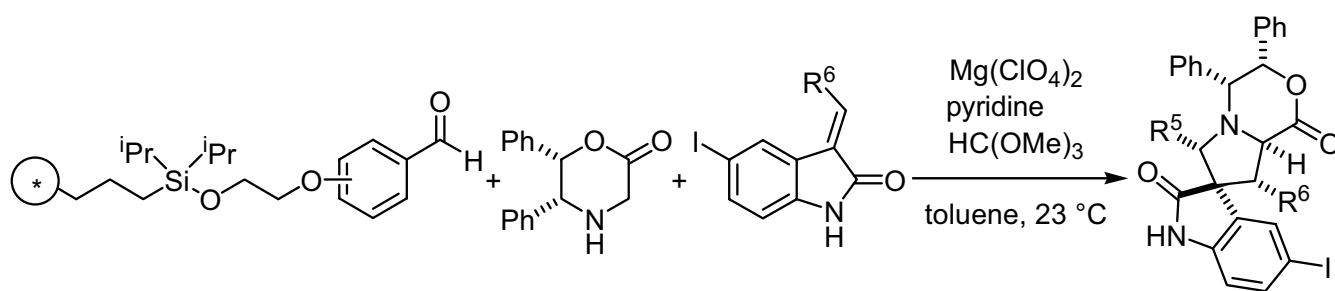


**(*E*)-2-(5-iodo-2-oxoindolin-3-ylidene)acetonitrile.** To a solution of lithium bromide (33 mmol, 1.3 equiv) in tetrahydrofuran (150 mL) was added diethyl (cyanomethyl)phosphonate (25 mmol, 1.0 equiv) and triethylamine (33 mmol, 1.3 equiv). The reaction was stirred at room temperature for 30 min before addition of 5-iodoisatin (25 mmol, 1.0 equiv). After stirred at room temperature for 7 h, the reaction was quenched with 1.0 N hydrochloric acid (200 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, concentrated in vacuo and purified by flash column chromatography (8% acetonitrile-benzene) followed by recrystallization (tetrahydrofuran-hexanes) to yield (*E*)-2-(5-iodo-2-oxoindolin-3-ylidene)acetonitrile (3.98 g, 54%) as a red solid:  $^1\text{H NMR}$  (500 MHz, acetone- $d_6$ )  $\delta$  9.91 (br, 1H), 8.25 (d,  $J = 1.8$  Hz, 1H), 7.79 (dd,  $J = 8.0, 1.8$  Hz, 1H), 6.90 (d,  $J = 8.0$  Hz, 1H), 6.51 (s, 1H);  $^{13}\text{C NMR}$  (100 MHz, acetone- $d_6$ )  $\delta$  166.0, 145.2, 143.4, 142.9, 133.4, 123.0, 116.9, 114.0, 99.6, 84.5, HRMS(EI $^+$ ) calcd for  $\text{C}_{10}\text{H}_5\text{IN}_2\text{O}$  (M) $^+$  295.9447, found 295.9454.

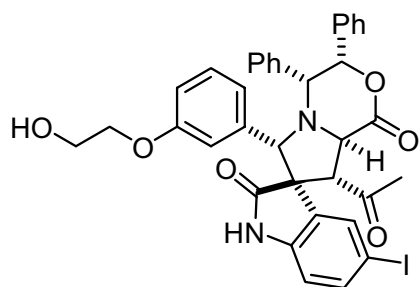


**(*E*)-2-(5-iodo-2-oxoindolin-3-ylidene)-*N*-methoxy-*N*-methylacetamide.** To a solution of diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (2.1 mmol, 1.2 equiv) in tetrahydrofuran (15 mL) cooled at  $-78$  °C was added a solution of *n*-butyl lithium (1.6 M in hexanes, 1.3 mL, 1.2 equiv) and stirred for 30 min before a solution of 5-iodoisatin (1.75 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added. The reaction

stirred at the same temperature for 18 h followed by quenched with saturated ammonium chloride (25 mL). After warmed to room temperature, the mixture was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, concentrated in vacuo, and purified by flash column chromatography (50% ethyl acetate-hexanes) to afford (*E*)-2-(5-iodo-2-oxoindolin-3-ylidene)-*N*-methoxy-*N*-methylacetamide (257 mg, 41%) as a yellow solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (br, 1H), 8.06 (br, 1H), 7.62 (dd,  $J = 8.0, 2.0$  Hz, 1H), 7.40 (s, 1H), 6.65 (d,  $J = 8.5$  Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.70, 165.19, 142.20, 140.41, 136.93, 135.11, 123.66, 122.59, 111.88, 85.38, 62.32, 32.44, 29.68; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{12}\text{H}_{11}\text{IN}_2\text{O}$  ( $\text{M}+\text{H}$ ) $^+$ , 358.9892; found, 358.9896.

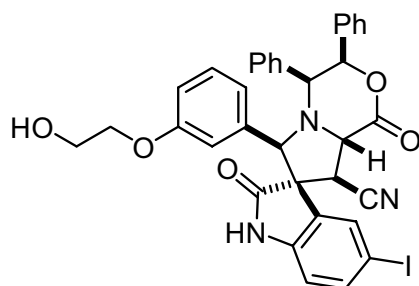


**General procedure for the sublibrary III synthesis.** To the polystyrene-bound aldehyde loaded in the same fashion as described above was added 5,6-diphenyl-4-morpholin-2-one (3.0 equiv), dipolarophile (3.0 equiv), magnesium perchlorate (1.3 equiv), pyridine (4.5 equiv), and trimethyl orthoformate (6.5 equiv) and toluene (0.014 M). This solution was tumbled for 72 h and the beads were filtered, washed with methylene chloride (3 $\times$ ), tetrahydrofuran (3 $\times$ ), *N,N*-dimethylformamide (3 $\times$ ), tetrahydrofuran (3 $\times$ ), methylene chloride (3 $\times$ ), and dried under vacuum for 24 h to give the polystyrene-bound spirooxindole as orange beads. A single bead of the polystyrene-bound spirooxindole intermediates of the demonstration compounds (**III-121**, **III-222**, **III-213**, **III-214**) was treated with a solution of hydrogen fluoride-pyridine/pyridine in tetrahydrofuran (5%-5% v-v/v, 0.03 mL) for 2 h followed by quenched with ethoxytrimethylsilane (0.06 mL). The polystyrene beads were filtered off and washed with methylene chloride (3 $\times$ ). The filtrate was collected and concentrated to give the corresponding spirooxindole for quality analysis. These four spirooxindole intermediates were synthesized separately in solution and purified by silica gel column chromatography with ethyl acetate as the eluent followed by preparative HPLC (ZORBAX<sup>®</sup> Rx-SIL column (9.4  $\times$  250 mm, 5  $\mu\text{m}$ ) in normal phase or ZORBAX<sup>®</sup> Eclipse XDB-C18 column (9.4  $\times$  250 mm, 5  $\mu\text{m}$ ) in reverse phase) to give pure spirooxindole for analytical purposes.



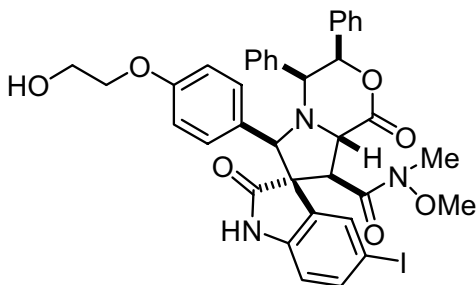
**(3*S*,2'*S*,3'*S*,6'*R*,7'*S*,9'*S*)-Spiro[(5-iodoindol-2-one)-3,8'-(7'-acetyl-9'-(3-(2-hydroxyethoxy)phenyl)-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]nonane)] (III-121).**  $[\alpha]_D^{30} +62.0^\circ$  (*c* 0.90, CH<sub>3</sub>OH); *R<sub>f</sub>* = 0.20 (75% ethyl acetate); FTIR (neat, cm<sup>-1</sup>) 3286 (br), 2929, 2875, 1738, 1732, 1714, 1613, 1488, 1471, 1453, 1359, 1316,

1256, 1179, 1126, 1080, 1059, 981, 886, 816, 737, 699; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.79 (s br, 1H), 7.51 (s, 1H), 7.42 (d, 1H, *J*=8.2), 7.26-7.27 (m, 4H), 7.17-7.23 (m, 3H), 7.06-7.14 (m, 5H), 6.78 (d, 1H, *J*=7.3), 6.74 (dd, 1H, *J*=1.9, 8.2), 6.67 (s, 1H), 6.42 (d, 1H, *J*=8.2), 6.22 (d, 1H, *J*=3.1), 5.18 (d, 1H, *J*=7.9), 4.99 (s, 1H), 4.22 (m, 2H), 3.64-3.90 (m, 4H), 1.89 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 200.1, 175.5, 171.1, 158.5, 139.4, 137.9, 136.0, 135.5, 135.3, 134.6, 129.5, 128.7, 128.6, 128.3, 128.0, 127.9, 127.6, 125.5, 111.7, 85.1, 77.2, 76.2, 75.4, 69.3, 61.33, 61.28, 60.9, 58.9, 55.9, 29.2; HRMS(ES<sup>+</sup>) calcd for C<sub>36</sub>H<sub>32</sub>IN<sub>2</sub>O<sub>6</sub> (M+H)<sup>+</sup> 715.1305, found 715.1307.



**(3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*)-Spiro[(5-iodoindol-2-one)-3,8'-(7'-cyano-9'-(3-(2-hydroxyethoxy)phenyl)-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]nonane)] (III-222).**  $[\alpha]_D^{29} +29^\circ$  (*c* 0.056, CH<sub>3</sub>OH); *R<sub>f</sub>* = 0.30 (75% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>)

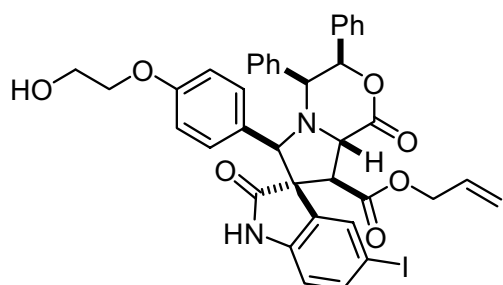
3389 (br), 2925, 1728, 1614, 1487, 1472, 1452, 1381, 1315, 1265, 1193, 1125, 1053, 986, 884, 737, 698; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.63 (s, 1H), 7.52 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.47 (s, 1H), 7.23-7.29 (m, 6H), 7.07-7.11 (m, 3H), 7.00-7.03 (m, 2H), 6.74-6.77 (m, 2H), 6.70 (s, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.18 (d, *J* = 2.9 Hz, 1H), 4.95 (s, 1H), 4.87 (d, *J* = 8.8 Hz, 1H), 4.23 (d, *J* = 3.3 Hz, 1H), 4.11 (d, *J* = 9.2 Hz, 1H), 3.84-3.86 (m, 2H), 3.77-3.79 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 174.2, 168.6, 158.6, 140.3, 138.7, 135.2, 135.0, 134.9, 134.8, 129.8, 128.6, 128.5, 128.43, 128.39, 128.2, 126.9, 125.8, 120.0, 115.3, 112.7, 85.3, 77.7, 73.4, 69.2, 61.1, 61.0, 60.5, 59.6, 40.7; HRMS(ES<sup>+</sup>) calcd for C<sub>35</sub>H<sub>29</sub>IN<sub>3</sub>O<sub>5</sub> (M+H)<sup>+</sup> 698.1152, found 698.1154.



