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**Article:**

Cooksey, JP, Saidi, O, Williams, JMJ et al. (2 more authors) (2020) Oxidative Pictet-Spengler cyclisations through acceptorless iridium-catalysed dehydrogenation of tertiary amines. *Tetrahedron*. 131785. p. 131785. ISSN 0040-4020

<https://doi.org/10.1016/j.tet.2020.131785>

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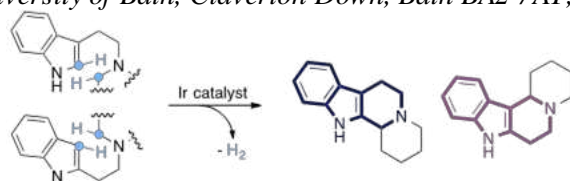
### Oxidative Pictet-Spengler cyclisations through acceptorless iridium-catalysed dehydrogenation of tertiary amines

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## Oxidative Pictet-Spengler cyclisations through acceptorless iridium-catalysed dehydrogenation of tertiary amines

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### ARTICLE INFO

#### Article history:

Received

Received in revised form

Accepted

Available online

Dedicated to the memory of our colleague, collaborator and friend Professor Jonathan Williams.

### ABSTRACT

The valuable tetrahydro- $\beta$ - and  $\gamma$ -carboline skeleta can be accessed through Pictet-Spengler cyclisation initiated by acceptorless dehydrogenation of saturated cyclic amines. The substrate scope for the  $\beta$ -isomers is found to be somewhat limited, but access to the  $\gamma$ -isomers through the more reactive 2-(aminoethyl)indoles is more general. The synthetic utility of hydrogen transfer catalysis is highlighted in a two-step preparation of the alkaloid desbromoarborescidine A by sequential redox-neutral alkylation/dehydrogenative cyclisation.

**Keywords:** Dehydrogenation; iridium; tetrahydrocarboline; alkaloid; Pictet-Spengler.

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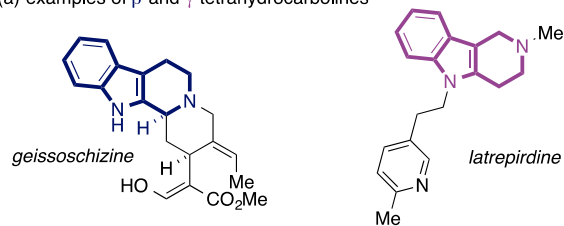
## 1. Introduction

Oxidation processes are widely used in organic synthesis, yet frequently have many undesirable features including large waste inventories and potential safety issues associated with the use of stoichiometric oxidants. The ‘acceptorless’ catalytic dehydrogenation of organic molecules with the liberation of hydrogen gas represents fundamentally the most atom economic approach to oxidation reactions, and much progress has been made in the development of homogeneous catalysts to realise this goal [1]. While most studies have focused on processes initiated by dehydrogenation of alcohols, there have been significant developments in the dehydrogenation of amines to imines [2], nitriles [3] and amidines [4], and of cyclic amines to heteroaromatics [5] and lactams [6]. Our efforts in acceptorless dehydrogenation were triggered by studies of the amine racemisation catalyst (Cp\*IrI<sub>2</sub>)<sub>2</sub> **1**, where oxidized by-products were observed in some reactions [7]. We subsequently demonstrated that **1** could perform the efficient acceptorless dehydrogenation of hemiaminals leading to oxidative formation of benzoxazoles from aminophenols and aldehydes [8], and formamides from amines and formaldehyde [9].

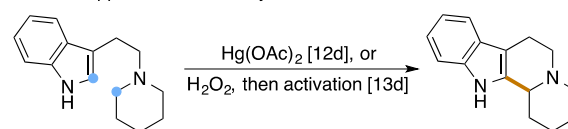
Tetrahydro- $\beta$ - and  $\gamma$ -carbolines are important structures in organic chemistry [10,11], found in natural alkaloids such as geissoschizine and clinical drugs including the anti-histamine latrepirdine (Figure 1, panel a). They are most typically made by Pictet-Spengler (or iso-Pictet-Spengler) cyclisation of

aminoethylindoles with aldehydes, but an alternative approach involves oxidative generation of iminium ions using mercury(II) salts [12] or *N*-oxidation and Polonovski rearrangement [13] (panel b).

