



Published in final edited form as:

*Tetrahedron*. 2015 September 2; 71(35): 5897–5905. doi:10.1016/j.tet.2015.05.093.

## Total synthesis of dihydrolysergic acid and dihydrolysergol: development of a divergent synthetic strategy applicable to rapid assembly of D-ring analogs

Kiyoun Lee, Yam B. Poudel, Christopher M. Glinkerman, and Dale L. Boger\*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

### Abstract

The total syntheses of dihydrolysergic acid and dihydrolysergol are detailed based on a Pd(0)-catalyzed intramolecular Larock indole cyclization for the preparation of the embedded tricyclic indole (ABC ring system) and a subsequent powerful inverse electron demand Diels–Alder reaction of 5-carbomethoxy-1,2,3-triazine with a ketone-derived enamine for the introduction of a functionalized pyridine, serving as the precursor for a remarkably diastereoselective reduction to the *N*-methylpiperidine D-ring. By design, the use of the same ketone-derived enamine and a set of related complementary heterocyclic azadiene [4 + 2] cycloaddition reactions permitted the late stage divergent preparation of a series of alternative heterocyclic derivatives not readily accessible by more conventional approaches.

### Keywords

1,2,3-triazine cycloaddition; ergot alkaloids; palladium catalyzed indole synthesis; Diels–Alder cycloaddition

## 1. Introduction

The ergot alkaloids isolated from the fungus *Claviceps purpurea* comprise a large group of pharmacologically potent indole alkaloids (Figure 1).<sup>1</sup> Among this family of natural products, lysergic acid<sup>2</sup> is the most widely recognized member and several semisynthetic derivatives are clinically used in the treatment of a range of neurological diseases. The dopamine agonists, pergolide<sup>3</sup> and bromocriptine,<sup>4</sup> are used for the treatment of Parkinson's disease and type 2 diabetes, respectively, and ergometrine<sup>5</sup> is used as a uterotonic agent in combination with oxytocin. Most notorious among the semisynthetic derivatives is lysergic acid diethylamide (LSD), a powerful psychoactive and psychedelic drug. Embedded in the

\*Corresponding author: boger@scripps.edu (D. Boger), phone: 858-784-7522, fax: 858-784-7550.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary data

Copies of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of all synthetic intermediates and final products are provided.

structures of the ergot alkaloids are conformationally-restricted variants of the phenethylamine pharmacophores of both dopamine and related biogenic amines as well as that of serotonin. Consequently, extensive studies have been conducted to explore not only the biological properties of the ergot alkaloids, but to also define the structural features responsible for the activity and the underlying origin of the pharmacological effects.

As a result, the total synthesis of the ergot alkaloids has been the subject of extensive study over the last half century.<sup>1a,6</sup> Herein, we report the total synthesis of dihydrolysergic acid (**1**)<sup>7,8</sup> and dihydrolysergol (**2**)<sup>9</sup> based on two key reactions we recently introduced. Notably, the latter natural product has only been prepared by semisynthesis from lysergic acid and the work herein discloses the first total synthesis of this natural product by an alternate route. The first of these reactions is a powerful intramolecular Larock indole cyclization<sup>10,11</sup> for formation of an embedded tricyclic indole isomeric with Uhle's<sup>12</sup> and Kornfeld's<sup>6a</sup> ketones widely used in accessing the ergot alkaloids (Figure 2). The second of the reactions is a powerful inverse electron demand Diels–Alder reaction of 5-carbomethoxy-1,2,3-triazine with a conjugated enamine for the regiospecific introduction of a functionalized pyridine,<sup>13</sup> serving as the precursor for a subsequent and remarkably diastereoselective reduction to the *N*-methylpiperidine D-ring. An additional and deliberate key feature of the approach is that use of the same advanced ketone-derived enamine and a series of inverse electron demand [4 + 2] cycloaddition reactions of heterocyclic azadienes<sup>14</sup> permitted the divergent<sup>15</sup> preparation of isomeric and alternative heterocyclic derivatives bearing deep-seated structural changes to the ergot skeleton not as readily accessible by conventional approaches.

## 2. Results and Discussion

The synthesis began with the preparation of the tricyclic ketone **12** as illustrated in Scheme 1. Although both the synthesis of **8** (in Supporting Information<sup>10a</sup>) and its participation in the key indole cyclization were detailed in our original studies disclosing the Pd(0)-catalyzed cyclization,<sup>10a</sup> the synthesis of **8** reported herein is significantly improved and its cyclization has been successfully increased to 0.5–1 g scales. Bis-acetylation of the known 2-bromoaniline **3**<sup>16</sup> and subsequent methanolysis of the *O*-acetate furnished the free alcohol (83%). This was followed by oxidation (MnO<sub>2</sub>) of the benzylic alcohol to provide the aldehyde **4** (92%). Wittig olefination of the resulting aldehyde with (methoxymethylene)-triphenylphosphorane<sup>17</sup> afforded the enol ether **5** (86% as a mixture of olefin isomers (71% yield over two steps without intermediate purification of **4**). Hydrolysis effected by treatment of **5** with aqueous 6 N HCl/acetone (1:1) furnished aldehyde **6**. The substrate for the key intramolecular indole annulation was accessed from **6** using an indium variant of a Grignard reagent, which was prepared from 1-(trimethylsilyl)propargyl bromide (**7**).<sup>18</sup> The addition reaction of the in situ generated indium reagent (3 equiv indium powder, THF, 25 °C to reflux, 2.5 h) proceeded smoothly to afford the homopropargylic alcohol **8** in excellent yield (82% over two steps from enol ether **5**) without detection of the isomeric allene or competitive reactions derived from enolization of the reactive starting aldehyde that were observed with the Grignard reagent itself. The key transformation for the preparation of the tricyclic ketone skeleton was realized with use of the intramolecular Pd(0)-catalyzed Larock

indole annulation of **8**, possessing the pendant alkyne and forming the desired tricyclic indole **9** in excellent yield (90%).

Our introduction and subsequent investigation<sup>10</sup> of the catalytic indole cyclization indicated that substrates including **8** were inert towards many candidate palladium catalysts including PdCl<sub>2</sub>, PdCl<sub>2</sub>(PhCN)<sub>2</sub> or PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, whereas other readily accessible catalysts including PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> supported the cyclization reaction. However, significantly improved results were observed with a Pd<sub>2</sub>(dba)<sub>3</sub> catalyst system that was first found to be remarkably successful in a challenging Suzuki coupling reaction in our vancomycin synthetic studies, arising from its unusually rapid oxidative addition to a hindered, electron-rich aryl bromide.<sup>19</sup> Optimization of this catalyst system revealed that DtBPF was the best added ligand of those examined, that DMF was the most effective solvent examined although others were effective, and that soluble organic bases such as Et<sub>3</sub>N were found to be superior to insoluble bases like K<sub>2</sub>CO<sub>3</sub><sup>10</sup>. With the use of 15 mol % of the catalyst and with the DtBPF ligand in DMF at 130 °C for 3 h, the reaction provided the indole **9** in yields as high as 90% now on scales ranging from 0.5–1 g. Despite the expectedly slow oxidative addition with substrates like **8** bearing a hindered, electron-rich *ortho* disubstituted aryl bromide, they are effective participants in the cyclization reaction under these conditions. Presumably, this may be attributed to a combination of the unique Pd<sub>2</sub>(dba)<sub>3</sub> derived catalyst reactivity<sup>19</sup> and potentially its coordination to the proximal polar amide of the substrate.

At this stage, oxidation of the secondary alcohol to the corresponding ketone was examined. However, all efforts were ineffective under a variety of oxidation conditions. Although clean oxidation product could be detected (TLC and LCMS), all efforts resulted in competitive benzylic oxidation, naphthalene aromatization, or potential decomposition upon SiO<sub>2</sub> purification. Thus, the reduced indoline precursor was prepared, which provided two advantages over the candidate indole precursor. In addition to preventing the competitive over-oxidation, the subsequent requisite enamine now could be generated regioselectively by virtue of the single stabilizing aryl conjugation. Thus, removal of the trimethylsilyl group in **9** (Bu<sub>4</sub>NF, THF) followed by methanolysis of the resulting crude *N*-acetate (K<sub>2</sub>CO<sub>3</sub>, MeOH) provided **10** (91%). After exploration of several reduction conditions, treatment of **10** with bis(trifluoroacetoxy)borane<sup>20</sup> generated in situ from BH<sub>3</sub>·THF in trifluoroacetic acid proved to be highly effective and afforded the corresponding indoline, which was protected as the benzoyl amide **11** (87% over two steps). Other reduction methods were also successful (Et<sub>3</sub>SiH, TFA/CH<sub>2</sub>Cl<sub>2</sub>, 69%; H<sub>2</sub>, PtO<sub>2</sub>, TFA/H<sub>2</sub>O; BH<sub>3</sub>·Py, TFA) but initially afforded **11** in lower conversions. Subsequent oxidation of the alcohol by PCC<sup>21</sup> now uneventfully provided the requisite tricyclic ketone **12** in 80% yield.

With the requisite tricyclic ketone **12** in hand, its use in a key inverse electron demand Diels–Alder reaction with 5-carbomethoxy-1,2,3-triazine<sup>13a</sup> (**14**, ALD00106)<sup>22</sup> was explored (Scheme 2). The enamine **13** was prepared by treatment of ketone **12** with pyrrolidine (4 Å MS, CHCl<sub>3</sub>, 25 °C, 8 h) and its Diels–Alder reaction with the 1,2,3-triazine **14** (4 equiv, 0.1 M CHCl<sub>3</sub>, 25 °C, 3 h)<sup>23</sup> proceeded rapidly to provide the pyridine cycloaddition product **15** (75% from ketone **12**) as a single regioisomer without detection of the intermediates even when conducted at room temperature. The inclusion of 4 Å MS in the

reaction mixture or use of higher reaction concentrations (0.3 M) or temperatures (65 °C) even with prolonged reaction times (15 h) did not further improve the already excellent cycloaddition yield. The reaction of the 1,2,3-triazine **14** exhibited the now characteristic exclusive N1/C4 cycloaddition regioselectivity<sup>13</sup> with the nucleophilic carbon of the electron-rich enamine attached to C4, benefiting from the complementary azadiene substitution (C5-CO<sub>2</sub>Me). Importantly, the remarkable reactivity of **14** imparted by the C5 electron-withdrawing substituent provides substantially improved cycloaddition reactivity toward enamine dienophiles such that the reaction with **13** occurred at 25 °C, representing a synthetic scope not observed with 1,2,3-triazine itself.