**(3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*)-Spiro[(5-iodoindol-2-one)-3,8'-(9'-(3-(2-hydroxyethoxy)phenyl)-7'-(*N*-methoxy-*N*-methylamino)carbonyl-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]nonane)] (III-213).**  $[\alpha]_D^{30} +32^\circ$  (*c* 0.009, CH<sub>3</sub>OH); *R<sub>f</sub>* = 0.14 (75% ethyl acetate-hexanes); FTIR (neat, cm<sup>-1</sup>) 3250 (br) 3135,

1731, 1714, 1667, 1651, 1613, 1512, 1471, 1454, 1392, 1306, 1249, 1181, 1127, 1060, 991, 953, 916,

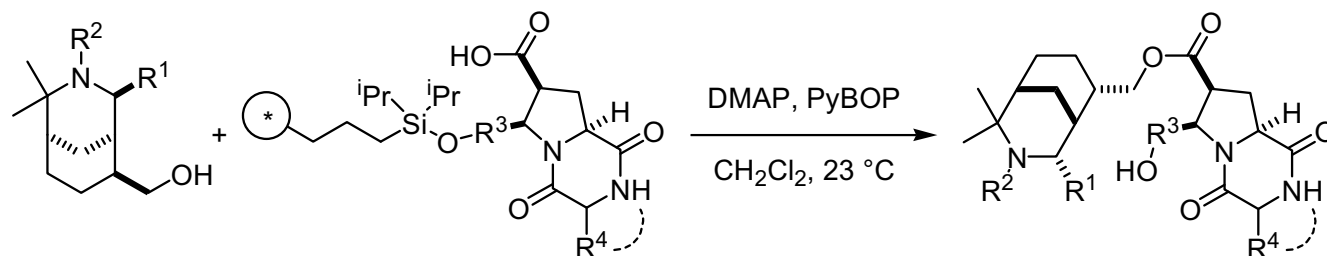
839, 814, 740, 700;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (1H, s), 7.37 (1H, dd,  $J=1.5, 8.1$ ), 7.15-7.25 (10H, m), 7.07-7.12 (4H, m), 6.70 (2H, d,  $J=8.4$ ), 6.33 (1H, d,  $J=8.1$ ), 6.21 (1H, d,  $J=3.3$ ), 5.32 (1H, d,  $J=6.2$ ), 4.86 (1H, s), 4.27 (1H, d,  $J=3.3$ ), 4.24 (1H, d,  $J=6.2$ ), 3.99-4.01 (2H, m), 3.90-3.94 (2H, m), 3.61 (3H, s), 2.75 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.0, 172.5, 168.5, 158.8, 140.2, 137.4, 136.1, 135.9, 135.4, 128.9, 128.5, 128.3, 127.9, 127.7, 125.5, 125.3, 114.2, 111.2, 83.9, 75.8, 75.6, 69.1, 61.4, 61.3, 61.2, 58.3, 57.8, 52.4, 32.7; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{37}\text{H}_{35}\text{IN}_3\text{O}_7$  ( $\text{M}+\text{H}$ ) $^+$  760.1520, found 760.1517.



**3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*-Spiro[(5-iodoindol-2-one)-3,8'-(9'-(3-(2-hydroxyethoxy)phenyl)-7'-allyloxycarbonyl-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]nonane)] (**III-214**).<sup>[4]</sup>  $[\alpha]_{\text{D}}^{29} +3.5^\circ$  ( $c$  1.01,  $\text{CH}_3\text{OH}$ );  $R_f = 0.25$  (75% ethyl acetate-hexanes); FTIR (neat,  $\text{cm}^{-1}$ ) 3330 (br), 2926, 1731,**

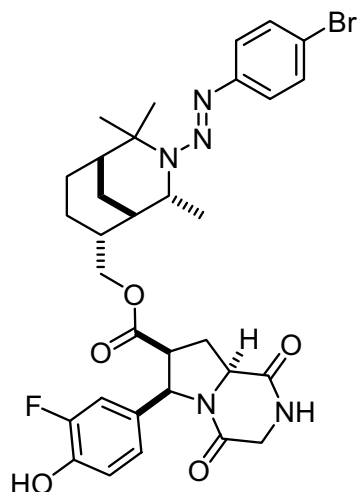
1613, 1511, 1472, 1454, 1306, 1249, 1186, 1127, 1084, 1056, 984, 917, 814, 699;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.45 (d,  $J = 2.0$  Hz, 1H), 7.42 (dd,  $J = 8.3, 2.0$  Hz, 1H), 7.18-7.26 (m, 6H), 7.04-7.11 (m, 6H), 6.70 (d,  $J = 8.3$  Hz, 2H), 6.47 (d,  $J = 8.3$  Hz, 1H), 6.30 (d,  $J = 3.4$  Hz, 1H), 5.34 (tdd,  $J = 17.1, 10.3, 5.9$  Hz, 1H), 4.99-5.06 (m, 4H), 4.22 (dd,  $J = 13.2, 5.9$  Hz, 1H), 4.19 (dd,  $J = 13.2, 5.9$  Hz, 1H), 4.14 (d,  $J = 3.4$  Hz, 1H), 4.04 (d,  $J = 8.3$  Hz, 1H), 3.88 (t,  $J = 4.6$  Hz, 2H), 3.72 (t,  $J = 4.6$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  55.2, 57.9, 60.6, 61.2, 61.9, 66.8, 70.4, 74.9, 77.6, 84.0, 112.7, 115.0, 119.3, 126.5, 126.8, 128.6, 128.8, 129.2, 129.3, 129.4, 129.8, 130.2, 132.1, 135.9, 137.3, 138.6, 142.5, 160.1, 168.9, 171.7, 175.9; HRMS( $\text{ES}^+$ ) calcd for  $\text{C}_{38}\text{H}_{34}\text{IN}_2\text{O}_7$  ( $\text{M}+\text{H}$ ) $^+$  757.1411, found 757.1415.

## Synthesis of Library IV



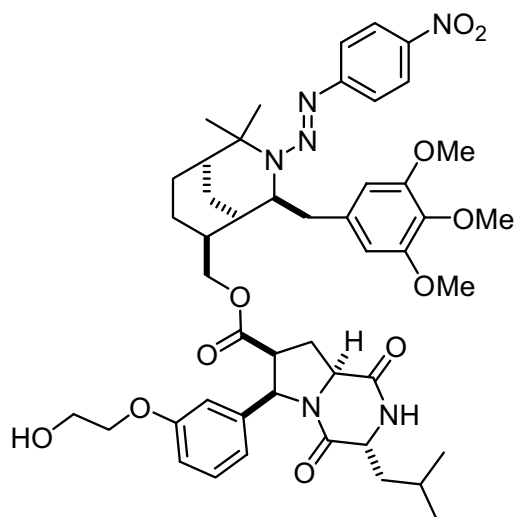
**General procedure for the sublibrary I-II coupling.** To a solution of sublibrary **I** (ca. 3.0 equiv) and **II** in methylene chloride (0.04 M) was added 4-(dimethylamino)pyridine (DMAP, 2.5 equiv) followed by (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 2.5 equiv). After agitated at room temperature for 16 h, the solution was filtered off and the beads were washed with

methylene chloride (5×) and dried. For analytical purposes, a portion of the polystyrene-bound **IV** obtained above (5 beads per compound) was treated for 2 h with a solution of hydrogen fluoride-pyridine/pyridine/tetrahydrofuran (0.01 mL/bead) (5%-5% v-v/v), or, for **IV-211121**, hydrogen fluoride-pyridine/triethylamine/tetrahydrofuran (0.01 mL/bead) (5%-30% v-v/v), and quenched with ethoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methanol/methylene chloride (1:1, 3×) and methylene chloride (3×). The filtrate was collected, concentrated and purified by silica gel column chromatography (triethylamine deactivated silica gel, 1→5% methanol in methylene chloride gradient with constant 1% triethylamine in the solvent) to give the pure alkaloid-diketopiperazine hybrids for analytical purposes, except **IV-132132**, which was purified on analytical HPLC with multiple injections (Agilent 1100 series with photodiode array detector and fraction collector, Merck KGaA Chromolith Performance RP-18e (4.6 x 100 mm), 3.0 mL/min, 5 min 5→95% CH<sub>3</sub>CN in H<sub>2</sub>O gradient, 220 nm for fraction collection). For **IV-211121**, so far it could not be purified without decomposition.



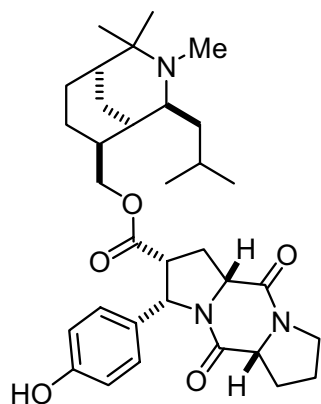
**{(1*R*,4*R*,5*S*,6*R*)-3-[2-(4-bromophenyl)-1-azeryl]-2,2,4-trimethyl-3-azabicyclo[3.3.1]non-6-yl}-methyl(6*S*,8*S*,9*R*)-9-(3-fluoro-4-hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate**

**(IV-211121)**.  $R_f = 0.25$  (10% methanol-methylene chloride); FTIR (neat,  $\text{cm}^{-1}$ ) 3249 (br), 2923, 2851, 1735, 1677, 1521, 1457, 1444, 1396, 1380, 1297, 1239, 1190, 1114, 1068, 1021, 1004, 830; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.43 (d,  $J = 8.8$  Hz, 2H), 7.24 (d,  $J = 8.8$  Hz, 2H), 6.85-6.79 (m, 2H), 6.73 (dd,  $J = 8.5, 2.0$  Hz, 1H), 5.26 (d,  $J = 9.0$  Hz, 1H), 4.52 (ddd,  $J = 13.0, 6.5, 1.5$  Hz, 1H), 4.12 (dd,  $J = 17.5, 1.5$  Hz, 1H), 4.04 (qd,  $J = 6.0, 5.8$  Hz, 1H), 3.97 (dd,  $J = 10.2, 8.8$  Hz, 1H), 3.93 (dd,  $J = 10.8, 5.8$  Hz, 1H), 3.70 (d,  $J = 16.5$  Hz, 1H), 3.64 (ddd,  $J = 14.0, 9.8, 6.5$  Hz, 1H), 2.58 (q,  $J = 13.5$  Hz, 1H), 2.40 (dt,  $J = 13.0, 6.5$  Hz, 1H), 2.26-2.17 (m, 3H), 1.92-1.88 (m, 1H), 1.70 (s, 3H), 1.69-1.67 (m, 1H), 1.61-1.53 (m, 3H), 1.44 (d,  $J = 6.5$  Hz, 3H), 1.44-1.41 (m, 1H), 1.37 (s, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>32</sub>H<sub>38</sub>BrFN<sub>5</sub>O<sub>5</sub> (M+H)<sup>+</sup> 670.2040, found 670.2042.