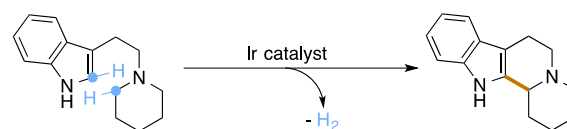
(a) examples of  $\beta$ - and  $\gamma$ -tetrahydrocarbolines



(b) oxidative approaches to tetrahydrocarbolines



(c) this work: dehydrogenative (iso-)Pictet-Spengler cyclisation



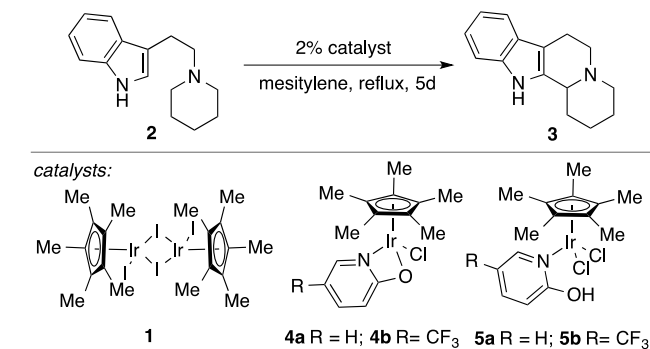
**Figure 1.** Oxidative approaches to  $\beta$ - and  $\gamma$ -tetrahydrocarbolines.

We considered that hydrogen transfer catalysis could offer significant advantages over these approaches by avoiding toxic stoichiometric waste and multi-step sequences respectively. Indeed, there have been two previous hydrogen transfer-induced approaches to  $\beta$ -tetrahydrocarboline synthesis: Yang and co-workers reported nickel-catalysed dehydrogenation of alcohols (using methyl cinnamate as a hydrogen acceptor) to generate carbonyls which engaged in Pictet-Spengler cyclisation with tryptophan *in situ* [14], while Achard and co-workers generated the reactive cyclic iminium ions by acceptorless dehydrogenation and capture of 1,n-diols by tryptophan [15]. We were intrigued to investigate if the iminium ions could instead be generated by hydride abstraction from saturated tertiary amines, leading to cyclisation and proton loss to ultimately generate hydrogen gas, closing the catalytic cycle (panel c). We report herein the reduction of this to practice, including a synthesis of the tetrahydro- $\beta$ -carboline alkaloid desbromoarborescidine by sequential catalytic borrowing hydrogen/dehydrogenation steps.

## 2. Results/Discussion

We began our studies by investigating the dehydrogenative cyclisation of 3-(piperidinoethyl)indole **2** with a range of iridium catalysts (Table 1). Using conditions of our dehydrogenative benzoxazole formation [8] ( $(\text{Cp}^*\text{IrI}_2)_2$  **1** in refluxing toluene for 20h), no reaction was observed (entry 1). Concerned that reversible hydride abstraction might be outcompeting the liberation of hydrogen gas, the addition of styrene as a hydrogen acceptor led to the observation of small quantities of the desired product **3**, with ca. 20% conversion being observed at longer reaction times in the higher-boiling solvent mesitylene (entries 2-4).