The dihydro analogues of lysergic acid comprise an important class of central nervous system drugs that includes pergolide mesylate, which is produced commercially through the hydrogenation of lysergic acid. Although the potential reduction of pyridine precursors to the ergot alkaloid D-ring has always been an attractive strategy, only one successful implementation has been reported<sup>6b</sup> and was conducted with a precursor lacking the intact ABCD-ring system. In a large measure, this may be attributed to a problematic pyridine reduction with substrates bearing the core indole, which suffers from a facile tautomerization to a core naphthalene. Our approach enlists a core indoline incapable of this competitive reaction and we first examined the use of **15** targeting the fully reduced pyridine ring to afford saturated derivatives of lysergic acid (Scheme 3).

To this end, pyridine **15** was *N*-methylated by treatment with MeI (80 °C, 10 h), providing the pyridinium salt **16** quantitatively. In turn, this crude salt was exposed to a variety of reduction conditions. After exploration of several methods, a stepwise reduction (NaCNBH<sub>3</sub>, MeOH, 65 °C, 18 h; then NaCNBH<sub>3</sub>, HOAc, 25 °C, 1 h) proved to be highly effective and directly produced near exclusively a single diastereomer **17** (58%, >10:1), whose structure and relative stereochemistry were established by a single-crystal X-ray structure determination.<sup>24</sup> The trans CD ring fusion (C5/C10), the thermodynamically more stable equatorial disposition of the C8 methyl ester, and the relative C3/C5 trans stereochemistry that places all substituents on the central C-ring in an equatorial disposition, collectively represent the thermodynamically most stable relative stereochemistry among all stereocenters. It is remarkable that essentially a single diastereomer emerged from the stepwise reduction and only a trace of a minor diastereomer(s) was detected (ca. 5%) that likely represents predominately the C8 diastereomer. These remarkable results sharply contrast prior efforts where reduction of such pyridyl precursors with the imbedded indole intact proved unmanageable<sup>25</sup> or were erroneously reported.<sup>26</sup> Removal of the *N*-benzoyl amide was found to occur under conditions that promote concomitant oxidation of the indoline to the corresponding indole. This was optimized such that treatment of **17** with HCl in MeOH (0.5 M, 95 °C, 72 h) provided **18** (55%) directly in a single step and subsequent hydrolysis of the methyl ester (1 N NaOH/MeOH, 40 °C, 3 h) afforded dihydrolysergic acid (**1**), whose spectroscopic properties perfectly matched those of authentic synthetic material.<sup>27</sup> The same intermediate **18** was also used to access dihydrolysergol (**2**) where ester reduction (LiAlH<sub>4</sub>, THF, 0 °C, 30 min, 92%) afforded dihydrolysergol (**2**), whose properties proved identical in all respects with those of an authentic sample of the natural product.<sup>28,29</sup>

A key element of the approach was the use of the enamine **13** derived from ketone **12** in a cycloaddition reaction with a heterocyclic azadiene for installation of a D-ring pyridine. This strategy deliberately permits additional cycloaddition reactions of the advanced electron-rich dienophile **13** with other reactive heterocyclic azadienes (**19–24**) for the late-stage, divergent preparation of a series of complementary heterocyclic derivatives (Scheme 4).

Representative of this and without individual optimization, this included the reaction of 1,2,3-triazine<sup>13d</sup> (**19**, ALD00112),<sup>22</sup> 5-bromo-1,2,3-triazine (**20**),<sup>13a</sup> 4-carbomethoxy-1,2,3-triazine<sup>13b</sup> (**21**, ALD00104),<sup>22</sup> and 4,6-dicarboethoxy-1,2,3-triazine<sup>13b</sup> (**22**, ALD00110),<sup>22</sup> each of which displayed the 1,2,3-triazine C4/N1 mode of cycloaddition and provided the alternatively substituted pyridines **25–28**, 1,3,5-triazine<sup>30</sup> (**23**)<sup>22</sup> that provided the pyrimidine **29**, and 3,6-dicarbomethoxy-1,2,4,5-tetrazine<sup>31</sup> (**24**, ALD00098)<sup>22</sup> that provided the substituted pyridazine **30** and served further as a precursor to the pyrrole **31** via a unique zinc-mediated reductive ring contraction.<sup>32</sup> It is of note that it was the exploration of the ergot alkaloids at Lilly and the preparation of their simplified ring systems that provided the first synthetic use of such heterocyclic azadiene Diels–Alder reactions (use of **30**) and the first report of the effective zinc-mediated pyridazine to pyrrole reductive ring contraction reaction.<sup>33</sup>

### 3. Conclusions

Herein, effective total syntheses of dihydrolysergic acid (**1**) and dihydrolysergol (**2**) are disclosed. The approach employed an inverse electron demand Diels–Alder reaction of the tricyclic ketone **12** derived enamine **13** with 5-carbomethoxy-1,2,3-triazine (**14**) for the late-stage preparation of the tetracyclic framework of the ergot alkaloid core structure. Key to the preparation of the tricyclic ketone **12** was our recently disclosed intramolecular Pd(0)-catalyzed Larock indole annulation of a *N*-acetyl 2-bromoaniline derivative substituted with a pendant alkyne to assemble the tricyclic fused indole found in ergot alkaloids. This strategy deliberately permits the late-stage cycloaddition reaction of the electron-rich dienophile **13** with additional reactive heterocyclic azadienes for the divergent preparation of a series of complementary heterocyclic D-ring derivatives not as readily accessible by more conventional approaches, including alternatively substituted pyridines, pyrimidines, pyridazines and pyrroles.

### 4. Experimental<sup>34</sup>

#### 4.1. (3-Acetylamino-2-bromophenyl)methanol

A stirred solution of **3**<sup>16</sup> (1.81 g, 9.00 mmol) in THF (90 mL) was treated with pyridine (4.4 mL, 54.0 mmol) and acetic anhydride (3.4 mL, 36.0 mmol) at 25 °C. After stirring for 12 h at the same temperature, the resulting mixture was concentrated under reduced pressure. The mixture was dissolved in MeOH (90 mL) and was treated with potassium carbonate (1.87 g, 13.5 mmol). After stirring for 3 h at 25 °C, the resulting mixture was quenched with the addition of H<sub>2</sub>O and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO<sub>2</sub>, 70% EtOAc–hexanes) to provide the

title compound (1.82 g, 83%) as a white solid:  $^1\text{H}$  NMR (600 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  8.50 (br s, 1H), 7.93 (d,  $J = 8.0$  Hz, 1H), 7.39 (d,  $J = 8.0$  Hz, 1H), 7.35 (t,  $J = 7.8$  Hz, 1H), 4.67 (d,  $J = 6.0$  Hz, 2H), 4.50 (t,  $J = 6.0$  Hz, 1H), 2.18 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  169.0, 142.8, 137.3, 128.1, 124.4, 123.6, 115.3, 64.8, 24.1; IR (film)  $\nu_{\text{max}}$  3278, 1659, 1592, 1536, 1353, 1300, 1074, 1025, 722  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  243.9968 [(M+H) $^+$ ],  $\text{C}_9\text{H}_{10}\text{BrNO}_2$  requires 243.9968].

#### 4.2. *N*-(2-Bromo-3-formylphenyl)acetamide (4)

A solution of *N*-acetyl 2-bromo-3-hydroxymethylaniline (1.76 g, 7.24 mmol) in THF (70 mL) was treated with  $\text{MnO}_2$  (3.15 g, 36.2 mmol) in a portion at 25 °C. The reaction mixture was stirred for 1 h, followed by another two additions of  $\text{MnO}_2$  (3.15 g, 36.2 mmol) every 1 h. After stirring for an additional 6 h at room temperature, the resulting mixture was filtered through a pad of Celite and concentrated in vacuo to provide crude **4** as a white solid:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  10.29 (s, 1H), 8.44 (d,  $J = 8.2$  Hz, 1H), 7.86 (br s, 1H), 7.60 (d,  $J = 7.6$  Hz, 1H), 7.37 (t,  $J = 7.9$  Hz, 1H), 2.25 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  191.2, 168.4, 136.4, 133.6, 128.1, 127.8, 125.6, 117.9, 24.6; IR (film)  $\nu_{\text{max}}$  3253, 2924, 1661, 1521, 1371, 1234, 1024, 792  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  241.9812 [(M+H) $^+$ ],  $\text{C}_9\text{H}_8\text{BrNO}_2$  requires 241.9811]. In initial studies, but on smaller scales (0.94 mmol), the purification of the product provided aldehyde **4** (135 mg) in 92% yield.

#### 4.3. (*E*)-*N*-(2-Bromo-3-(2-methoxyvinyl)phenyl)acetamide (5)

A cooled ( $-78$  °C) solution of (methoxymethyl)triphenylphosphonium chloride (7.45 g, 21.7 mmol) in anhydrous THF (100 mL) was treated with a solution of potassium *tert*-butoxide (18.1 mL, 1.0 M in THF, 18.1 mmol) and the mixture was warmed to 0 °C. The bright red solution was stirred for 10 min and a solution of aldehyde **4** in THF (45 mL) was added dropwise by syringe. The reaction mixture was allowed to warm to 25 °C and stirred for 30 min before the resulting mixture was quenched with the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  and diluted with EtOAc and  $\text{H}_2\text{O}$ . The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by flash chromatography ( $\text{SiO}_2$ , 50% EtOAc–hexanes) and provided **5** (1.38 g, 71% over two steps) as a mixture of *E/Z* (1.4:1) isomers. For major *E* isomer:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (t,  $J = 8.9$  Hz, 1H), 7.79 (s, 1H), 7.11 (t,  $J = 7.9$  Hz, 1H), 7.02 (d,  $J = 7.7$  Hz, 1H), 6.89 (d,  $J = 12.8$  Hz, 1H), 6.00 (d,  $J = 12.8$  Hz, 1H), 3.66 (s, 3H), 2.15 (s, 3H). For minor *Z* isomer:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (t,  $J = 8.9$  Hz, 1H), 7.79 (s, 1H), 7.73 (d,  $J = 7.9$  Hz, 1H), 7.16 (t,  $J = 8.0$  Hz, 1H), 6.19 (d,  $J = 7.2$  Hz, 1H), 5.50 (d,  $J = 7.2$  Hz, 1H), 3.70 (s, 3H), 2.15 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , a mixture of *E/Z* isomers)  $\delta$  168.13, 168.08, 150.6, 149.3, 136.7, 135.8, 135.4, 135.3, 127.4, 126.9, 125.8, 121.2, 119.8, 119.6, 114.6, 114.3, 104.5, 103.7, 60.6, 56.4, 24.4; IR (film)  $\nu_{\text{max}}$  3274, 2931, 2863, 1646, 1521, 1210, 1101, 668  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  270.0123 [(M+H) $^+$ ],  $\text{C}_{11}\text{H}_{12}\text{BrNO}$  requires 270.0124].