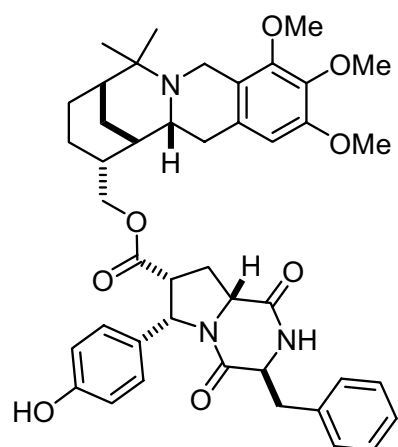
**{(1R,4S,5R,6S)-3-[2-(4-nitrophenyl)-1-azeny]-2,2-dimethyl-4-(3,4,5-trimethoxybenzyl)-3-azabicyclo[3.3.1]non-6-yl}-methyl (6S,8S,9R)-9-(3-(2-hydroxyethoxy)phenyl)-3-(2-methylpropyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (IV-132132).**  
 $[\alpha]_D^{29} +57^\circ$  ( $c$  0.0070, CH<sub>3</sub>OH);  $R_f = 0.32$  (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3357 (br), 2923, 1732, 1682, 1588, 1506, 1455, 1428, 1384, 1367, 1311, 1258, 1238, 1157, 1125, 1106, 1022, 857; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  8.14 (d,  $J = 9.5$  Hz, 2H), 7.27 (d,  $J = 9.0$

Hz, 2H), 7.08 (t,  $J = 8.0$  Hz, 1H), 6.72-6.70 (m, 1H), 6.66-6.65 (m, 2H), 6.45 (s, 2H), 5.29 (d,  $J = 9.0$  Hz, 1H), 4.60 (m, 2H), 4.24 (dd,  $J = 10.0, 7.0$  Hz, 1H), 4.00 (dd,  $J = 10.2, 8.2$  Hz, 1H), 3.96 (dd,  $J = 14.2, 9.8$  Hz, 1H), 3.90 (t,  $J = 4.8$  Hz, 2H), 3.85-3.77 (m, 4H), 3.65 (s, 3H), 3.65 (ddd,  $J = 12.8, 9.2, 6.0$  Hz, 1H), 3.62 (s, 6H), 2.82 (dd,  $J = 9.2, 4.2$  Hz, 1H), 2.59 (q,  $J = 12.7$  Hz, 1H), 2.54-2.49 (m, 1H), 2.40 (dt,  $J = 13.0, 6.5$  Hz, 1H), 2.17-2.14 (m, 1H), 2.10-2.04 (m, 1H), 1.92-1.84 (m, 1H), 1.79-1.72 (m, 4H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59-1.50 (m, 1H), 1.37-1.31 (m, 3H), 0.99 (dd,  $J = 6.0$  Hz, 3H), 0.95 (dd,  $J = 6.0$  Hz, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>47</sub>H<sub>61</sub>N<sub>6</sub>O<sub>11</sub> (M+H)<sup>+</sup> 885.4398, found 885.4406.



**{(1S,4S,5R,6S)-2,2,3-trimethyl-4-(2-methylpropyl)-3-azabicyclo[3.3.1]non-6-yl}methyl (3R,5R,6S,9R)-6-(4-hydroxyphenyl)-2,8-dioxo-1,7-diazatricyclo[7.3.0.0<sup>3,7</sup>]dodecan-5-carboxylate (IV-123214).**  
 $[\alpha]_D^{30} +33^\circ$  ( $c = 0.016$ , CH<sub>3</sub>OH);  $R_f = 0.33$  (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3417 (br), 2924, 1732, 1667, 1614, 1516, 1455, 1435, 1417, 1394, 1367, 1261, 1238, 1173, 1105, 1021, 844, 806; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  6.84 (d,  $J = 8.5$  Hz, 2H), 6.66 (d,  $J = 8.5$  Hz, 2H), 5.24 (d,  $J = 8.5$  Hz, 1H), 4.60 (dd,  $J = 10.5, 6.5$  Hz, 1H), 4.38 (t,  $J = 7.0$  Hz, 1H),

3.98 (dd,  $J = 10.5, 5.5$  Hz, 1H), 3.67-3.56 (m, 5H), 2.64 (q,  $J = 12.2$  Hz, 1H), 2.33 (dt,  $J = 13.0, 8.2$  Hz, 1H), 2.24 (m, 1H), 2.19-2.07 (m, 8H), 2.01-1.94 (m, 3H), 1.64-1.54 (m, 1H), 1.54-1.28 (m, 6H), 1.22 (s, 3H), 1.06 (s, 3H), 0.88 (d,  $J = 7.0$  Hz, 3H), 0.86 (d,  $J = 6.5$  Hz, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>33</sub>H<sub>48</sub>N<sub>3</sub>O<sub>5</sub> (M+H)<sup>+</sup> 566.3594, found 566.3590.



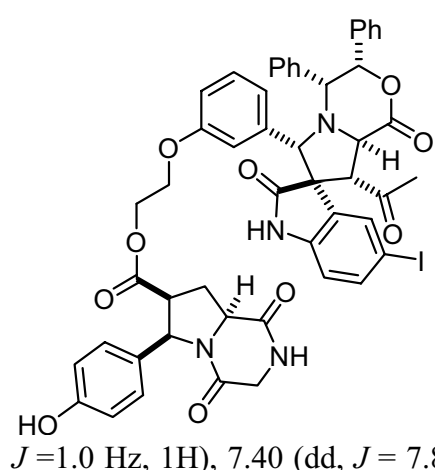
{(1*R*,12*R*,13*S*,14*R*)-2,2-dimethyl-6,7,8-trimethoxy-benzo[*e*]-3-azatricyclo[7.3.1.0<sup>5,10</sup>]tridec-14-yl}methyl (3*S*,6*R*,8*R*,9*S*)-3-benzyl-9-(4-hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (*IV-234213*).  $[\alpha]_D^{28} -23^\circ$  (*c* 0.021, CH<sub>3</sub>OH);  $R_f = 0.32$  (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3382 (br), 2923, 1732, 1668, 1614, 1600, 1516, 1495, 1462, 1416, 1386, 1337, 1294, 1240, 1174, 1109, 1034, 942, 844; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.37- 7.31 (m, 3H), 7.24 (d,  $J = 6.5$  Hz, 2H), 6.90 (d,  $J = 9.0$  Hz, 2H), 6.65 (d,  $J = 9.0$  Hz, 2H), 6.38 (s, 1H), 5.18 (d,  $J = 9.5$  Hz, 1H), 4.11 (t,  $J = 5.8$  Hz, 1H), 3.98-3.94 (m, 2H), 3.81 (s, 3H), 3.76(4) (s, 3H), 3.76(2) (s, 3H), 3.63-3.57 (m, 2H), 3.28 (m, 2H), 3.20 (dd,  $J = 13.5, 6.0$  Hz, 1H), 3.09 (dd,  $J = 12.2, 5.8$  Hz, 1H), 3.00 (dd,  $J = 13.5$  Hz, 5.0 Hz, 1H), 2.58-2.50 (m, 2H), 2.36 (q,  $J = 12.7$  Hz, 1H), 2.21-2.16 (m, 2H), 2.12 (dt,  $J = 12.5, 6.2$  Hz, 1H), 2.12-2.08 (m, 1H), 2.04-2.00 (m, 1H), 1.78-1.74 (m, 1H), 1.64-1.57 (m, 3H), 1.52-1.47 (m, 1H), 1.33 (s, 3H), 1.18 (s, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>43</sub>H<sub>52</sub>N<sub>3</sub>O<sub>8</sub> (M+H)<sup>+</sup> 738.3754, found 738.3758.

## Synthesis of Library V



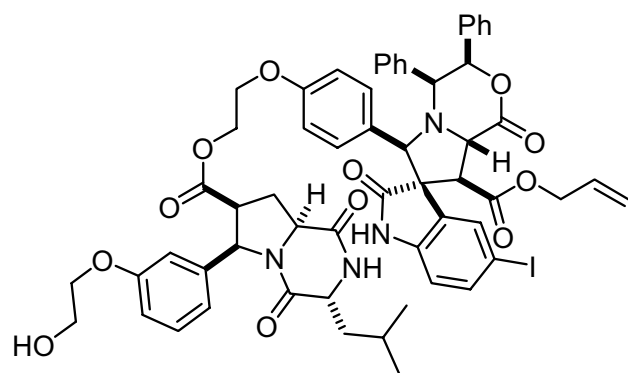
**General procedure for the sublibrary II-III coupling.** The polystyrene-bound sublibrary **III** above was treated with a solution of hydrogen fluoride-pyridine/pyridine/tetrahydrofuran (0.01 mL/bead) (5%-5% v-v/v) for 2 h followed by quenched with ethoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methylene chloride (3×). The filtrate was collected and concentrated to give free spirooxindole **III**. To a solution of sublibrary **III** (3.0 equiv) and **II** in methylene chloride (0.03-0.1 M) was added 4-(dimethylamino)pyridine (DMAP, 2.5 equiv) followed by (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 2.5 equiv). After agitated at room temperature for 16 h, the solution was filtered off and the beads were washed with methylene chloride (5×) and dried. A portion of the polystyrene-bound **V** obtained above

(5 beads per compound) was treated with a solution of hydrogen fluoride-pyridine/pyridine/tetrahydrofuran (0.01 mL/bead) (5%-5% v-v/v) for 2 h followed by quenched with ethoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methanol/methylene chloride (1:1, 3×), methylene chloride (3×) and dried. The filtrate was collected, concentrated and purified by silica gel column chromatography (triethylamine deactivated silica gel, 1→5% methanol in methylene chloride gradient (1→10% for V-121121) with constant 1% triethylamine in the solvent) to give the pure spirooxindole-diketopiperazine hybrid for analytical purposes.