**Table 1:** Catalyst screening and optimization of dehydrogenative cyclisation.

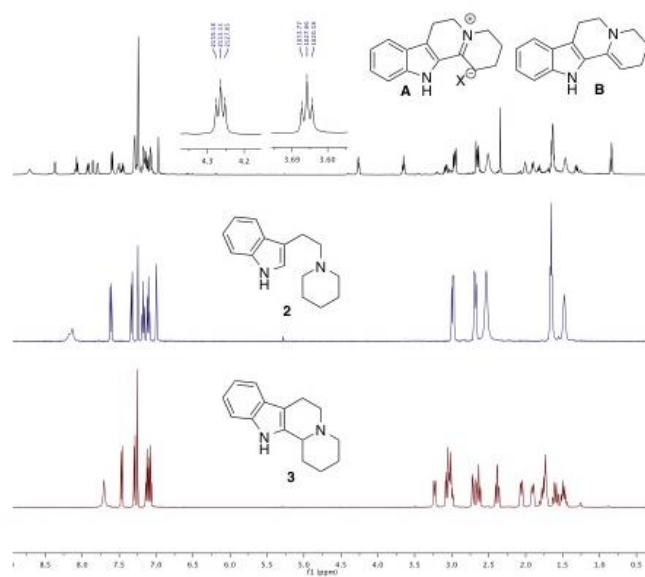


Entry	Catalyst	Variation from conditions in scheme	Ratio <b>2</b> : <b>3</b> <sup>a</sup>
1	<b>1</b>	toluene, reflux, 20h	100:0
2	<b>1</b>	2 eq. styrene, toluene, reflux, 20h	93:7
3	<b>1</b>	2 eq. styrene, toluene, 150 °C $\mu$ w, 30min	97:3
4	<b>1</b>	2 equiv. styrene, reflux, 3d	78:22
5	<b>4a</b>	toluene, reflux, 20h	100:0
6	<b>4a</b>	toluene, 150 °C $\mu$ w, 1h	95:5
7	<b>4a</b>	---	60:40
8	<b>4b</b>	---	60:40
9	<b>5a</b>	---	77:23
10	<b>5b</b>	---	39:61

<sup>a</sup> determined by <sup>1</sup>H NMR analysis of crude material

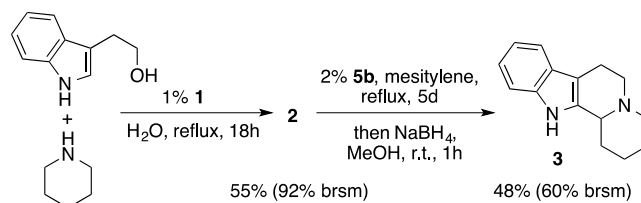
Switching to catalyst **4a**, first described by Fujita for acceptorless dehydrogenation of tetrahydroquinolines [5a], again limited activity was observed using toluene as solvent (entries 5,6) but switching to mesitylene gave higher conversions over 5 days (entry 7). Screening catalysts **4b** [5a], **5a** and **5b** [16] under the same conditions, we found that complex **5b** (previously used

by Fujita for acceptorless alcohol dehydrogenation) returned the highest conversion to **3** (entry 10) and these were adopted as our optimized reaction conditions. In most cases where conversion was observed, we saw LC-MS evidence for formation of a more highly oxidized product ( $m/z$  for  $\text{MH}^+$  of 225 versus  $\text{MH}^+$  of 227 for **3**). Attempts to isolate the by-product in pure form were unsuccessful, but <sup>1</sup>H NMR analysis (Figure 2, top spectrum) showed signals at  $\delta = 4.26$  (t,  $J = 6.1$ ) and 3.65 (t,  $J = 6.7$ ) which are distinct from either **2** or **3** (Figure 2, middle and lower spectra). Comparison with literature values for potential structures **A** [17] and **B** [18] did not show agreement, and isomeric variants would be expected to give more complex spectra. We are therefore not able to assign a structure to the by-product at this time, but we found that brief treatment of the cooled reaction mixture with sodium borohydride in methanol removed this contaminant and facilitated isolation of pure **3** after column chromatography.