#### 4.4. *N*-(2-Bromo-3-(2-hydroxy-5-(trimethylsilyl)pent-4-yn-1-yl)phenyl)acetamide (8)

**[Hydrolysis]** A cooled (0 °C) solution of **5** (1.79 g, 6.65 mmol) in acetone (50 mL) was treated dropwise with 6 N HCl (50 mL). After stirring for 30 min at 0 °C, the reaction

mixture was warmed to 25 °C and stirred for an additional 1 h. The resulting mixture was quenched with the addition of saturated aqueous NaHCO<sub>3</sub> and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and azeotroped with toluene to afford the crude **6** as a white solid, which was employed in the next step without further purification: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 9.74 (s, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 3.89 (s, 2H), 2.26 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 198.0, 168.5, 136.5, 133.3, 128.3, 127.2, 121.8, 116.5, 51.3, 24.8; IR (film)  $\nu_{\max}$  3274, 2934, 1719, 1657, 1533, 1323, 1299, 1101, 1026, 665 cm<sup>-1</sup>; HRMS (ESI) *m/z* 255.9967 [(M+H)<sup>+</sup>, C<sub>10</sub>H<sub>10</sub>BrNO<sub>2</sub> requires 255.9968]. **[Indium Grignard Addition]** A two neck flask charged with indium powder (2.29 g, 19.96 mmol) in THF (60 mL) was treated with (3-bromoprop-1-ynyl)trimethylsilane (2.2 mL, 13.31 mmol) at 25 °C. After stirring for 15 min, the mixture was subsequently treated dropwise with a solution of the above aldehyde **6** in THF (60 mL). The reaction mixture was allowed to stir for 2.5 h at reflux before the resulting mixture was cooled to room temperature. The resulting mixture was filtered through a pad of Celite and diluted with EtOAc and H<sub>2</sub>O. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO<sub>2</sub>, gradient elution: 30–50% EtOAc–hexanes) and provided **8** (2.00 g, 82% for 2 steps) as a white solid: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.71 (s, 1H), 7.19–7.34 (m, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 1H), 3.12 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.96 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.52 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.45 (dd, *J* = 16.8, 6.1 Hz, 1H), 2.24 (s, 3H), 0.17 (s, 9H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 168.2, 138.1, 136.0, 127.8, 127.0, 120.6, 116.2, 102.5, 88.3, 69.1, 43.3, 28.3, 24.9, 0.0; IR (film)  $\nu_{\max}$  3398, 2957, 1670, 1521, 1404, 1247, 1022, 839, 733 cm<sup>-1</sup>; HRMS (ESI) *m/z* 368.0677 [(M+H)<sup>+</sup>, C<sub>16</sub>H<sub>22</sub>BrNO<sub>2</sub> Si requires 368.0676].

#### 4.5. 1-(4-Hydroxy-2-(trimethylsilyl)-4,5-dihydrobenzo[*cd*]indol-1(3*H*)-yl)ethan-1-one (**9**)

A solution of **8** (778 mg, 2.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (291 mg, 0.318 mmol) and D*t*BPF (301 mg, 0.636 mmol) in DMF (106 mL, 0.02 M) in a sealed vessel was degassed with argon for 20 min. This solution was treated with triethylamine (1.5 mL, 10.6 mmol) and the reaction mixture was allowed to stir at 130 °C for 3 h. The resulting mixture was cooled to room temperature, filtered through a short pad of silica gel and diluted with Et<sub>2</sub>O. Excess DMF was removed by washing with H<sub>2</sub>O and extracting with Et<sub>2</sub>O. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was purified by column chromatography (SiO<sub>2</sub>, gradient elution: 25–40% EtOAc–hexanes) to afford **9** (548 mg, 90%) as a light tan oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 7.6 Hz, 1H), 3.22 (dd, *J* = 16.0, 3.9 Hz, 1H), 3.14 (d, *J* = 14.9 Hz, 1H), 3.00 (d, *J* = 7.4 Hz, 1H), 2.97 (d, *J* = 7.9 Hz, 1H), 2.77 (s, 3H), 2.07 (d, *J* = 4.9 Hz, 1H), 0.36 (s, 9H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 169.1, 135.7, 135.0, 130.4, 129.7, 128.4, 125.8, 121.2, 111.8, 67.8, 35.9, 33.3, 26.0, 2.3; IR (film)  $\nu_{\max}$  3366, 2897, 1689, 1609, 1376, 1326, 1243, 839, 730 cm<sup>-1</sup>; HRMS (ESI) *m/z* 288.1413 [(M+H)<sup>+</sup>, C<sub>16</sub>H<sub>21</sub>NO<sub>2</sub>Si requires 288.1414].

#### 4.6. 1,3,4,5-Tetrahydrobenzo[*cd*]indol-4-ol (**10**)

**[Desilylation]** A cooled (0 °C) solution of **9** (435 mg, 1.52 mmol) in THF (15.2 mL, 0.1 M) was treated with Bu<sub>4</sub>NF (4.55 mL, 1.0 M in THF, 4.55 mmol). After stirring for 2 h at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NH<sub>4</sub>Cl and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude indole was taken to next step without further purification. **[Methanolysis]** The crude product was dissolved in MeOH (7.6 mL) and was treated with K<sub>2</sub>CO<sub>3</sub> (628 mg, 4.54 mmol). After stirring for 2 h at 25 °C, the resulting mixture was quenched with the addition of H<sub>2</sub>O and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO<sub>2</sub>, 70% EtOAc–hexanes) to provide **10** (241 mg, 91%) as a viscous light tan oil: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.02 (s, 1H), 7.10–7.22 (m, 2H), 6.90 (dd, *J* = 5.2, 2.4 Hz, 1H), 6.87–6.89 (m, 1H), 4.48 (tt, *J* = 7.1, 3.8 Hz, 1H), 3.21 (dd, *J* = 15.8, 3.7 Hz, 1H), 3.15 (dd, *J* = 15.1, 3.9 Hz, 1H), 3.07 (dd, *J* = 15.7, 6.9 Hz, 1H), 2.96 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.08 (d, *J* = 7.9 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 133.5, 128.2, 126.3, 123.2, 118.9, 117.0, 110.3, 108.6, 68.2, 36.3, 31.0; IR (film) ν<sub>max</sub> 3388, 2923, 1605, 1442, 1338, 1034, 907, 728 cm<sup>-1</sup>; HRMS (ESI) *m/z* 174.0913 [(M+H)<sup>+</sup>, C<sub>11</sub>H<sub>11</sub>NO requires 174.0913].

#### 4.7. (4-Hydroxy-2a,3,4,5-tetrahydrobenzo[*cd*]indol-1(2*H*)-yl)(phenyl)methanone (**11**)

**[Reduction of Indole]** A cooled (0 °C) solution of **10** (302 mg, 1.75 mmol) in THF and TFA (8 mL/8 mL) was treated dropwise with borane-tetrahydrofuran complex (3.5 mL, 1.0 M in THF, 3.50 mmol). The reaction mixture was allowed to stir for 10 min at 0 °C at which time an additional portion of borane-tetrahydrofuran complex (3.5 mL, 1.0 M in THF, 3.50 mmol) was added dropwise. After stirring for an additional 30 min at the same temperature, the mixture was quenched with the addition of MeOH and H<sub>2</sub>O. The resulting mixture was neutralized by addition of 1 N NaOH and diluted with EtOAc (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash chromatography (SiO<sub>2</sub>, 70% EtOAc–hexanes) to provide indoline as a colorless oil. **[Benzoylation]** A cooled (0 °C) solution of the indoline (300 mg, 1.71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was treated with Et<sub>3</sub>N (716 μL, 5.14 mmol) followed by dropwise addition of benzoyl chloride (289 μL, 2.056 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). After stirring for 30 min at 25 °C, the resulting mixture was quenched with the addition of saturated aqueous NaHCO<sub>3</sub> and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO<sub>2</sub>, 70% EtOAc–hexanes) to provide a diastereomeric mixture of **11** (423 mg, 87% for 2 steps). For less polar **11a**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 7.57 (d, *J* = 7.3 Hz, 2H), 7.38–7.52 (m, 3H), 6.99 (br s, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 4.47 (s, 1H), 4.36 (br s, 1H), 3.52–3.70 (m, 2H), 2.97 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.85 (d, *J* = 18.0 Hz, 1H), 2.21–2.31 (m, 1H), 2.15 (br s, 1H), 1.48 (t, *J* =