**(6*S*,8*S*,9*R*)-2-((2'*S*,3'*S*,6'*R*,7'*S*,9'*S*)-3-[[Spiro[(5-iodoindol-2-one)-3,8'-(7'-acetyl-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]non-9'-yl)]]phenoxy)ethyl 9-(4-hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (V-121121).**

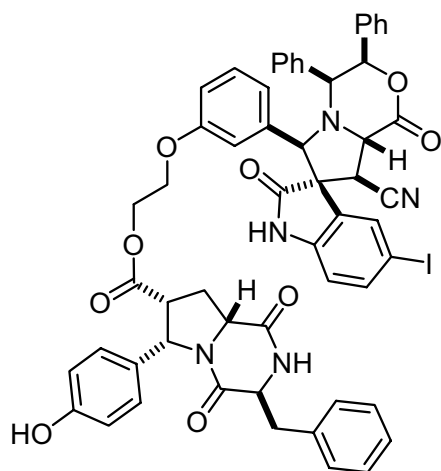
$[\alpha]_D^{29} +71^\circ$  (*c* 0.011, CH<sub>3</sub>OH);  $R_f = 0.17$  (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3418 (br), 2918, 2850, 1738, 1732, 1715, 1682, 1668, 1614, 1520, 1471, 1455, 1359, 1301, 1259, 1187, 1159, 1114, 944, 806, 699; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.43 (d, *J* = 1.0 Hz, 1H), 7.40 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.26 (t, *J* = 3.2 Hz, 3H), 7.22-7.17 (m, 4H), 7.11-7.08 (m, 5H), 6.81-6.79 (m, 1H), 6.74-6.71 (m, 4H), 6.62 (m, 1H), 6.40 (d, *J* = 3.5 Hz, 1H), 5.26 (d, *J* = 9.0 Hz, 1H), 5.22 (d, *J* = 8.5 Hz, 1H), 5.14 (s, 1H), 4.52 (dd, *J* = 11.0, 6.0 Hz, 1H), 4.33 (d, *J* = 8.0 Hz, 1H), 4.21 (d, *J* = 3.0 Hz, 1H), 4.13 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.07-4.04 (m, 1H), 3.81-3.77 (m, 1H), 3.71 (d, *J* = 17.0 Hz, 1H), 3.70-3.62 (m, 3H), 2.53 (q, *J* = 13.0 Hz, 1H), 2.35 (dt, *J* = 13.0, 6.5 Hz, 1H), 1.85 (s, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>50</sub>H<sub>43</sub>FIN<sub>4</sub>O<sub>10</sub> (M+H)<sup>+</sup> 1005.2008, found 1005.2036.



**(3*S*,6*R*,8*R*,9*S*)-2-((3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*)-4-[[Spiro[(5-iodoindol-2-one)-3,8'-(7'-allyloxycarbonyl-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]non-9'-yl)]]phenoxy)ethyl 9-(3-(2-hydroxyethoxy)phenyl)-3-(2-methylpropyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (V-214132).**

$[\alpha]_D^{28} -16^\circ$  (*c* 0.035, CH<sub>3</sub>OH);  $R_f = 0.36$  (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3389 (br), 2924, 2854,

1732, 1668, 1614, 1513, 1470, 1455, 1379, 1304, 1257, 1187, 1103, 1084, 1052, 1010, 980, 805, 699; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.51 (d, *J* = 1.5 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.28 (dd, *J* = 5.3, 1.7 Hz, 3H), 7.21- 7.09 (m, 10H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.62-6.58 (m, 2H), 6.45 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 5.34 (tdd, *J* = 17.0, 11.0., 5.5 Hz, 1H), 5.27 (d, *J* = 9.5 Hz, 1H), 5.07-5.00 (m, 4H), 4.58 (dd, *J* = 11.3, 6.3 Hz, 1H), 4.25 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.24 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.21 (d, *J* = 3.5 Hz, 1H), 4.15 (d, *J* = 7.5 Hz, 1H), 4.10 (dt, *J* = 12.2, 4.5 Hz, 1H), 4.02 (dt, *J* = 12.4, 4.6 Hz, 1H), 3.91 (t, *J* = 4.8 Hz, 2H), 3.81-3.78 (m, 5H), 3.65 (ddd, *J* = 13.8, 9.3, 6.0 Hz, 1H), 2.55 (q, *J* = 12.8 Hz, 1H), 2.35 (dt, *J* = 13.0, 6.5 Hz, 1H), 1.80-1.71 (m, 2H), 1.61-1.54 (m, 1H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>58</sub>H<sub>58</sub>IN<sub>4</sub>O<sub>12</sub> (M+H)<sup>+</sup> 1129.3096, found 1129.3115.



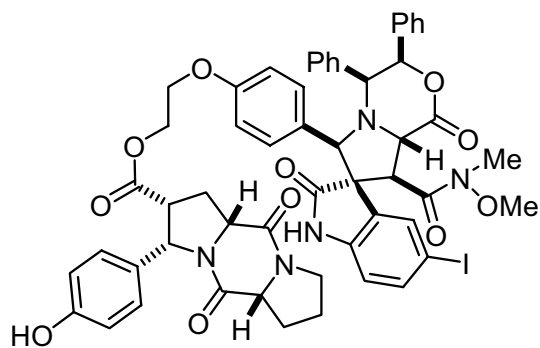
**(3*S*,6*R*,8*R*,9*S*)-2-[(3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*)-3-[Spiro[(5-iodoindol-2-one)-3,8'-(7'-cyano-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]non-9'-yl)]phenoxy]ethyl 3-benzyl-9-(4-**

**hydroxyphenyl)-2,5-dioxo-1,4-diazabicyclo[4.3.0]nonan-8-carboxylate (V-222213).** [α]<sub>D</sub><sup>29</sup> +31° (*c* 0.026, CH<sub>3</sub>OH); *R*<sub>f</sub> = 0.29

(10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3242 (br), 1917, 2850, 1732, 1715, 1682, 1668, 1614, 1516, 1471, 1455, 1383, 1294, 1268, 1175, 1108, 1054, 885, 736, 701; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.72 (s, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.37-7.32 (m,

4H), 7.30-7.20 (m, 9H), 7.08 (dd, *J* = 12.0, 3.0 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 2H), 6.75 (d, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.71 (s, 1H), 6.68-6.65 (m, 1H), 6.40 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 3.0 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 5.18 (s, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 10.0 Hz, 1H), 4.15-4.12 (m, 2H), 3.90 (m, 2H), 3.61 (m, 2H), 3.27 (ddd, *J* = 12.5, 10.0, 6.0 Hz, 1H), 3.21 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.10 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.29 (q, *J* = 12.7 Hz, 1H), 2.06 (dt, *J* = 13.5, 6.0 Hz, 1H); HRMS(ES<sup>+</sup>) calcd for C<sub>56</sub>H<sub>47</sub>IN<sub>5</sub>O<sub>9</sub>

(M+H)<sup>+</sup> 1060.2418, found 1060.2426.

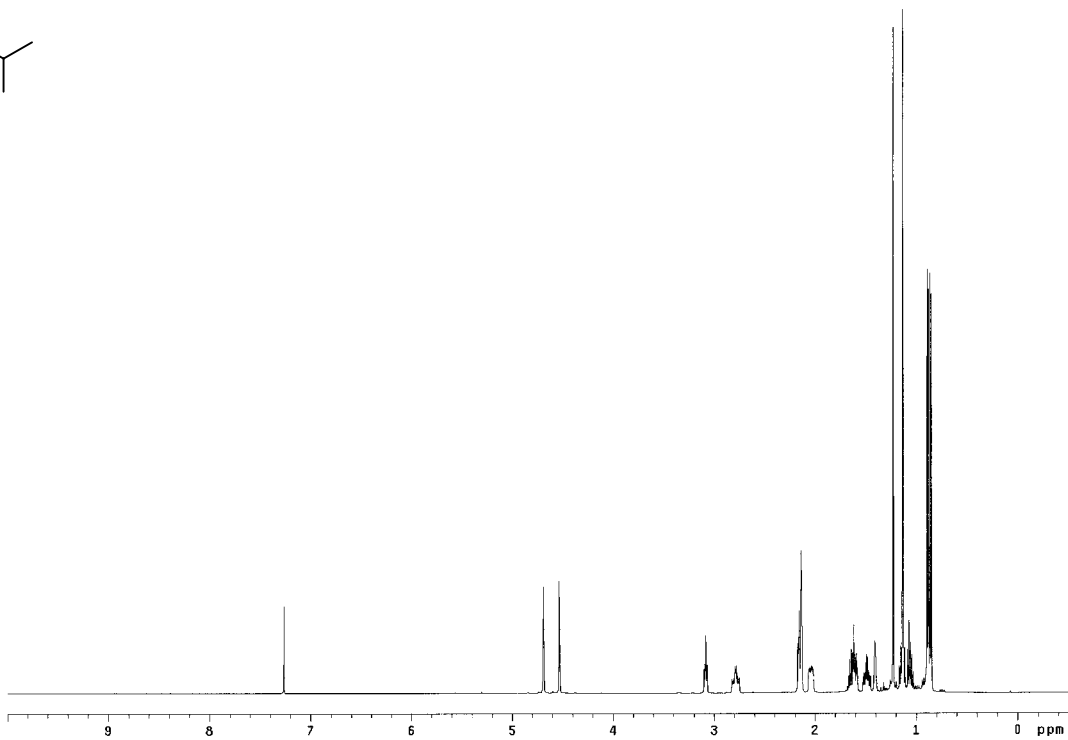
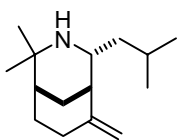
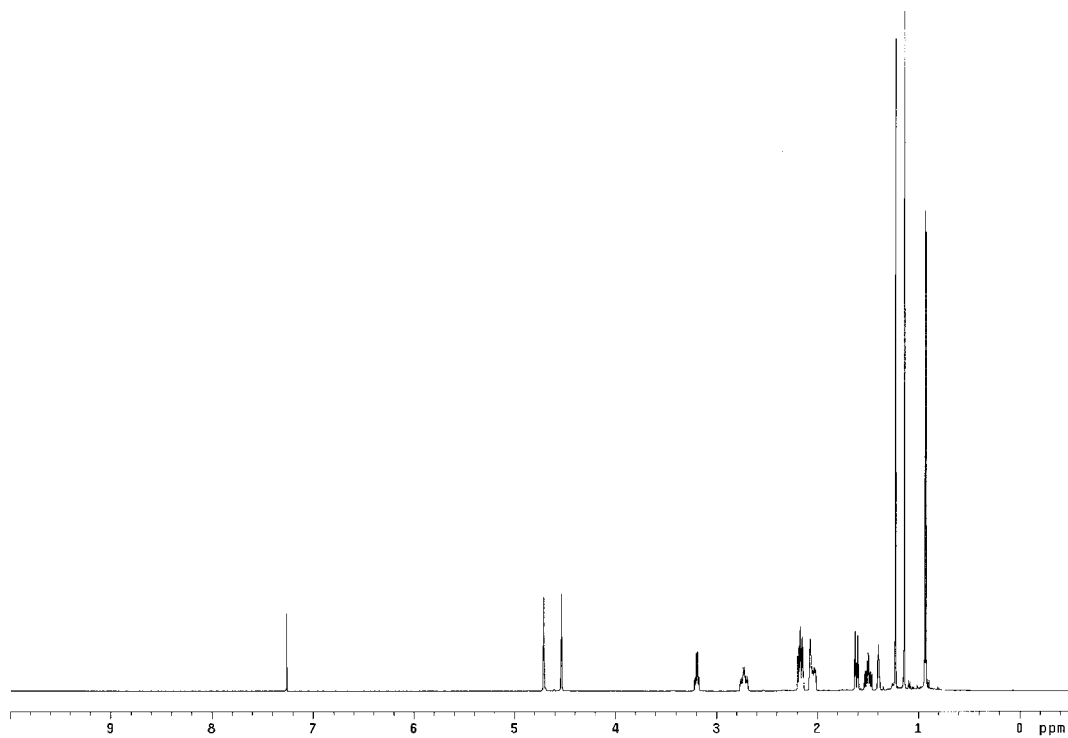
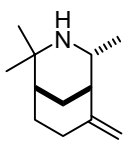