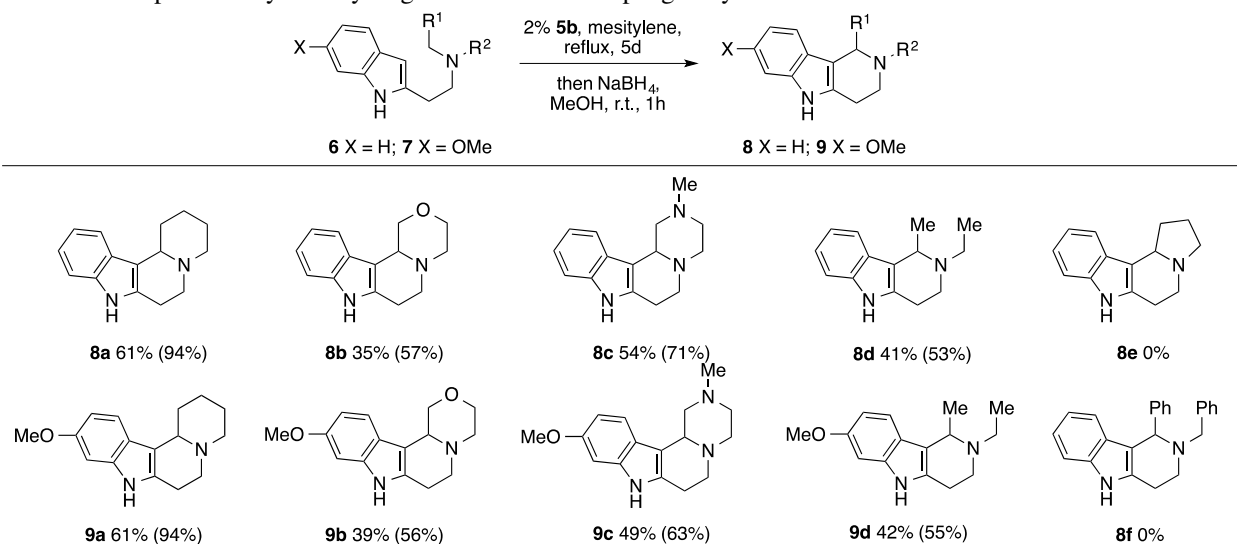


**Figure 2.** <sup>1</sup>H NMR spectra of crude unknown oxidative by-product (top), **2** (middle) and **3** (bottom).

Compound **3** corresponds to the natural product desbromoarborescidine [12d,13d,19,20] and in completing the preparative synthesis of this material, we were attracted to the idea that the starting material **2** might also be prepared using catalytic hydrogen transfer chemistry. One of us (JM JW) has previously reported the synthesis of **2** by redox-neutral alkylation of tryptamine with pentane-1,5-diol [21], but we wished here to exploit an alternative disconnection. We have demonstrated that catalyst **1** is effective for the redox-neutral alkylation of amines in water [22], and were pleased to observe that reaction of commercial tryptophol with piperidine under the previously disclosed conditions gave clean if incomplete conversion to the desired substrate **2** (55% isolated yield, 92% based on recovered unreacted tryptophol). Exposure to the optimized dehydrogenation conditions described above returned



**Scheme 1.** Two-step hydrogen transfer-mediated synthesis of desbromoarborescidine **3**.

**Table 2.** Substrate scope of catalytic dehydrogenative iso-Pictet-Spengler cyclisations

<sup>a</sup>Yields given are for isolated product; values in parentheses are corrected values based on recovered starting material.

desbromoarborescidine **3** in 48% yield, along with some unreacted **2** (60% yield based on recovered **3**).

Although we had successfully demonstrated hydrogen abstraction-initiated cyclisation for substrate **2**, screening of alternative *N,N*-dialkylated tryptamines showed that these were less reactive still (see Supplementary Material) and, given the forcing conditions already required we were not encouraged to push the reaction conditions further. Instead, we considered whether the synthesis of tetrahydro- $\gamma$ -carbolines might be more fruitful, exploiting the greater nucleophilicity of the indolyl 3-position [23]. Substrates **6a-f/7a-d** were readily prepared from 2-iodoanilines by a sequence involving palladium-catalysed annulation [24] (Supplementary Material) and exposed to our optimized cyclisation conditions above (Table 2).