11.6 Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  168.7, 141.3, 136.6, 132.9, 131.8, 130.5, 128.5, 127.7, 127.4, 123.4, 113.7, 65.8, 58.4, 34.9, 33.5, 31.0; IR (film)  $\nu_{\text{max}}$  3374, 2919, 1625, 1455, 1391, 1228, 770  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  280.1333 [(M+H) $^+$ ,  $\text{C}_{18}\text{H}_{17}\text{NO}_2$  requires 280.1332]. For polar **11b**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  7.58 (d,  $J = 7.4$  Hz, 2H), 7.40–7.53 (m, 3H), 7.02 (br s, 1H), 6.80 (d,  $J = 7.5$  Hz, 1H), 4.34 (br s, 1H), 4.23 (dq,  $J = 10.1, 5.7, 4.3$  Hz, 1H), 3.68 (t,  $J = 11.1$  Hz, 1H), 3.36 (dq,  $J = 18.0, 11.5, 8.2$  Hz, 1H), 3.24 (dd,  $J = 16.7, 6.5$  Hz, 1H), 2.63 (dd,  $J = 16.7, 9.6$  Hz, 1H), 2.29–2.42 (m, 1H), 1.85 (br s, 1H), 1.52 (q,  $J = 11.3$  Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  168.7, 141.4, 136.6, 132.7, 132.3, 130.6, 128.6, 128.1, 127.5, 123.1, 114.0, 68.6, 58.1, 36.7, 36.3, 36.2; IR (film)  $\nu_{\text{max}}$  3305, 2922, 1626, 1455, 1395, 770, 668  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  280.1333 [(M+H) $^+$ ,  $\text{C}_{18}\text{H}_{17}\text{NO}_2$  requires 280.1332]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **11** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.8. 1-Benzoyl-1,2,2a,5-tetrahydrobenzo[*cd*]indol-4(3*H*)-one (**12**)

A cooled (0 °C) solution of **11** (650 mg, 2.33 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL, 0.12 M) was treated with PCC (2.51 g, 11.64 mmol, 5 equiv) and the mixture was warmed to 25 °C. After stirring for 2 h at the same temperature, the resulting mixture was diluted with  $\text{Et}_2\text{O}$  (100 mL) and stirred for 30 min. The solid residue was filtered through a pad of Celite and washed with  $\text{Et}_2\text{O}$ . The crude residue was concentrated under reduced pressure and the residue was purified by flash chromatography ( $\text{SiO}_2$ , gradient elution: 30–50%  $\text{EtOAc}$ –hexanes) to provide **12** (517 mg, 80%) as a yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  7.58 (d,  $J = 7.5$  Hz, 2H), 7.43–7.53 (m, 3H), 7.10 (s, 1H), 6.84 (d,  $J = 7.7$  Hz, 1H), 4.49 (s, 1H), 3.78 (q,  $J = 11.0$  Hz, 2H), 3.54 (s, 3H), 2.94 (d,  $J = 15.9$ , 1H), 2.22–2.40 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  207.5, 168.8, 141.3, 136.4, 131.8, 130.9, 130.7, 129.0, 128.7, 127.4, 122.6, 114.8, 58.1, 43.8, 42.0, 34.9; IR (film)  $\nu_{\text{max}}$  3365, 2922, 1717, 1600, 1459, 1241, 743, 670  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  278.1174 [(M+H) $^+$ ,  $\text{C}_{18}\text{H}_{15}\text{NO}_2$  requires 278.1175]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **12** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

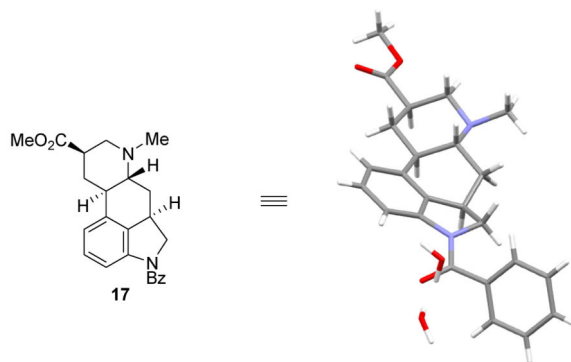
#### 4.9. Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**15**)

**[Enamine Formation]** A solution of **12** (90.2 mg, 0.325 mmol) and 4Å molecular sieves (~450 mg) in  $\text{CHCl}_3$  (3.3 mL, 0.1 M, passed through basic alumina) was treated dropwise with pyrrolidine (152  $\mu\text{L}$ , 1.63 mmol) at 25 °C. After stirring for 8 h at room temperature, the mixture was filtered through a pad of Celite (10%  $\text{MeOH}$ – $\text{CH}_2\text{Cl}_2$  + 1%  $\text{Et}_3\text{N}$ ) and the solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. **[Inverse Electron Demand Diels–Alder Reaction]** A solution of the enamine **13** in  $\text{CHCl}_3$  (2.5 mL, passed through basic alumina) was treated dropwise with 5-carbomethoxy-1,2,3-triazine (**14**, 90.5 mg, 0.651 mmol) in  $\text{CHCl}_3$  (0.8 mL) during which smooth evolution of gas took place. The reaction mixture was stirred for 1 h, followed by another addition of 5-carbomethoxy-1,2,3-triazine (**14**, 90.5 mg, 0.651 mmol) in  $\text{CHCl}_3$  (0.8 mL). After stirring for additional 2 h at 25 °C, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography ( $\text{SiO}_2$ , 5%  $\text{MeOH}$ – $\text{CH}_2\text{Cl}_2$ ) to provide **15** (90.2 mg, 75%) as a dark red solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  9.03 (d,  $J = 2.0$  Hz, 1H), 8.58 (d,  $J = 2.0$  Hz, 1H), 7.61 (d,  $J = 7.1$  Hz, 2H), 7.45–7.54

(m, 3H), 7.41 (d,  $J = 7.7$  Hz, 1H), 7.24 (s, 1H), 4.53 (s, 1H), 3.99 (s, 3H), 3.92 (t,  $J = 10.7$  Hz, 1H), 3.72–3.86 (m, 1H), 3.46 (dd,  $J = 15.7, 6.3$  Hz, 1H), 3.01 (t,  $J = 15.1$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  168.7, 165.5, 160.8, 149.0, 141.7, 136.3, 132.2, 131.0, 130.6, 129.4, 129.2, 128.6, 128.5, 127.2, 125.1, 117.9, 58.5, 52.2, 37.0, 34.7; IR (film)  $\nu_{\text{max}}$  3309, 1646, 1428, 1257, 668  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  371.1391 [(M+H)<sup>+</sup>,  $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$  requires 371.1390]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **15** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.10. Methyl (5aR,6aR,9R,10aR)-4-Benzoyl-7-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[4,3-fg]quinoline-9-carboxylate (**17**)

**[Formation of Pyridinium Salt]** A sealed tube charged with **15** (90.0 mg, 0.243 mmol) in MeI (2.4 mL, 0.1 M) was warmed to 80 °C and stirred for 10 h, at which point complete conversion of the starting material to the pyridinium salt had been achieved as monitored by LCMS. The brown mixture was cooled to room temperature and concentrated in vacuo to provide crude **16**. **[Reduction of Pyridinium Salt]** A solution of **16** in anhydrous MeOH (8.1 mL, 0.03 M) was treated with  $\text{NaCNBH}_3$  (153 mg, 2.43 mmol) at 25 °C under Ar. The reaction mixture was warmed to 65 °C and stirred for 18 h before it was cooled to 0 °C and quenched with the addition of saturated aqueous  $\text{NaHCO}_3$ . The organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by passage through a short pad of silica gel to provide a mixture of partial and full reduction products and concentrated under reduced pressure. A solution of the mixture of reduction products in acetic acid (8.1 mL, 0.03 M) was treated with  $\text{NaCNBH}_3$  (153 mg, 2.43 mmol) at 25 °C under Ar. The reaction mixture was allowed to stir for 1 h at 25 °C before being cooled to 0 °C. The resulting mixture was quenched with the addition of saturated aqueous  $\text{NaHCO}_3$  and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were further washed with 1 N NaOH, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography ( $\text{Et}_3\text{N}$  pre-treated  $\text{SiO}_2$ , 3% MeOH– $\text{CH}_2\text{Cl}_2$  eluted 3 $\times$ ) to provide **17** (55.3 mg, 58%) and an inseparable mixture of minor reduction products (4.6 mg, 5%): For **17**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  7.55 (d,  $J = 7.4$  Hz, 2H), 7.41–7.50 (m, 3H), 7.09 (br s, 1H), 6.88 (d,  $J = 7.5$  Hz, 1H), 4.48 (s, 1H), 3.73 (s, 3H), 3.68 (t,  $J = 10.8$  Hz, 1H), 3.48 (qd,  $J = 10.2, 6.1$  Hz, 1H), 3.17 (dd,  $J = 11.6, 3.6$  Hz, 1H), 2.85 (tt,  $J = 12.0, 3.7$  Hz, 1H), 2.74 (d,  $J = 13.0$  Hz, 1H), 2.45–2.56 (m, 1H), 2.30 (s, 3H), 2.18 (t,  $J = 11.6$  Hz, 1H), 2.05–2.15 (m, 1H), 1.86 (dt,  $J = 13.8, 7.1$  Hz, 1H), 1.74 (q,  $J = 8.8$  Hz, 1H), 1.59 (q,  $J = 12.5$  Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  174.0, 168.8, 140.5, 137.6, 136.8, 132.5, 130.4, 128.6, 127.8, 127.3, 118.6, 114.4, 65.5, 60.3, 58.5, 51.7, 43.2, 41.3, 38.6, 32.32, 32.31, 29.9; IR (film)  $\nu_{\text{max}}$  2924, 1731, 1635, 1456, 1388, 1254, 732  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  391.2017 [(M+H)<sup>+</sup>,  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3$  requires 391.2016]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **17** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>



The structure and relative stereochemistry of **17** were confirmed upon X-ray (CCDC 1047936) analysis enlisting a colorless monoclinic plate crystal obtained from MeOH.

#### 4.11. Methyl (6a*R*,9*R*,10a*R*)-7-Methyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*fg*]quinoline-9-carboxylate (**18**)

A microwave sealed vessel charged with **17** (4.7 mg, 0.012 mmol) was treated with a solution of HCl (0.5 M in MeOH, 1 mL). The reaction mixture was warmed to 95 °C and stirred for 72 h. The resulting mixture was cooled to room temperature and basified with the addition of 1 N aqueous NaOH and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (Et<sub>3</sub>N pre-treated SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub> eluted 2×) to afford **18** (1.9 mg, 55%) as an off-white solid: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.96 (s, 1H), 7.15–7.21 (m, 2H), 6.96 (d, *J* = 6.6 Hz, 1H), 6.89 (s, 1H), 3.41 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.26 (dt, *J* = 11.5, 2.9 Hz, 1H), 2.92–3.01 (m, 3H), 2.69 (dd, *J* = 14.6, 11.2 Hz, 1H), 2.51 (s, 3H), 2.36 (t, *J* = 11.7 Hz, 1H), 2.16–2.24 (m, 1H), 1.60 (q, *J* = 13.2 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 174.3, 133.3, 132.5, 126.1, 123.1, 117.8, 113.3, 111.6, 108.7, 66.7, 58.5, 51.8, 42.9, 41.3, 40.0, 30.5, 26.8, 8.9; IR (film) ν<sub>max</sub> 3360, 2922, 2851, 1731, 1456, 749 cm<sup>-1</sup>; HRMS (ESI) *m/z* 285.1597 [(M+H)<sup>+</sup>, C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> requires 285.1597].