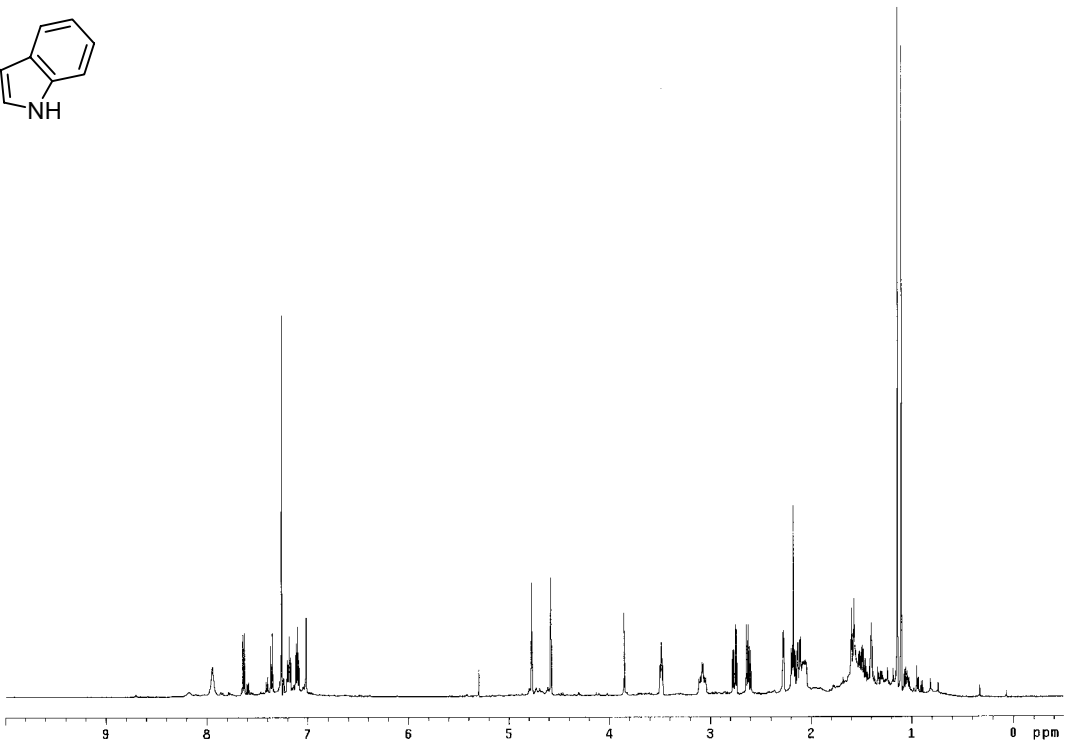
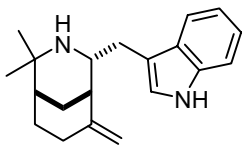
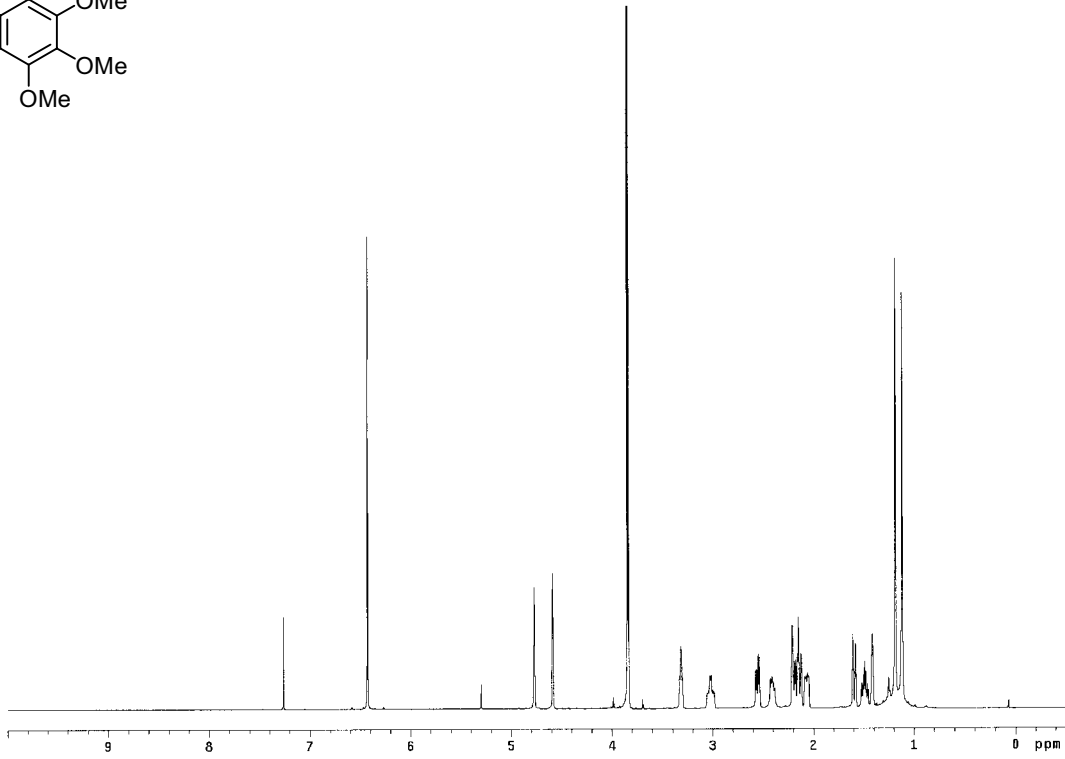
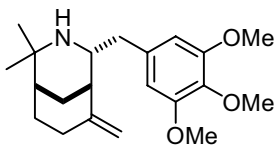
**(3*S*,6*R*,8*R*,9*S*)-2-[4-[(3*R*,2'*R*,3'*R*,6'*S*,7'*S*,9'*R*)-Spiro[(5-iodoindol-2-one)-3,8'-(7'-(*N*-methoxy-*N*-methylamino)carbonyl-5'-oxo-2',3'-diphenyl-1'-aza-4'-oxa-bicyclo[4.3.0]non-9'-yl)]phenoxy]ethyl (3*R*,5*R*,6*S*,9*R*)-6-**

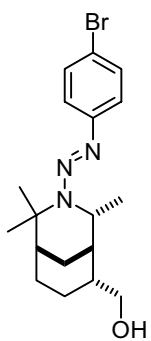
**(4-hydroxyphenyl)-2,8-dioxo-1,7-diazatricyclo[7.3.0.0<sup>3,7</sup>] dodecan-5-carboxylate (IV-213214).**  
[ $\alpha$ ]<sub>D</sub><sup>29</sup> +39° (c 0.019, CH<sub>3</sub>OH);  $R_f$  = 0.33 (10% methanol-methylene chloride); FTIR (neat, cm<sup>-1</sup>) 3418 (br), 2924, 1732, 1668, 1652, 1614, 1514, 1471, 1455, 1434, 1392, 1237, 1176, 1108, 1032, 1002, 954, 840, 808, 732, 700; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.45 (d,  $J$  = 1.5 Hz, 1H), 7.34 (dd,  $J$  = 8.3, 1.3 Hz, 1H), 7.27-7.10 (m, 12H), 6.79 (d,  $J$  = 7.0 Hz, 2H), 6.67 (d,  $J$  = 8.0 Hz, 2H), 6.49 (d,  $J$  = 8.5 Hz, 2H), 6.37 (d,  $J$  = 3.5 Hz, 1H), 6.22 (d,  $J$  = 3.0 Hz, 1H), 5.22 (d,  $J$  = 6.5 Hz, 1H), 5.19 (d,  $J$  = 9.0 Hz, 1H), 4.94 (s, 1H), 4.62-4.58 (m, 1H), 4.38 (dd,  $J$  = 7.5, 6.5 Hz, 1H), 4.32 (d,  $J$  = 4.0 Hz, 1H), 4.25 (d,  $J$  = 6.5 Hz, 1H), 4.11-4.07 (m, 1H), 4.03-3.97 (m, 2H), 3.93-3.88 (m, 1H), 3.66 (ddd,  $J$  = 13.5, 8.5, 6.0 Hz, 1H), 3.62 (s, 3H), 3.56 (dd,  $J$  = 6.5, 5.0 Hz, 2H), 2.74 (m, 3H), 2.61 (q,  $J$  = 12.7 Hz, 1H), 2.32 (dt,  $J$  = 13.5, 6.5 Hz, 1H), 2.23 (td,  $J$  = 7.4, 4.5 Hz, 1H), 2.00-1.95 (m, 3H); HRMS(ES<sup>+</sup>) calcd for C<sub>54</sub>H<sub>51</sub>N<sub>5</sub>O<sub>11</sub> (M+H)<sup>+</sup> 1072.2630, found 1072.2646.