We were pleased to find that the cyclisations proceeded more readily than for the corresponding  $\beta$ -isomers. Piperidinyl substrates **6a/7a** underwent cyclisation leading in each case to 61% isolated yields of the tetrahydro- $\gamma$ -carbolines **8a/9a** (94% based upon recovered starting materials). More pleasingly still, in contrast to the  $\beta$ -isomers, the reaction tolerated different amines: the morpholinyl and *N*-methylpiperazinyl substrates **6b,c/7b,c** underwent cyclisations in 35–54% isolated yields, and acyclic amines could also be cyclized, with the *N,N*-diethyl substrates **6d/7d** giving 41% and 42% yields. Cyclisation could not be effected with the *N*-pyrrolidinyl substrate **6e**, possibly owing to ready oxidative formation of reactive pyrroles which underwent decomposition under the forcing conditions. Cyclisation could not be effected to either cyclic or acyclic benzylic amines such as **6f**, with only unreacted starting material recovered; although hydride abstraction might be expected to be more facile for such substrates, the greater stabilization of the resulting iminium ions might slow the cyclisation, with back hydride transfer outcompeting the forward reaction.

### 3. Conclusion

We have demonstrated that homogeneous iridium catalysts can effect hydride abstraction from tertiary amines and that the resulting iminium ions can undergo productive Pictet-Spengler reactions, leading to the synthesis of tetrahydro- $\beta$ - and  $\gamma$ -carbolines through overall acceptorless dehydrogenative cyclisation. A two-step synthesis of the simple alkaloid

desbromoarborescidine was developed which employs catalytic hydrogen transfer in both steps. Although the reaction conditions are currently rather forcing, this demonstrates further proof of principle of the synthetic potential of catalytic dehydrogenation reactions in atom-economic organic transformations.

### 4. Experimental Section

For details of general experimental considerations, please see Supplementary Material.

#### 1.1. 3-(2-(Piperidin-1-yl)ethyl)-1H-indole (**2**)

A solution of commercially available tryptophol (250 mg, 1.55 mmol, 1.0 equiv), piperidine (0.15 mL, 1.55 mmol, 1.0 equiv) and [Cp\*Ir]<sub>2</sub> **7** (18.0 mg, 155  $\mu$ mol, 1 mol%) in H<sub>2</sub>O (3 mL) was heated under reflux for 18 h. The reaction mixture was allowed to cool to rt, poured onto H<sub>2</sub>O (10 mL), CH<sub>2</sub>Cl<sub>2</sub> (10 mL) added, the layers separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to give a brown solid. Purification by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] followed by crystallisation from EtOH gave the title compound **2** (195 mg, 853  $\mu$ mol, 55%) as a white solid and recovered tryptophol (100 mg, 620  $\mu$ mol, 40%) as a brown/orange solid. mp (EtOH) 150–152 °C;  $v_{\text{max}}$  (solid) 3600–2300 br, s, 2921 s, 1621 m, 1577 m, 1551 w, 1505 m, 1471 m, 1455 s, 1389 w, 1356 s, 1304 s, 1268 m, 1231 s cm<sup>-1</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.10 (1H, broad s, NH), 7.62 (1H, d, *J* = 8.1, C4H), 7.34 (1H, d, *J* = 8.1, C7H), 7.18 (1H, t, *J* = 7.5, C6H), 7.11 (1H, t, *J* = 7.1, C5H), 7.01 (1H, s, C2H), 2.99 (2H, dd, *J* = 9.6, 6.6, C5'H<sub>2</sub>), 2.68 (2H, dd, *J* = 9.6, 6.6, C4'H<sub>2</sub>), 2.60–2.46 (4H, m, C7'H<sub>2</sub>), 1.66 (4H, quint, *J* = 5.6, C8'H<sub>2</sub>), 1.52–1.44 (2H, m, C9'H<sub>2</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  136.4 (C8), 127.6 (C3'), 122.0 (C6H), 121.6 (C2H), 119.3 (C5H), 119.0 (C4H), 114.6 (C3), 111.3 (C7H), 60.3 (C4'H<sub>2</sub>), 54.8 (C7'H<sub>2</sub>), 26.1, (2C, C8'H<sub>2</sub>), 24.6 (2C, C9'H<sub>2</sub>), 23.0 (C5'H<sub>2</sub>); *m/z* (ES<sup>+</sup>) 229 [MH<sup>+</sup>, 100%]; HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 229.1706. C<sub>15</sub>H<sub>21</sub>N<sub>2</sub> requires 229.1699.