#### 4.12. Dihydrolysergic Acid (**1**)

A solution of **18** (2.6 mg, 9.1 μmol) in MeOH (600 μL) was treated with 1 N NaOH (600 μL). After stirring for 3 h at 40 °C, 1 N HCl was added to the mixture to carefully adjust the pH to 6. The resulting mixture was concentrated in vacuo. The residue was washed with ice cold water three times and the resulting solid was dried in vacuo to afford dihydrolysergic acid (**1**, 2.2 mg, 89%) as an off-white solid identical in all respects with authentic material previously reported<sup>27</sup>: <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 10.63 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.97 (br s, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 3.29 (d, *J* = 14.7 Hz, 1H), 3.11 (d, *J* = 11.3 Hz, 1H), 2.70–2.85 (m, 3H), 2.50–2.56 (m, 1H), 2.37 (s, 3H), 2.16 (t, *J* = 11.5 Hz, 1H), 2.00 (t, *J* = 11.1 Hz, 1H), 1.34 (q, *J* = 13.0 Hz, 1H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 175.0, 133.1, 132.3, 125.9, 122.1, 118.5, 112.0, 110.0, 108.7, 66.6, 58.6, 42.6, 40.9, 30.5, 26.5; IR (film) ν<sub>max</sub> 3192, 2919, 2851, 1611, 1573, 1259, 1094, 779 cm<sup>-1</sup>; HRMS (ESI) *m/z* 271.1440 [(M+H)<sup>+</sup>, C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 271.1441].

#### 4.13. Dihydrolysergol (2)

A cooled (0 °C) solution of **18** (3.2 mg, 11.3 μmol) in anhydrous THF (0.2 mL, 0.056 M) was treated dropwise with a solution of LiAlH<sub>4</sub> (56 μL, 1.0 M in THF, 56.3 μmol). After stirring for 30 min at the same temperature, the resulting mixture was quenched with the addition of MeOH followed by saturated aqueous Rochelle's salt solution and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The resulting biphasic mixture was stirred for 3 h. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (Et<sub>3</sub>N pre-treated SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide dihydrolysergol (**2**, 2.7 mg, 92%) as a white solid identical in all respects with data reported for authentic material and with a sample of authentic material<sup>28,29</sup>: <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD) δ 7.12 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.83 (d, *J* = 7.1 Hz, 1H), 3.58 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.48 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.43 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.14 (dt, *J* = 11.4, 2.8 Hz, 1H), 2.91 (ddd, *J* = 12.8, 9.9, 3.9 Hz, 1H), 2.48 (s, 3H), 2.07–2.15 (m, 2H), 2.00 (t, *J* = 11.5 Hz, 1H), 1.10 (q, *J* = 12.4 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>OD) δ 135.1, 133.6, 127.4, 123.5, 119.2, 113.4, 111.4, 109.7, 69.1, 66.4, 61.8, 43.6, 41.4, 39.5, 32.0, 27.7; IR (film) ν<sub>max</sub> 3228, 2920, 2849, 1443, 1348, 1226, 1028, 745, 668 cm<sup>-1</sup>; HRMS (ESI) *m/z* 257.1649 [(M+H)<sup>+</sup>, C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O requires 257.1648].

#### 4.14. Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-fg]quinoline-9-carboxylate (25)

A solution of **12** (7.0 mg, 0.025 mmol) and 4Å molecular sieves (35 mg) in CHCl<sub>3</sub> (0.51 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (10 μL, 0.13 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and the solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine **13** in CHCl<sub>3</sub> (0.1 mL, passed through basic alumina) was treated dropwise with 1,2,3-triazine (**19**, 4.1 mg, 0.12 mmol) in CHCl<sub>3</sub> (0.15 mL). The reaction mixture was stirred for 14 h at 60 °C before the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **25** (1.4 mg, 18%) as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 8.45 (d, *J* = 4.9 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.44–7.55 (m, 3H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.13–7.30 (m, 2H), 4.52 (br s, 1H), 3.91 (t, *J* = 10.7 Hz, 1H), 3.73–3.85 (m, 1H), 3.38 (dd, *J* = 15.2, 6.2 Hz, 1H), 2.98 (t, *J* = 14.8 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 50 °C) δ 168.9, 156.6, 148.3, 141.7, 136.6, 132.4, 130.7, 130.5, 129.1, 128.9, 128.7, 127.4, 122.5, 117.8, 116.4, 58.7, 37.1, 35.1; IR (film) ν<sub>max</sub> 3360, 2921, 2851, 1638, 1470, 1413, 1384, 1085, 779, 698 cm<sup>-1</sup>; HRMS (ESI) *m/z* 313.1336 [(M+H)<sup>+</sup>, C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O requires 313.1335]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **25** in CDCl<sub>3</sub> at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.15. (9-Bromo-5a,6-dihydroindolo[4,3-fg]quinolin-4(5H)-yl)(phenyl)methanone (26)

A solution of **12** (16.9 mg, 0.0609 mmol) and 4Å molecular sieves (85 mg) in CHCl<sub>3</sub> (1.2 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (22 μL, 0.30 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and the solvent was removed

under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine **13** in CHCl<sub>3</sub> (0.31 mL, passed through basic alumina) was treated dropwise with 5-bromo-1,2,3-triazine (**20**, 19.4 mg, 0.122 mmol) in CHCl<sub>3</sub> (0.3 mL). The reaction mixture was stirred for 48 h at 25 °C before the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **26** (3.1 mg, 13%) as a light tan solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 8.50 (d, *J* = 2.2 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.44–7.55 (m, 3H), 7.10–7.36 (m, 2H), 4.51 (br s, 1H), 3.90 (t, *J* = 10.7 Hz, 1H), 3.70–3.84 (m, 1H), 3.35 (dd, *J* = 15.4, 6.3 Hz, 1H), 2.90 (t, *J* = 14.9 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 50 °C) δ 168.9, 155.0, 149.0, 141.9, 136.4, 133.0, 132.6, 130.7, 130.6, 129.3, 128.7, 127.4, 119.5, 117.9, 117.2, 58.6, 36.6, 35.0; IR (film)  $\nu_{\max}$  3345, 2923, 1642, 1419, 1384, 1077, 787, 667 cm<sup>-1</sup>; HRMS (ESI) *m/z* 391.0439 [(M+H)<sup>+</sup>, C<sub>21</sub>H<sub>15</sub>BrN<sub>2</sub>O requires 391.0440]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **26** in CDCl<sub>3</sub> at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.16. Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-fg]quinoline-8-carboxylate (**27**)

A solution of **12** (19.3 mg, 0.0696 mmol) and 4 Å molecular sieves (~100 mg) in CHCl<sub>3</sub> (1.4 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (29 μL, 0.35 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and the solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine **13** in CHCl<sub>3</sub> (0.4 mL, passed through basic alumina) was treated dropwise with 4-carbomethoxy-1,2,3-triazine (**21**, 19.4 mg, 0.139 mmol) in CHCl<sub>3</sub> (0.3 mL). The reaction mixture was warmed to 60 °C and stirred for 8 h before the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **27** (9.3 mg, 36%) as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 9.03 (d, *J* = 2.0 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.45–7.54 (m, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.24 (s, 1H), 4.53 (s, 1H), 3.99 (s, 3H), 3.92 (t, *J* = 10.7 Hz, 1H), 3.72–3.86 (m, 1H), 3.46 (dd, *J* = 15.7, 6.3 Hz, 1H), 3.01 (t, *J* = 15.1 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 50 °C) δ 168.7, 165.5, 160.8, 149.0, 141.7, 136.3, 132.2, 131.0, 130.6, 129.4, 129.2, 128.6, 128.5, 127.2, 125.1, 117.9, 58.5, 52.2, 37.0, 34.7; IR (film)  $\nu_{\max}$  3309, 1646, 1428, 1257, 668 cm<sup>-1</sup>; HRMS (ESI) *m/z* 371.1391 [(M+H)<sup>+</sup>, C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> requires 371.1390]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **27** in CDCl<sub>3</sub> at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.17. Diethyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-fg]quinoline-8,10-dicarboxylate (**28**)

A solution of **12** (18.1 mg, 0.0653 mmol) and 4 Å molecular sieves (~100 mg) in CHCl<sub>3</sub> (1.3 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (27 μL, 0.33 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine **13** in CHCl<sub>3</sub> (0.4 mL, passed through basic alumina) was treated dropwise with 4,6-dicarboethoxy-1,2,3-triazine (**22**, 29.4 mg, 0.139 mmol) in CHCl<sub>3</sub> (0.25 mL). The reaction mixture was warmed to 60 °C and stirred for 8 h before the solvent was removed

under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **28** (7.7 mg, 26%) as a light yellow solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 8.12 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.45–7.55 (m, 3H), 7.10–7.23 (m, 2H), 4.37–4.57 (m, 5H), 3.91 (t, *J* = 10.4 Hz, 1H), 3.73–3.85 (m, 1H), 3.58 (dd, *J* = 15.5, 5.9 Hz, 1H), 2.98 (t, *J* = 14.8 Hz, 1H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 50 °C) δ 168.9, 168.0, 164.4, 159.3, 146.4, 141.7, 138.0, 136.3, 134.8, 130.8, 129.5, 128.7, 128.4, 127.4, 123.2, 121.8, 117.8, 62.5, 62.1, 58.0, 38.2, 34.6, 14.3, 13.9; IR (film) ν<sub>max</sub> 2927, 1723, 1644, 1387, 1244, 1019, 732 cm<sup>-1</sup>; HRMS (ESI) *m/z* 457.1759 [(M+H)<sup>+</sup>, C<sub>27</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> requires 457.1758]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **28** in CDCl<sub>3</sub> at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.18. (5a,6-Dihydroindolo[4,3-*fg*]quinazolin-4(5*H*)-yl)(phenyl)methanone (**29**)