#### Reference:

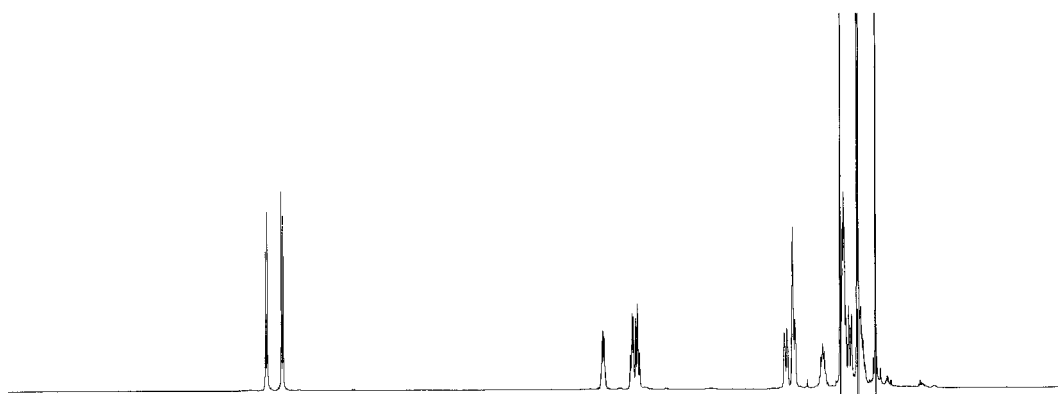
- [1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
- [2] C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174-10175.
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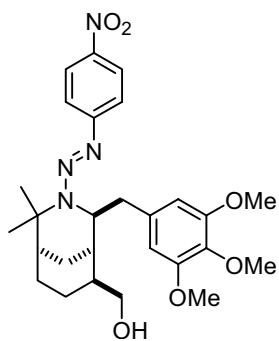
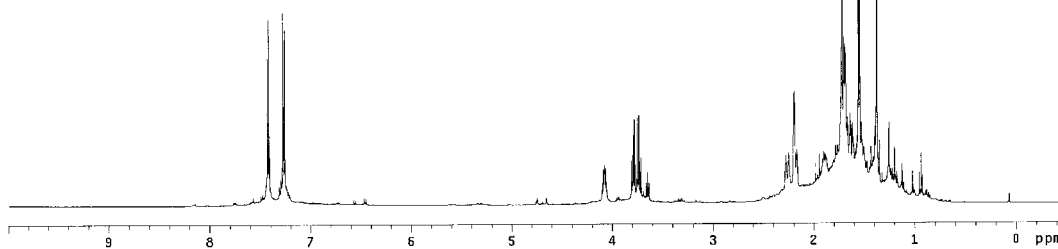




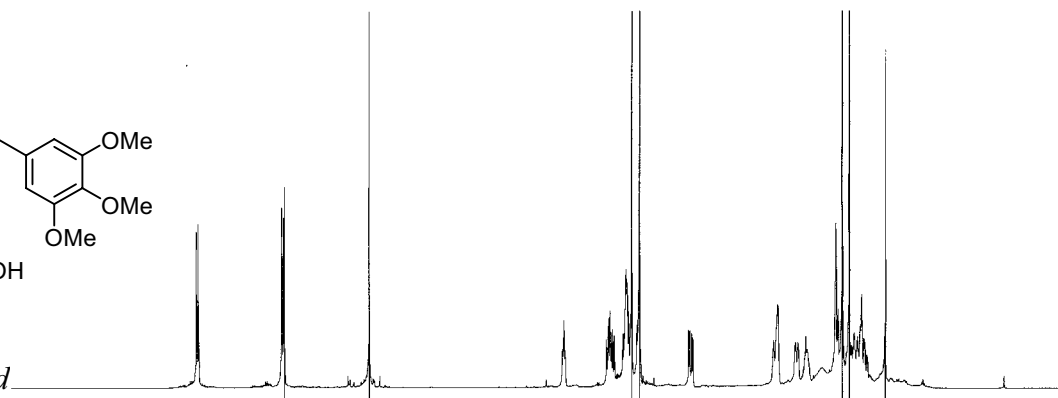
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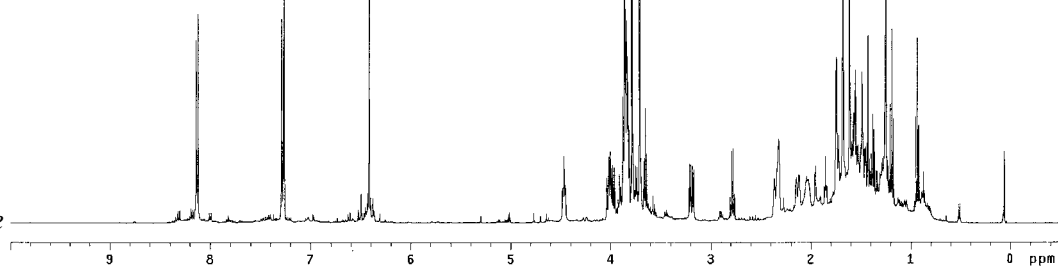
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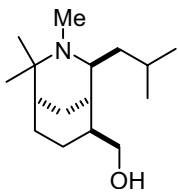


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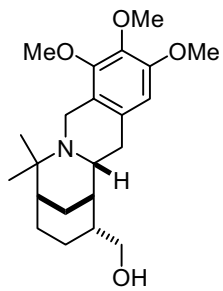
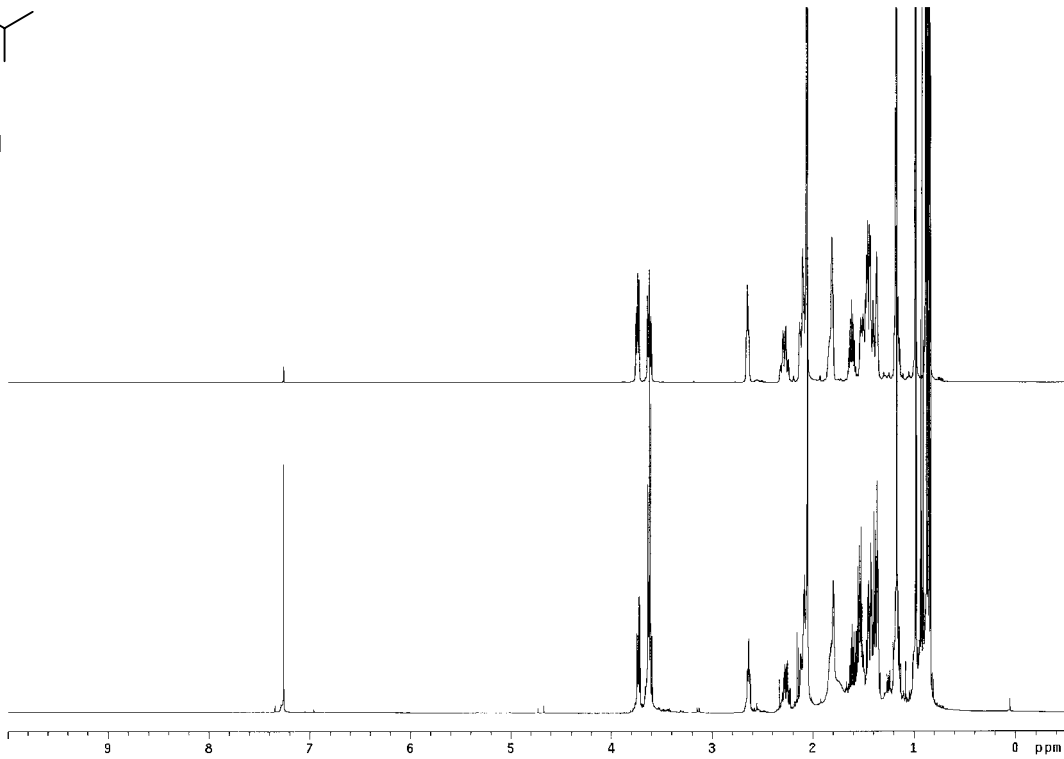
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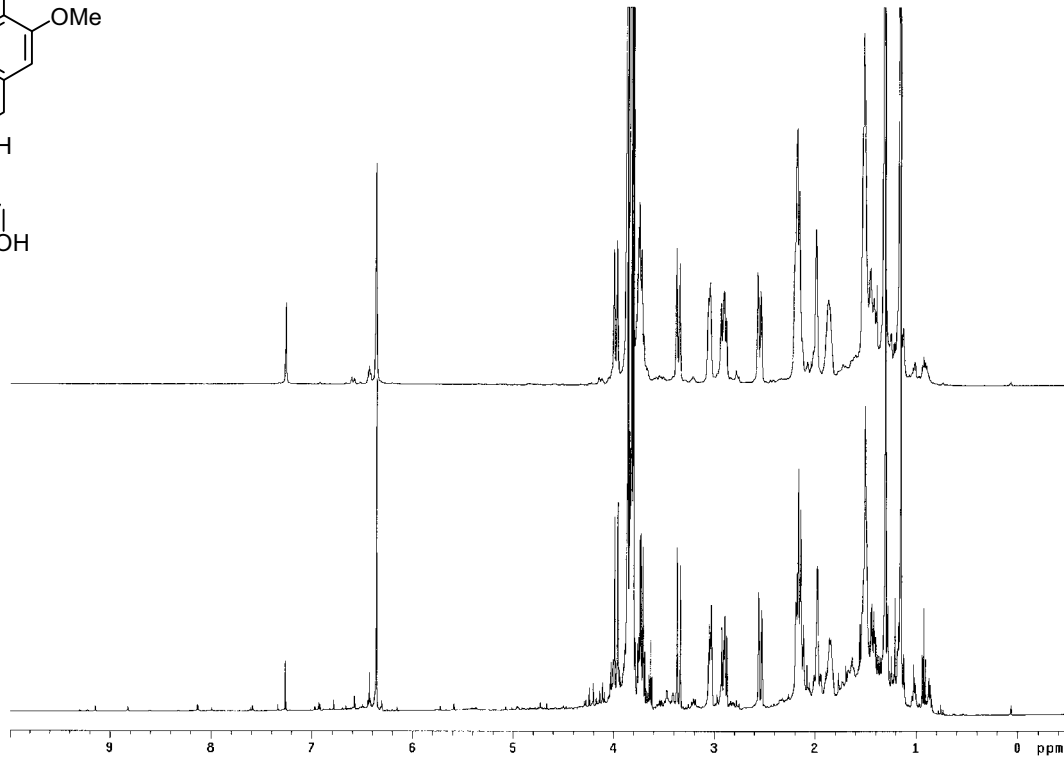
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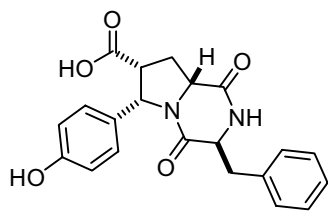
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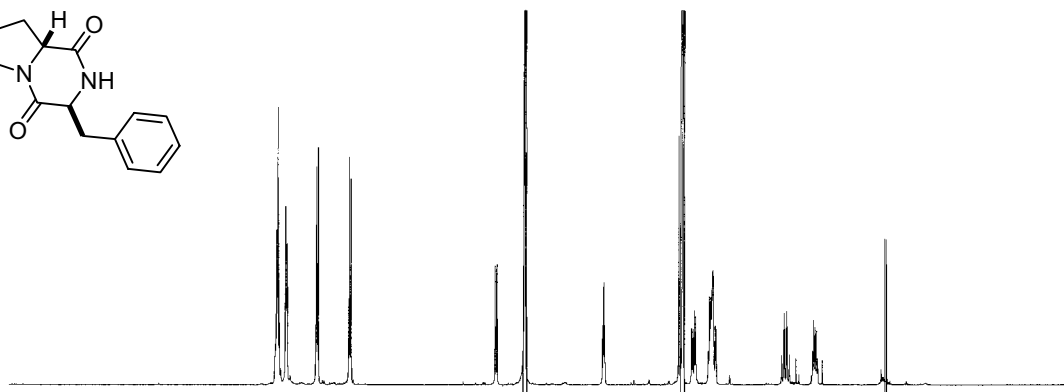
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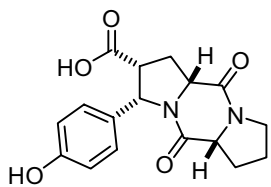
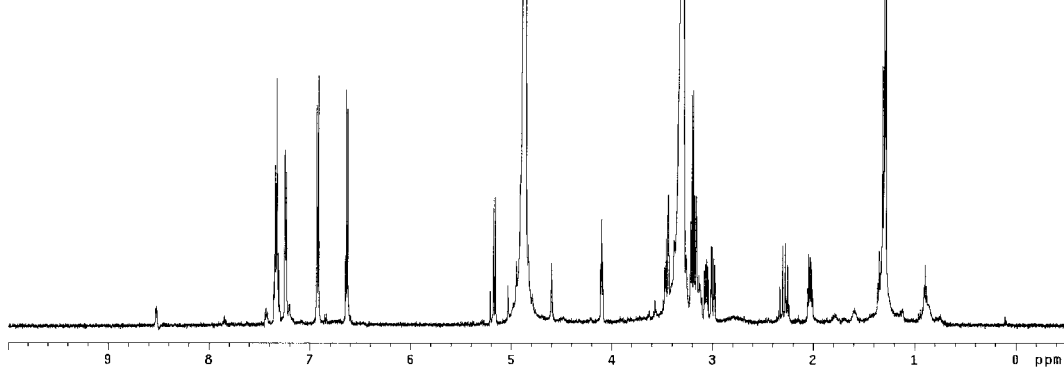