#### 1.2. Desbromoarborescidine (**3**)

A solution of indole **2** (183 mg, 800  $\mu$ mol, 1.0 equiv) and iridium complex **5b** (1.60  $\mu$ mol, 2 mol%) in mesitylene (2 mL) was heated under reflux for 5 d. The reaction mixture was allowed to cool to rt and MeOH (5 mL) added. NaBH<sub>4</sub> (45.5 mg, 1.2 mmol, 1.5 equiv) was added in one portion to the reaction

mixture at 0 °C and the resulting brown solution stirred at rt for 1 h. The reaction mixture was quenched with NaHCO<sub>3</sub> (saturated aqueous; 10 mL), CH<sub>2</sub>Cl<sub>2</sub> (10 mL) added, the layers separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a brown oily solid. Purification by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] gave recovered **2** (38 mg, 21%) along with the title compound **3** (87 mg, 48%; 61% based on recovered starting material) as a yellow/brown solid after crystallisation from EtOH/H<sub>2</sub>O mp (EtOH/H<sub>2</sub>O) 148–149 °C (lit. [25] 147–150 °C). Spectroscopic data for compound **X** [<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) and IR] are in accordance with those reported. [21]  $\nu_{\max}$  (solid) 3800–2600 br, s, 2923 s, 2848 s, 2805 s, 2763 s, 1624 m, 1569 w, 1464 s, 1449 s, 1392 m, 1371 m, 1350 s, 1318 s, 1274 s, 1249 w cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (1H, broad s, NH), 7.47 (1H, d, *J* = 7.7, C4H), 7.29 (1H, d, *J* = 8.1, C7H), 7.12 (1H, t, *J* = 7.3, C6H) 7.08 (1H, t, *J* = 7.3, C5H), 3.24 (1H, br d, *J* = 10.7, C11'H), 3.10–2.97 (3H, m, C4'H<sub>A</sub>H<sub>B</sub>/C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>), 2.74–2.67 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 2.63 (1H, td, *J* = 11.1, 4.4, C5'H<sub>A</sub>H<sub>B</sub>), 2.39 (1H, td, *J* = 11.1, 3.4, C4'H<sub>A</sub>H<sub>B</sub>), 2.06 (1H, dd, *J* = 12.4, 2.1, C10'H<sub>A</sub>H<sub>B</sub>), 1.90 (1H, broad d, *J* = 12.4, C9'H<sub>A</sub>H<sub>B</sub>), 1.82–1.69 (2H, m, C8'H<sub>A</sub>H<sub>B</sub>/C9'H<sub>A</sub>H<sub>B</sub>), 1.60 (1H, qd, *J* = 12.4, 3.4, C10'H<sub>A</sub>H<sub>B</sub>), 1.54–1.43 (1H, m, C8'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  136.1 (C8), 135.3 (C3'), 127.6 (C2), 121.3 (C6H), 119.4 (C5H), 118.2 (C4H), 110.9 (C7H), 108.2 (C3), 60.4 (C11'H), 55.9 (C4'H<sub>2</sub>), 53.7 (C7'H<sub>2</sub>), 30.1 (C5'H<sub>2</sub>), 25.8 (C10'H<sub>2</sub>), 24.4 (C8'H<sub>2</sub>), 21.7 (C9'H<sub>2</sub>); *m/z* (ES+) 228 (15%), 227 [MH<sup>+</sup>, 100%]. HRMS (ES+): MH<sup>+</sup>, found 227.1550. C<sub>15</sub>H<sub>19</sub>N<sub>2</sub> requires 227.1543.