A solution of **12** (24 mg, 0.087 mmol) and 4Å molecular sieves (120 mg) in CHCl<sub>3</sub> (1.7 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (36 μL, 0.43 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and the solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine **13** in CHCl<sub>3</sub> (430 μL, passed through basic alumina) was treated dropwise with 1,3,5-triazine (**23**, 42 mg, 0.519 mmol) in dioxane (430 μL). The reaction mixture was stirred for 14 h at 90 °C before the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **29** (6.2 mg, 23%) as a off white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 50 °C) δ 9.04 (s, 1H), 9.02 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.44–7.55 (m, 3H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.15–7.30 (m, 1H), 4.53 (br s, 1H), 3.91 (t, *J* = 10.7 Hz, 1H), 3.74–3.84 (m, 1H), 3.33 (dd, *J* = 15.9, 6.4 Hz, 1H), 2.96 (t, *J* = 15.1 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 50 °C) δ 168.9, 164.8, 157.6, 150.8, 142.0, 136.3, 132.1, 130.8, 129.6, 128.7, 127.5, 127.4, 126.8, 117.4, 58.6, 36.2, 34.5; IR (film) ν<sub>max</sub> 2925, 1723, 1643, 1383, 1247, 787, 667 cm<sup>-1</sup>; HRMS (ESI) *m/z* 314.1287 [(M+H)<sup>+</sup>, C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O requires 314.1288]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **29** in CDCl<sub>3</sub> at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.19. Dimethyl 4-Benzoyl-4,5,5a,6-tetrahydroindolo[4,3-*fg*]phthalazine-7,10-dicarboxylate (**30**)

A solution of **12** (11.4 mg, 0.0411 mmol) and 4Å molecular sieves (55 mg) in CHCl<sub>3</sub> (0.8 mL, 0.05 M, passed through basic alumina) was treated dropwise with pyrrolidine (17 μL, 0.21 mmol) at 25 °C. After stirring for 10 h at room temperature, the mixture was filtered through a pad of Celite (10% MeOH–CH<sub>2</sub>Cl<sub>2</sub> + 1% Et<sub>3</sub>N) and the solvent was removed under reduced pressure. The crude enamine was dried under high vacuum for 5 h. A solution of the enamine in CHCl<sub>3</sub> (0.4 mL, passed through basic alumina) was treated dropwise with 3,6-dicarbomethoxy-1,2,4,5-tetrazine (**24**, 16.3 mg, 0.0822 mmol) in CHCl<sub>3</sub> (0.41 mL). The reaction mixture was stirred for 3 h at 25 °C before the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO<sub>2</sub>, 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub>) to provide **30** (12.4 mg, 70%) as a white solid: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25 °C) δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.03–7.21 (m, 2H), 4.53 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.93 (t, *J* = 10.6 Hz, 1H), 3.67–

3.77 (m, 1H), 3.58–3.67 (m, 1H), 2.73 (dd,  $J = 16.4, 14.4$  Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  168.8, 166.4, 165.1, 152.9, 150.9, 142.1, 135.9, 135.0, 131.1, 131.0, 129.5, 128.8, 127.4, 125.2, 120.3, 118.9, 58.0, 53.4, 53.3, 33.4, 29.0; IR (film)  $\nu_{\text{max}}$  3446, 2953, 1732, 1644, 1455, 1387, 1237, 1155, 730  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  430.1397 [(M+H) $^+$ ,  $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_5$  requires 430.1397]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **30** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

#### 4.20. Dimethyl 4-Benzoyl-5,5a,6,8-tetrahydro-4*H*-isoindolo[6,5,4-*cd*]indole-7,9-dicarboxylate (31)

A solution of **12** (4.5 mg, 0.011 mmol) in acetic acid (0.2 mL, 0.05 M) was treated with zinc dust (34.3 mg, 0.525 mmol) in a portion at 25 °C. After stirring for 22 h at the same temperature, the resulting mixture was filtered through a short pad of Celite and the solvent was removed under reduced pressure. The residue was purified by preparative thin-layer chromatography ( $\text{SiO}_2$ , 5%  $\text{MeOH}-\text{CH}_2\text{Cl}_2$ ) to provide **31** (3.4 mg, 78%) as a white solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  9.53 (s, 1H), 8.01 (d,  $J = 7.8$  Hz, 1H), 7.60 (d,  $J = 7.2$  Hz, 2H), 7.48 (dq,  $J = 14.5, 7.3$  Hz, 3H), 7.16 (br s, 1H), 4.48 (br s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.85 (t,  $J = 10.7$  Hz, 1H), 3.71 (dd,  $J = 15.3, 6.7$  Hz, 1H), 3.52–3.65 (m, 1H), 2.46 (t,  $J = 14.5$  Hz, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 50 °C)  $\delta$  168.7, 160.8, 160.4, 141.1, 136.7, 133.0, 130.5, 128.6, 128.4, 128.2, 127.7, 127.4, 125.8, 121.6, 120.8, 120.2, 115.7, 57.8, 52.0, 51.8, 36.3, 26.1; IR (film)  $\nu_{\text{max}}$  3325, 1699, 1635, 1472, 1395, 1256, 1013, 668  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  417.1446 [(M+H) $^+$ ,  $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5$  requires 417.1445]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **31** in  $\text{CDCl}_3$  at 25 °C exhibit broadened peaks due to Bz rotamers.<sup>34</sup>

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

### Acknowledgements

We gratefully acknowledge the financial support of the National Institutes of Health (CA042056 and CA041101) and wish to thank Curtis Moore (UCSD) for the X-ray structure of **17**.

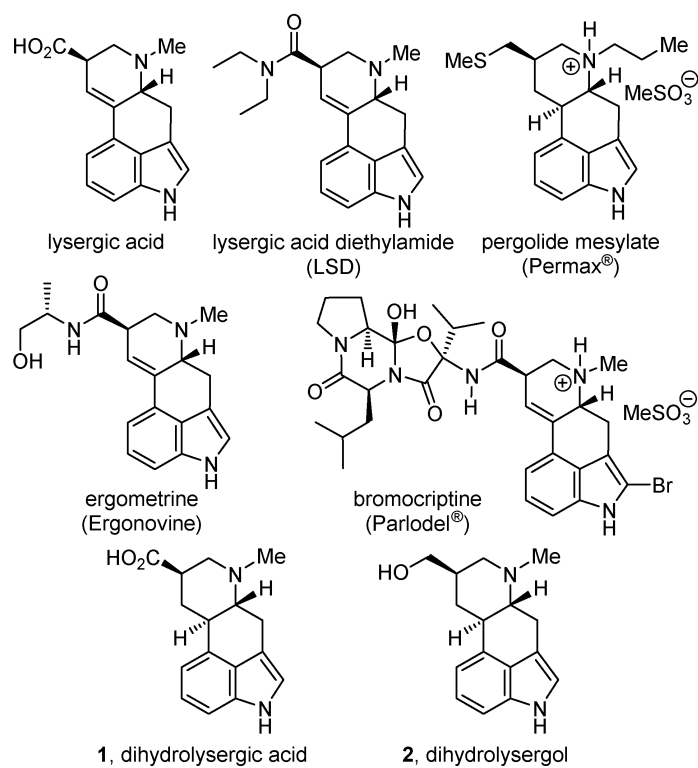
### References and notes

1. (a) Ninomiya, I.; Kiguchi, T. *The Alkaloids*. Brossi, A., editor. Vol. 38. Academic; San Diego: 1990. p. 1-156. (b) *The Merck Index*. 12th ed.. Merck; Whitehouse Station, NY: 1996. p. 231. (c) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. *The Alkaloids*. Cordell, G., editor. Vol. 54. Academic; San Diego: 2000. p. 191-257.
2. (a) Jacobs WA, Craig LC. *J. Biol. Chem.* 1934; 104:547. (b) Stoll A, Hofmann A, Troxler F. *Helv. Chim. Acta.* 1949; 32:506. [PubMed: 18116964]
3. (a) Yen TT, Stamm NB, Clemens JA. *Life Sci.* 1979; 25:209. [PubMed: 39213] (b) Pezzoli G, Martignoni E, Pacchetti C, Angeleri V, Lamberti P, Muratorio A, Bonuccelli U, De Mari M, Foschi N, Cossutta E. *Neurology.* 1995; 45:22.
4. (a) Flückiger E, Wagner H. *Experientia.* 1968; 24:1130. [PubMed: 5752992] (b) Schneider HR, Stadler PA, Stütz P, Troxler F, Seres J. *Experientia.* 1977; 33:1412. [PubMed: 923690] (c) Kebabian JW, Calne DB. *Nature.* 1979; 277:93. [PubMed: 215920]
5. (a) Dudley HW, Moir JC. *Br. Med. J.* 1935; 1:520. [PubMed: 20778930] (b) Moir JC. *Br. Med. J.* 1936; 2:799. [PubMed: 20780191] (c) De Costa C. *Lancet.* 2002; 359:1768. [PubMed: 12049883]