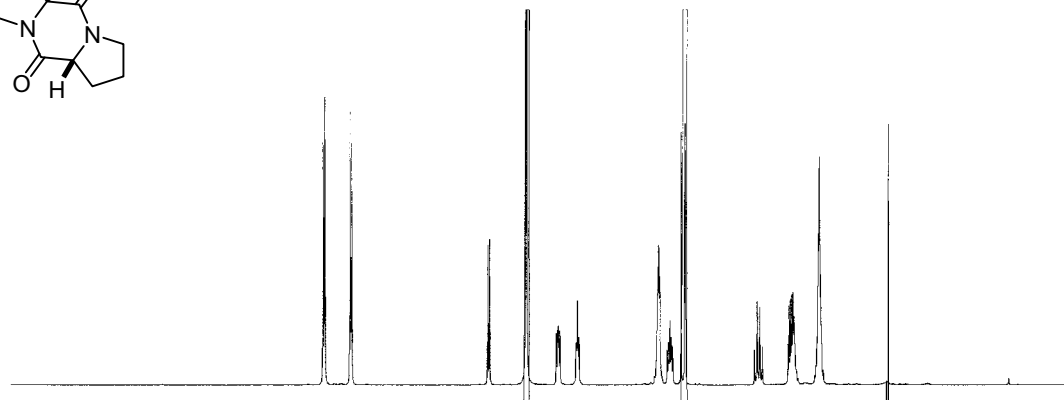
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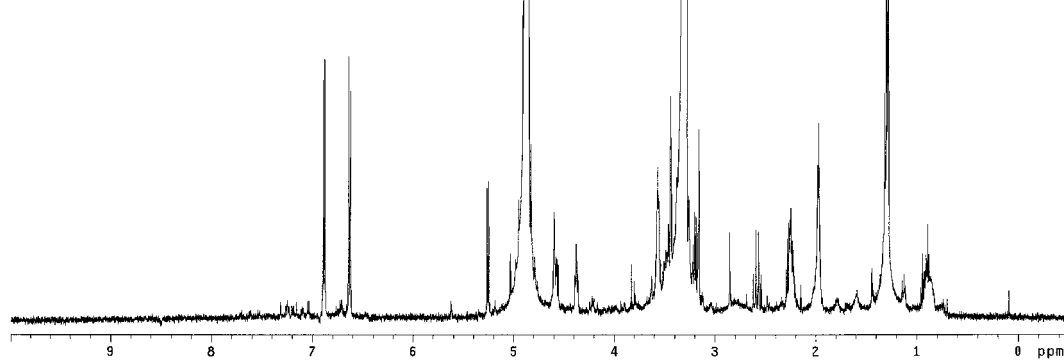
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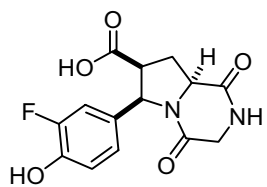


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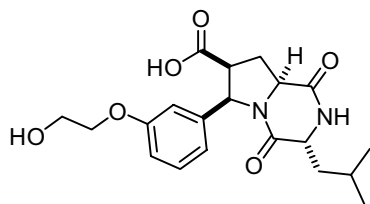
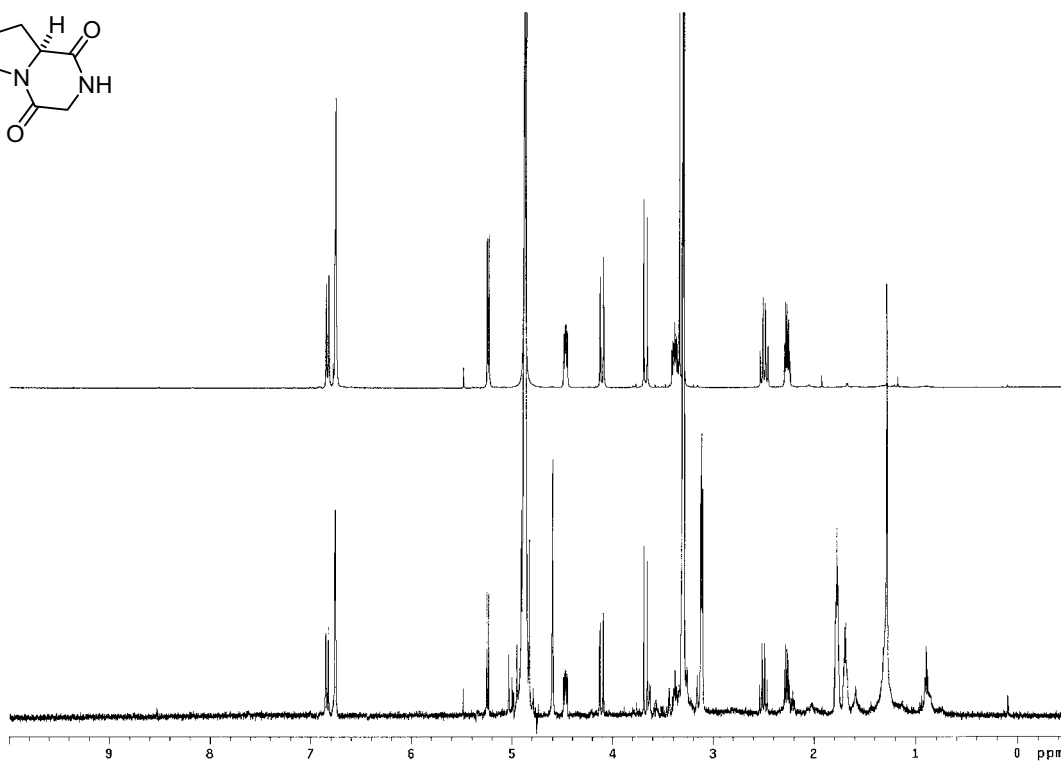
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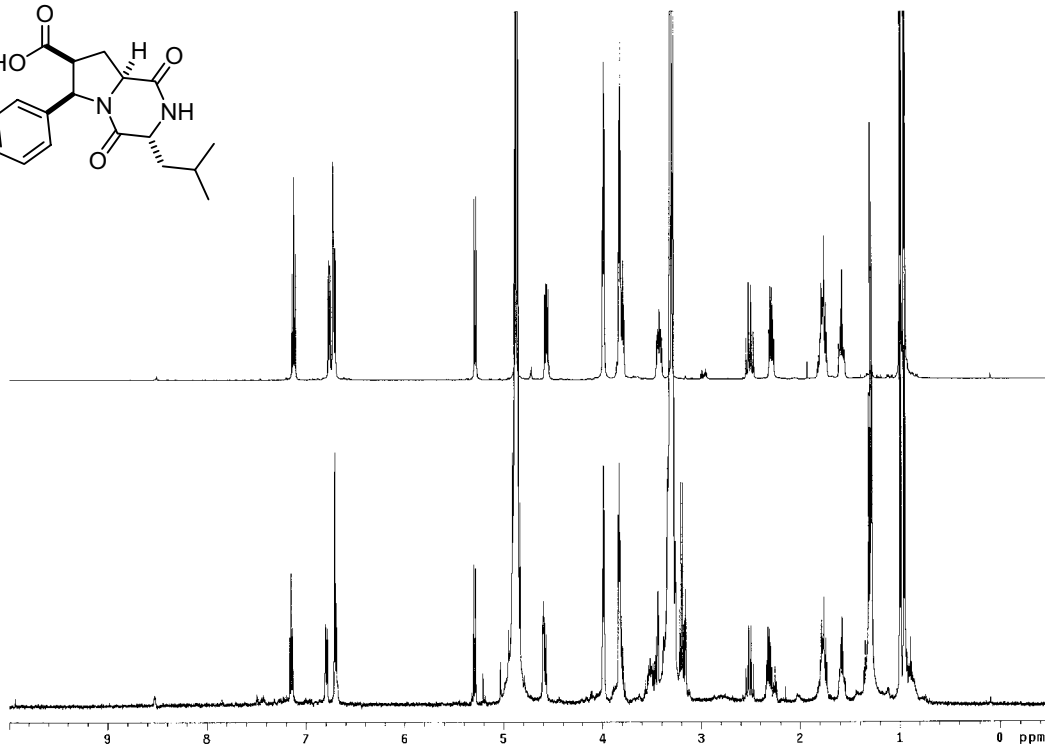
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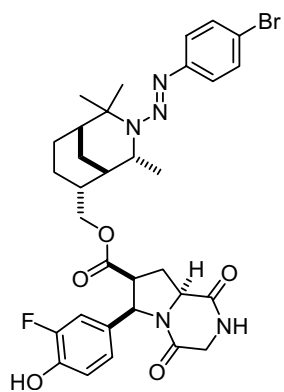
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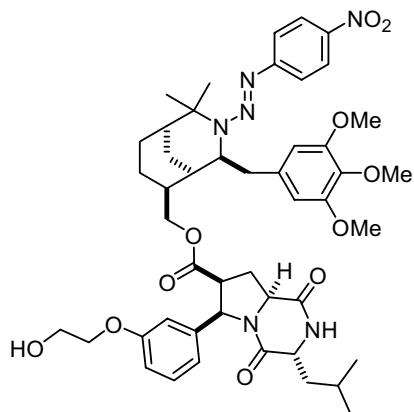
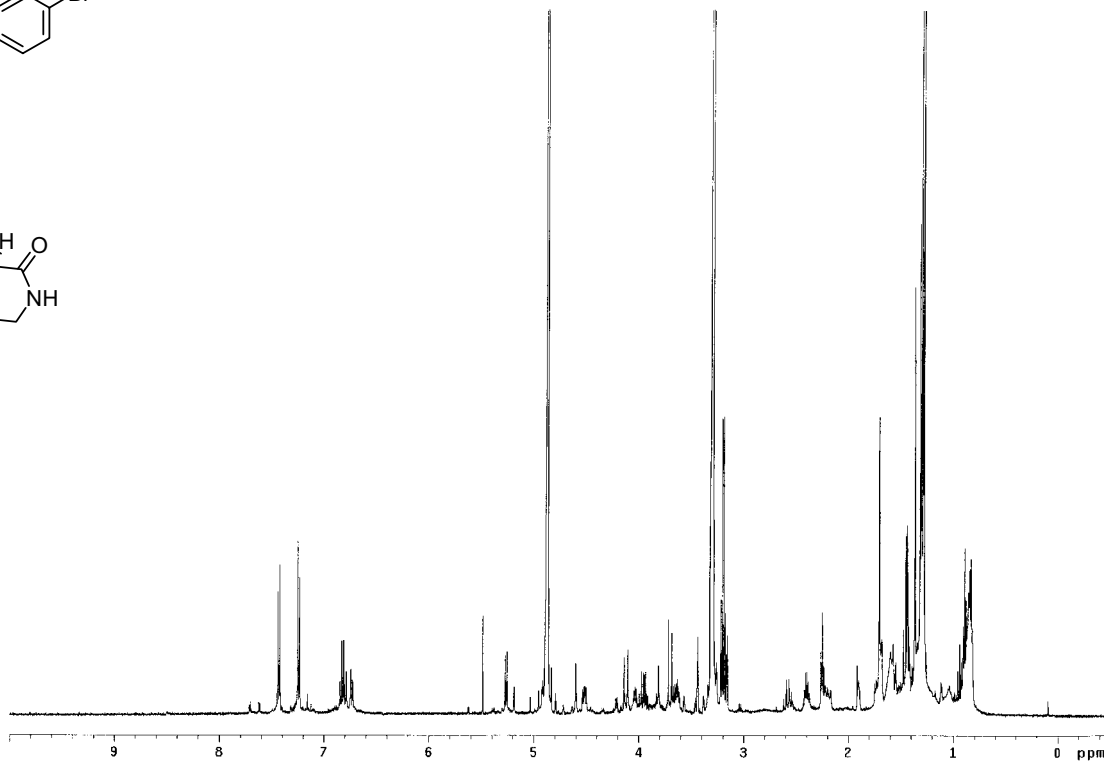
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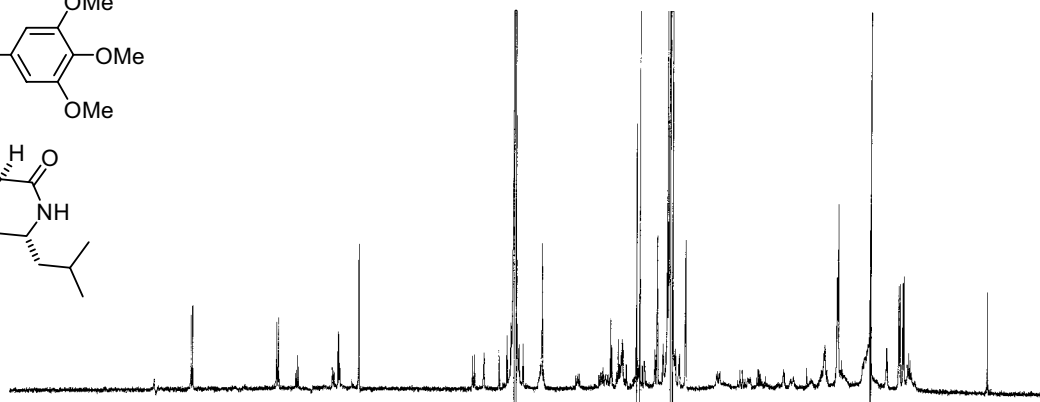