### 1.3. General procedure for catalytic dehydrogenative iso-Pictet-Spengler cyclisations (Table 2)

A solution of indole **6a-f/7a-d** (462  $\mu$ mol, 1.0 equiv) and iridium catalyst **5b** (5.24 mg, 9.34  $\mu$ mol, 2 mol%) in xylenes (1 mL) was heated under reflux for 2 d. The reaction mixture was allowed to cool to rt and MeOH (5 mL) added. NaBH<sub>4</sub> (70.0 mg, 1.85 mmol, 4.0 equiv) was added in one portion to the reaction mixture at 0 °C and the resulting brown solution stirred at rt for 1 h. The reaction mixture was quenched with NaHCO<sub>3</sub> (saturated aqueous; 10 mL), CH<sub>2</sub>Cl<sub>2</sub> (10 mL) added, the layers separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give the crude product **8a-d/9a-d** and recovered starting material that was purified by column chromatography/recrystallisation using the solvents specified.

### 1.4. 1,2,3,4,6,7,8,12c-Octahydroindolo[3,2-a]quinolizine (**8a**)

The title compound **8a** was prepared in 61% yield on a 438  $\mu$ mol scale [along with recovered **6a** (35%)] using the general procedure. Compound **8a** was purified by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] followed by crystallisation from EtOH/H<sub>2</sub>O as an off-white solid. mp (EtOH/H<sub>2</sub>O) 212–213 °C;  $\nu_{\max}$  (solid) 3600–2400 br, s, 2920 s, 2222 br, s, 1901 w, 1869 w, 1840 w, 1793 w, 1653 w, 1621 m, 1579 m, 1505 s, 1455 s cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (1H, s, NH), 7.57 (1H, d, *J* = 7.8, C4H), 7.26–7.23 (1H, m, C7H), 7.08 (1H, t, *J* = 7.3, C6H), 7.04 (1H, t, *J* = 7.3, C5H), 3.37 (1H, d, *J* = 8.4, C11'H), 3.14–3.07 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 3.02 (1H, dd, *J* = 10.7, 6.5, C5'H<sub>A</sub>H<sub>B</sub>), 3.05–2.98 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 2.70–2.58 (3H, m, C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>/C10'H<sub>A</sub>H<sub>B</sub>), 2.50 (1H, td, *J* = 11.6, 3.0, C4'H<sub>A</sub>H<sub>B</sub>), 1.93–1.87 (1H, m, C9'H<sub>A</sub>H<sub>B</sub>), 1.83–1.71 (2H, m, C8H<sub>2</sub>), 1.61–1.51 (2H, m, C9'H<sub>A</sub>H<sub>B</sub>/C10'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  136.5 (C8), 132.5 (C3'), 126.0 (C2), 120.9 (C6H), 119.4 (C4H), 119.3 (C5H), 112.5 (C3), 110.9 (C7H), 61.4 (C11'H), 56.2 (C4'H<sub>2</sub>), 52.6 (C5'H<sub>2</sub>), 31.4 (C10'H<sub>2</sub>),

26.2 (C8'H<sub>2</sub>), 24.9 (C9'H<sub>2</sub>), 24.4 (C7'H<sub>2</sub>); *m/z* (ES+) 227 [MH<sup>+</sup>, 100%]; HRMS (ES+): MH<sup>+</sup>, found 227.1551. C<sub>15</sub>H<sub>19</sub>N<sub>2</sub> requires 227.1543.