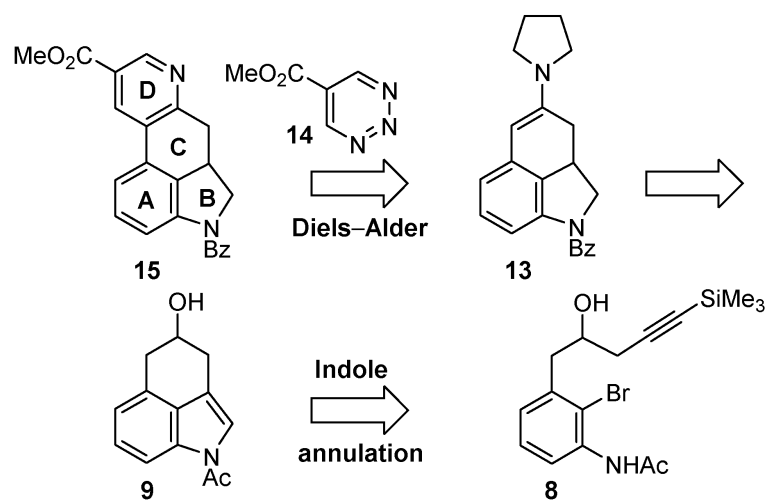
6. Kornfeld EC, Fornefeld EJ, Kline GB, Mann MJ, Morrison DE, Jones RG, Woodward RB. *J. Am. Chem. Soc.* 1956; 78:3087. Julia M, Legoffic F, Igolen J, Baillarg M. *Tetrahedron Lett.* 1969:1569. Oppolzer W, Francotte E, Bättig K. *Helv. Chim. Acta.* 1981; 64:478. Ramage R, Armstrong VW, Coulton S. *Tetrahedron.* 1981; 37:157. Rebek J, Tai DF, Shue Y-K. *J. Am. Chem. Soc.* 1984; 106:1813. Ninomyia I, Hashimoto C, Kiguchi T, Naito T. *J. Chem. Soc., Perkin Trans. 1.* 1985:941. Kurihara T, Terada T, Harusawa S, Yoneda R. *Chem. Pharm. Bull.* 1987; 35:4793. Cacchi S, Ciattini PG, Morera E, Ortar G. *Tetrahedron Lett.* 1988; 29:3117. Saá C, Crotts DD, Hsu G, Vollhardt KPC. *Synlett.* 1994:487. Moldvai I, Temesvári-Major E, Incze M, Szentirmay É, Gács-Baitz E, Szántay C. *J. Org. Chem.* 2004; 69:5993. [PubMed: 15373483] Inuki S, Oishi S, Fujii N, Ohno H. *Org. Lett.* 2008; 10:5239. [PubMed: 18956869] Kurokawa T, Isomura M, Tokuyama H, Fukuyama T. *Synlett.* 2009:775. Inuki S, Iwata A, Oishi S, Fujii N, Ohno H. *J. Org. Chem.* 2011; 76:2072. [PubMed: 21361331] Iwata A, Inuki S, Oishi S, Fujii N, Ohno H. *J. Org. Chem.* 2011; 76:5506. [PubMed: 21598967] Liu Q, Jia Y. *Org. Lett.* 2011; 13:4810. [PubMed: 21866948] Umezaki S, Yokoshima S, Fukuyama T. *Org. Lett.* 2013; 15:4230. [PubMed: 23919892] Liu Q, Zhang Y-A, Xu P, Jia Y. *J. Org. Chem.* 2013; 78:10885. [PubMed: 24111583] Lysergol and isolysergol: Kiguchi T, Hashimoto C, Ninomiya I. *Heterocycles.* 1985; 23:1377. Ninomiya I, Hashimoto C, Kiguchi T. *Heterocycles.* 1984; 22:1035. Ninomiya I, Hashimoto C, Kiguchi T, Naito T, Barton DHR, Lusinch X, Milliet P. *J. Chem. Soc., Perkin Trans. 1.* 1990:707. Deck JA, Martin SF. *Org. Lett.* 2010; 12:2610. [PubMed: 20462232]
7. Stoll A, Petrzilka Th. Rutschmann J, Hofmann A, Günthard Hs. H. *Helv. Chim. Acta.* 1954; 37:2039.
8. Total synthesis of dihydrolysergic acid: Uhle FC, Jacobs WA. *J. Org. Chem.* 1945; 10:76. Stoll A, Rutschmann J, Schlientz W. *Helv. Chim. Acta.* 1950; 33:375. Haefliger WE. *Helv. Chim. Acta.* 1984; 67:1942.
9. (a) Der Marderosian AH, Cho E, Chao JM. *Planta Med.* 1974; 25:6. [PubMed: 4818014] (b) Lee TM, Chao JM, Der Marderosian AH. *Planta Med.* 1979; 35:247. [PubMed: 432303]
10. (a) Breazzano SP, Poudel YB, Boger DL. *J. Am. Chem. Soc.* 2013; 135:1600. [PubMed: 23298368] (b) Shimamura H, Breazzano SP, Garfunkle J, Kimball FS, Trzuppek JD, Boger DL. *J. Am. Chem. Soc.* 2010; 132:7776. [PubMed: 20469945] (c) Garfunkle J, Kimball FS, Trzuppek JD, Takazawa S, Shimamura H, Tomishima M, Boger DL. *J. Am. Chem. Soc.* 2009; 131:16036. [PubMed: 19839632]
11. Larock RC, Yum E, Refvik M. *J. Org. Chem.* 1998; 63:7652.
12. Uhle FC. *J. Am. Chem. Soc.* 1949; 71:761. [PubMed: 18113518]
13. (a) Anderson ED, Boger DL. *J. Am. Chem. Soc.* 2011; 133:12285. [PubMed: 21736324] (b) Anderson ED, Duerfeldt AS, Zhu K, Glinkerman CM, Boger DL. *Org. Lett.* 2014; 16:5084. [PubMed: 25222918] (c) Duerfeldt AS, Boger DL. *J. Am. Chem. Soc.* 2014; 136:2119. [PubMed: 24410439] (d) Anderson ED, Boger DL. *Org. Lett.* 2011; 13:2492. [PubMed: 21488676]
14. (a) Boger DL. *Tetrahedron.* 1983; 39:2869. (b) Boger DL. *Chem. Rev.* 1986; 86:781. (c) Boger, DL.; Weinreb, SM. *Hetero Diels–Alder Methodology in Organic Synthesis.* Academic; San Diego: 1987.
15. (a) Boger DL, Brotherton CE. *J. Org. Chem.* 1984; 49:4050. (b) Mullican MD, Boger DL. *J. Org. Chem.* 1984; 49:4033. (c) Mullican MD, Boger DL. *J. Org. Chem.* 1984; 49:4045.
16. Ozlu Y, Cladingboel D, Parsons P. *Tetrahedron.* 1994; 50:2183.
17. Levine SG. *J. Am. Chem. Soc.* 1958; 80:6150.
18. Lin M-J, Loh T-P. *J. Am. Chem. Soc.* 2003; 125:13042. [PubMed: 14570474]
19. (a) Boger DL, Miyazaki S, Kim SH, Wu JH, Loiseleur O, Castle SL. *J. Am. Chem. Soc.* 1999; 121:3226. (b) Boger DL, Miyazaki S, Kim SH, Wu JH, Castle SL, Loiseleur O, Jin Q. *J. Am. Chem. Soc.* 1999; 121:10004.
20. Maryanoff BE, McComsey DF. *J. Org. Chem.* 1978; 43:2733.
21. (a) Corey EJ, Suggs JW. *Tetrahedron Lett.* 1975:2647. (b) Corey EJ, Boger DL. *Tetrahedron Lett.* 1978:2461.
22. Commercially available from Aldrich.
23.  $\text{CHCl}_3$  was slurried with neutral  $\text{Al}_2\text{O}_3$  and decanted prior to use.



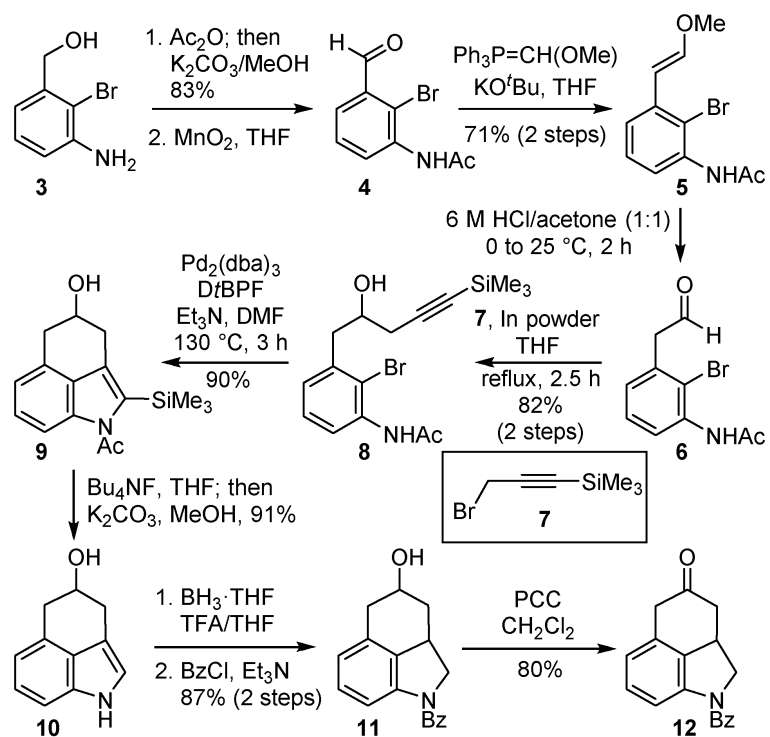
24. The structure and stereochemistry of **17** were established with a single crystal X-ray structure determination conducted on colorless monoclinic plate obtained from MeOH (CCDC 1047936).
25. Burley SD, Lam VV, Lakner FJ, Bergdahl BM, Parker MA. *Org. Lett.* 2013; 15:2598. [PubMed: 23659323]
26. (a) Hendrickson JB, Wang J. *Org. Lett.* 2004; 6:3. [PubMed: 14703336] (b) Bekkam M, Mo H, Nichols DE. *Org. Lett.* 2012; 14:296. [PubMed: 22176338]
27. (a) Wagger J, Požes A, Požgan F. *RSC Adv.* 2013; 3:23146.(b) Dosa PI, Ward T, Walters MA, Kim SW. *ACS Med. Chem. Lett.* 2013; 4:254. [PubMed: 23606928]
28. (a) Ohno S, Adachi Y, Koumori M, Mizukoshi K, Nagasaka M, Ichihara K, Kato E. *Chem. Pharm. Bull.* 1994; 42:1463. [PubMed: 7923470] (b) Chirivi C, Fontana G, Monti D, Ottolina G, Riva S, Danieli B. *Chem.–Eur. J.* 2012; 18:10355. [PubMed: 22777708]
29. Although not exhaustive, initial efforts to generate a tetrahydropyridine through partial reduction of **16** have not yet been successful.
30. (a) Boger DL, Schumacher J, Panek JS, Mullican MD, Patel M. *J. Org. Chem.* 1982; 47:2673.(b) Boger DL, Mullican MD, Patel M. *Tetrahedron Lett.* 1982; 23:4559.(c) Boger DL, Dang Q. *Tetrahedron.* 1988; 44:3379.(d) Boger DL, Honda T, Dang Q. *J. Am. Chem. Soc.* 1994; 116:5619. (e) Boger DL, Kochanny MJ. *J. Org. Chem.* 1994; 59:4950.
31. (a) Boger DL, Panek JS, Coleman RS, Sauer J, Huber FX. *J. Org. Chem.* 1985; 50:5377.(b) Boger DL, Panek JS. *J. Am. Chem. Soc.* 1985; 107:5745.(c) Boger DL, Panek JS, Duff SR, Yasuda M. *J. Org. Chem.* 1985; 50:5790.(d) Boger DL, Coleman RS. *J. Am. Chem. Soc.* 1987; 109:2717.(e) Boger DL, Zhang M. *J. Am. Chem. Soc.* 1991; 113:4230.
32. (a) Boger DL, Coleman RS, Panek JS, Yohannes D. *J. Org. Chem.* 1984; 49:4405.(b) Boger DL, Patel M. *J. Org. Chem.* 1988; 53:1405.(c) Boger DL, Baldino CM. *J. Am. Chem. Soc.* 1993; 115:11418.(d) Boger DL, Boyce CW, Labroli MA, Sehon CA, Jin Q. *J. Am. Chem. Soc.* 1999; 121:54.(e) Boger DL, Soenen DR, Boyce CW, Hedrick MP, Jin Q. *J. Org. Chem.* 2000; 65:2479. [PubMed: 10789460] (f) Boger DL, Hong J. *J. Am. Chem. Soc.* 2001; 123:8515. [PubMed: 11525659] (g) Hamasaki A, Zimpleman JM, Hwang I, Boger DL. *J. Am. Chem. Soc.* 2005; 127:10767. [PubMed: 16045367] (h) Oakdale JS, Boger DL. *Org. Lett.* 2010; 12:1132. [PubMed: 20148525]
33. Bach NJ, Kornfeld EC, Jones ND, Chaney MO, Dorman DE, Paschal JW, Clemens JA, Smalstig EB. *J. Med. Chem.* 1980; 23:481. [PubMed: 7189782]
34. Intermediates bearing the  $N^1$ -benzoyl group display broadened signals in the NMR. At room temperature, the three aromatic protons of the indoline in **11-13**, **15-17**, and **25-31** are so broad in the  $^1\text{H}$  NMR that they are not observed. At 50 °C, two of the three aromatic protons are observed as broadened signals and the third is still so broad that it is not observable.