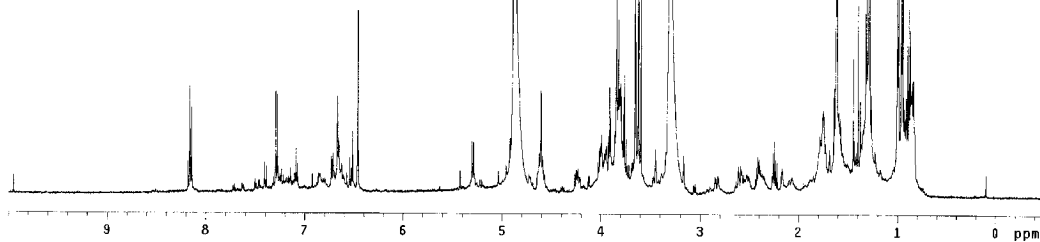
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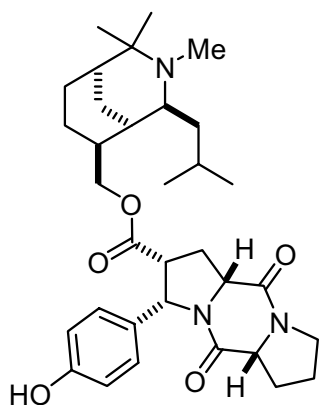


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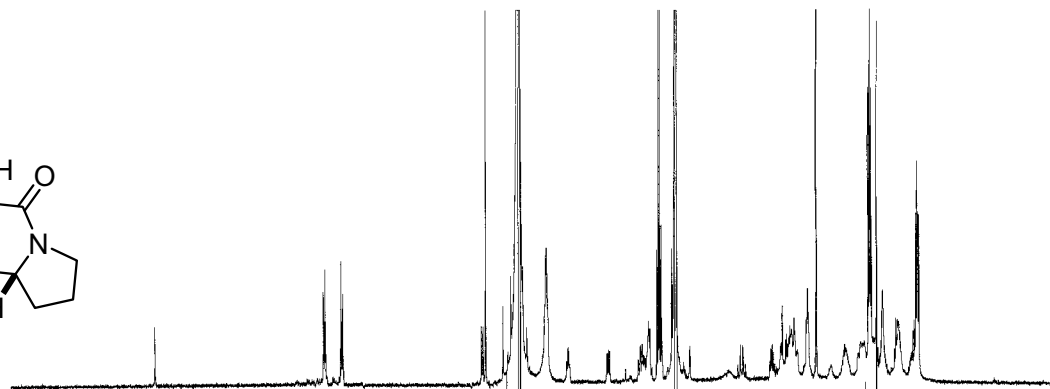


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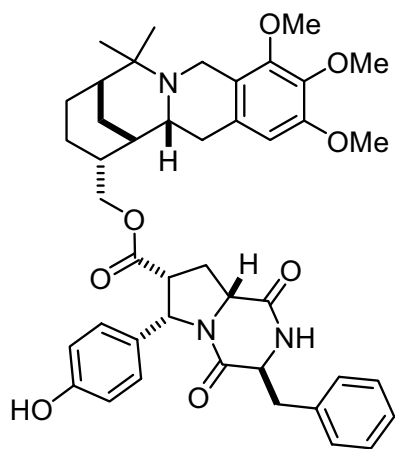
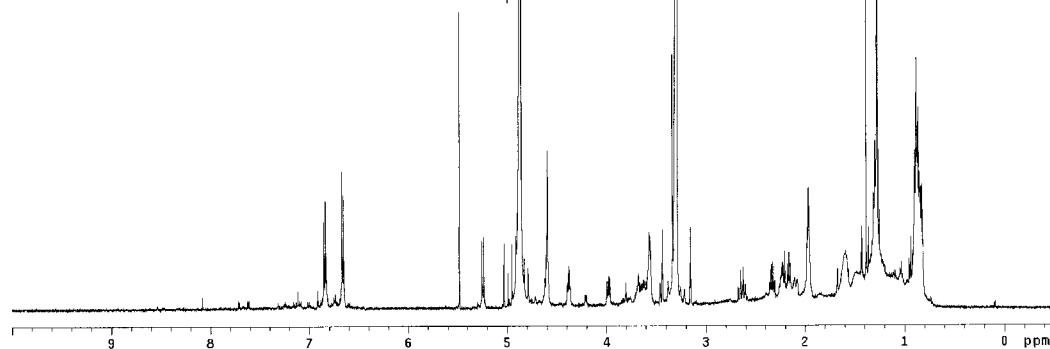




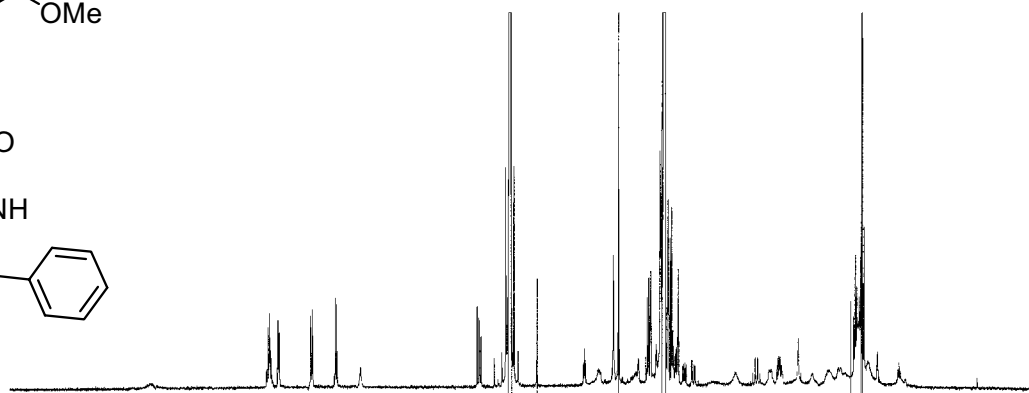
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