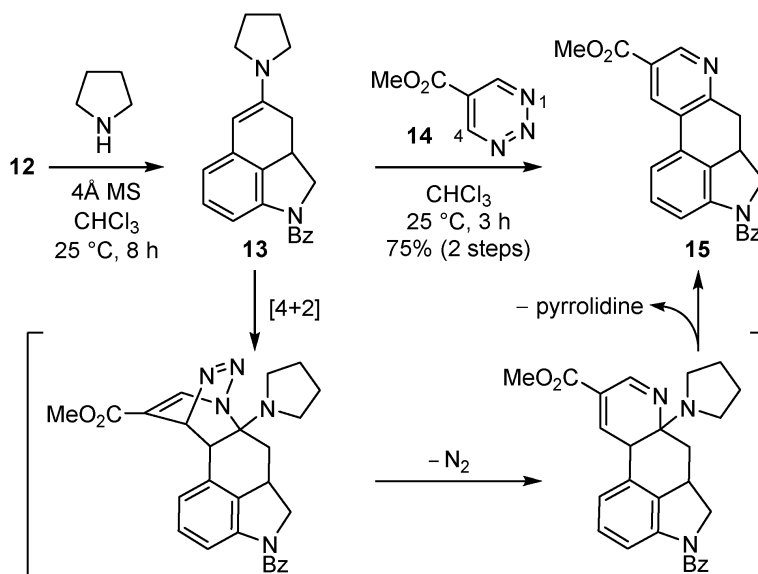
**Figure 1.**  
Natural products and key semisynthetic analogues.



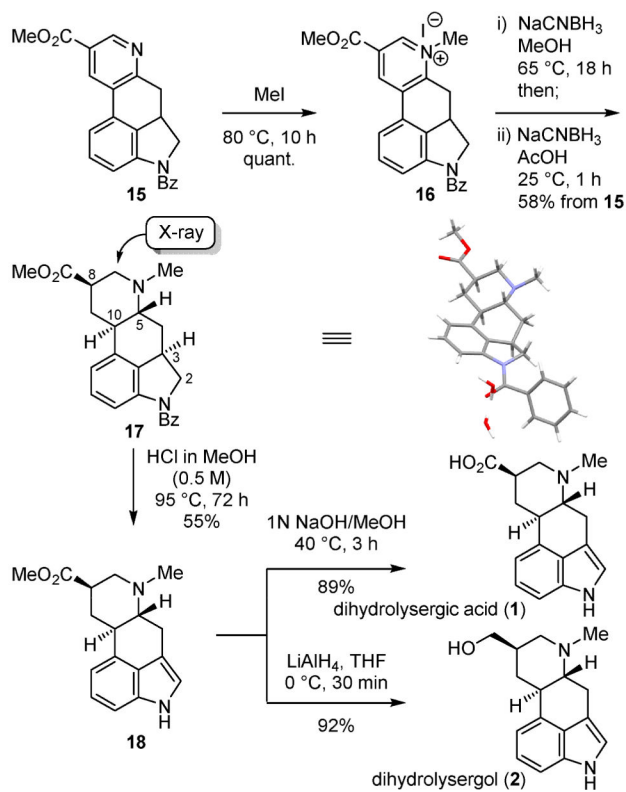
**Figure 2.**  
Strategic reactions employed.



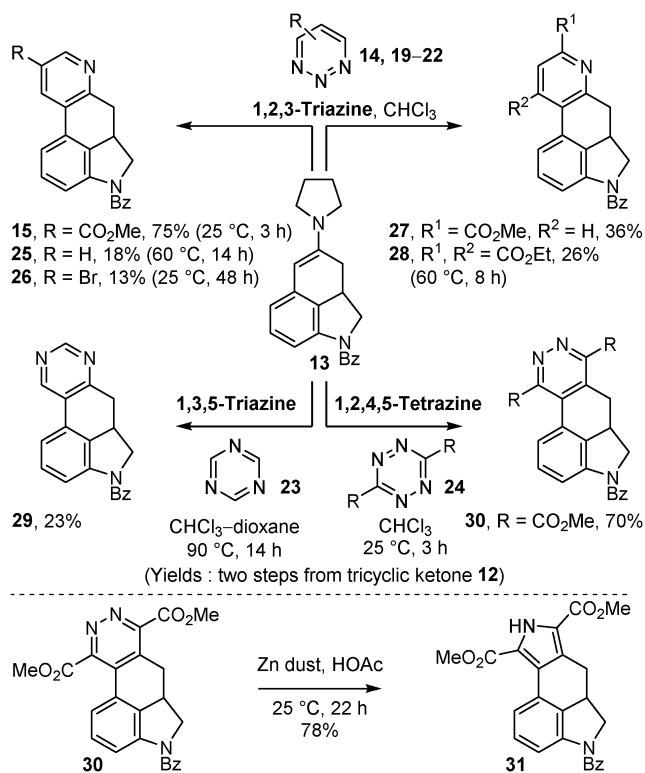
**Scheme 1.**  
Preparation of tricyclic ketone **12**.



**Scheme 2.**  
Inverse electron demand Diels–Alder reaction.

**Scheme 3.**

Completion of the total synthesis of dihydrolysergic acid (**1**) and dihydrolysergol (**2**).



**Scheme 4.**  
Divergent synthesis of heterocyclic derivatives.

**Table 1**Comparison of  $^1\text{H}$  NMR data for **1** (Solvent: DMSO- $d_6$ ;  $\delta$  in ppm,  $J$  in Hz)

chemical shifts ( $\delta$ )	
Semi synthetic <sup>a</sup> (500 MHz)	Synthetic <b>1</b> (600 MHz)
10.65 (s, 1H)	10.63 (s, 1H)
7.13 (d, $J = 8.1$ Hz, 1H)	7.12 (d, $J = 8.0$ Hz, 1H)
7.01 (t, $J = 7.6$ Hz, 1H)	7.01 (t, $J = 7.6$ Hz, 1H)
6.98 (bs, 1H)	6.97 (br s, 1H)
6.79 (d, $J = 7.1$ Hz, 1H)	6.79 (d, $J = 7.0$ Hz, 1H)
3.29 (dd, $J = 14.6, 4.1$ Hz, 1H)	3.29 (d, $J = 14.7$ Hz, 1H)
3.12 (dd, $J = 11.0, 2.1$ Hz, 1H)	3.11 (d, $J = 11.3$ Hz, 1H)
2.70–2.85 (m, 3H)	2.70–2.85 (m, 3H)
2.48–2.55 (m, 1H)	2.50–2.56 (m, 1H)
2.37 (s, 3H)	2.37 (s, 3H)
2.17 (t, $J = 11.5$ Hz, 1H)	2.16 (t, $J = 11.5$ Hz, 1H)
2.00 (dt, $J = 10.9, 4.1$ Hz, 1H)	2.00 (t, $J = 11.1$ Hz, 1H)
1.34 (q, $J = 12.9$ Hz, 1H)	1.34 (q, $J = 13.0$ Hz, 1H)

<sup>a</sup>Wagger, J.; Požes, A.; Požgan, F. *RSC Adv.* **2013**, *3*, 23146.



**Table 2**Comparison of  $^{13}\text{C}$  NMR data for **1** (Solvent: DMSO- $d_6$ ;  $\delta$  in ppm)

chemical shifts ( $\delta$ )	
Semi synthetic <sup>a</sup> (125 MHz)	Synthetic 1 (150 MHz)
175.1	175.0
133.2	133.1
132.3	132.3
125.9	125.9
122.1	122.1
118.6	118.5
112.0	112.0
110.0	110.0
108.8	108.7
66.6	66.6
58.6	58.6
42.6	42.6
40.9	40.9
30.5	30.5
26.5	26.5

<sup>a</sup>Wagger, J.; Požes, A.; Požgan, F. *RSC Adv.* **2013**, 3, 23146.