### 1.5. 10-Methoxy-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizine (**9a**)

The title compound **9a** was prepared in 61% yield on a 387  $\mu$ mol scale [along with recovered **7a** (35%)] using the general procedure. The mixture was purified by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] followed by crystallisation from EtOH/H<sub>2</sub>O to give **9a** as an off-white solid. mp (EtOH/H<sub>2</sub>O) 188–190 °C;  $\nu_{\max}$  (solid) 3700–2500 br, m, 2992 m, 2931 s, 2808 s, 2762 s, 1627 s, 1593 m, 1566 m, 1468 s, 1434 m cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.90 (1H, s, NH), 7.43 (1H, d, *J* = 8.7, C4H), 6.76 (1H, d, *J* = 2.0, C7H), 6.70 (1H, dd, *J* = 8.7, 2.2, C5H), 3.79 (3H, s, OCH<sub>3</sub>), 3.32 (1H, d, *J* = 8.3, C11'H), 3.11–3.03 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 3.04–2.97 (2H, m, C4'H<sub>A</sub>H<sub>B</sub>/C5'H<sub>A</sub>H<sub>B</sub>), 2.66 (1H, td, *J* = 11.0, 4.2, C5'H<sub>A</sub>H<sub>B</sub>), 2.61–2.52 (2H, m, C7'H<sub>A</sub>H<sub>B</sub>/C10'H<sub>A</sub>H<sub>B</sub>), 2.48 (1H, td, *J* = 11.5, 3.0, C4'H<sub>A</sub>H<sub>B</sub>), 1.93–1.85 (1H, m, C9'H<sub>A</sub>H<sub>B</sub>), 1.85–1.66 (2H, m, C8'H<sub>2</sub>), 1.60–1.49 (2H, m, C9'H<sub>A</sub>H<sub>B</sub>/C10'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  155.6 (C6), 137.3 (C8), 131.2 (C3'), 120.2 (C6), 119.8 (C4H), 111.8 (C3), 108.6 (C5H), 95.0 (C7H), 61.4 (C11'H), 56.1 (C4'H<sub>2</sub>), 55.7 (OCH<sub>3</sub>), 52.7 (C5'H<sub>2</sub>), 31.3 (C10'H<sub>2</sub>), 26.0 (C8'H<sub>2</sub>), 24.8 (C9'H<sub>2</sub>), 24.1 (C7'H<sub>2</sub>); *m/z* (ES+) 257 [MH<sup>+</sup>, 100%]; HRMS (ES+): MH<sup>+</sup>, found 257.1651. C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O [MH<sup>+</sup>]; requires 257.1648.

### 1.6. 3,4,6,7,8,12c-Hexahydro-1H-[1,4]oxazino[4',3':1,2]-pyridol[4,3-b]indole (**8b**)

The title compound **8b** was prepared in 35% yield on a 400  $\mu$ mol scale [along with recovered **6b** (39%)] using the general procedure. The mixture was purified by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (10:1)] followed by crystallisation from PhH/petrol to give the title compound **8b** as an off-white solid. mp (PhH/petrol) 153–156 °C;  $\nu_{\max}$  (solid) 3400–2500 br, s, 2920 s, 2949 s, 2847 s, 2789 s, 1622 w, 1588 w, 1565 w, 1502 m, 1455 s cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.19 (1H, s, NH), 7.44 (1H, d, *J* = 7.7, C4H), 7.20 (1H, d, *J* = 7.8, C7H), 7.09 (1H, td, *J* = 7.6, 1.1, C6H), 7.05 (1H, td, *J* = 7.6, 1.1, C5H), 4.68 (1H, dd, *J* = 11.0, 2.7, C10'H), 3.93 (1H, d, *J* = 10.6, C8'H<sub>A</sub>H<sub>B</sub>), 3.84 (1H, td, *J* = 10.6, 4.0, C8'H<sub>A</sub>H<sub>B</sub>), 3.67 (1H, dd, *J* = 10.1, 1.9, C9'H<sub>A</sub>H<sub>B</sub>), 3.53 (1H, t, *J* = 10.6, C9'H<sub>A</sub>H<sub>B</sub>), 3.00–3.08 (2H, m, C5'H<sub>A</sub>H<sub>B</sub> /C4'H<sub>A</sub>H<sub>B</sub>), 2.79–2.85 (2H, m, C7'H<sub>A</sub>H<sub>B</sub>), 2.70–2.75 (1H, m, C5' H<sub>A</sub>H<sub>B</sub>), 2.57 (1H, dd, *J* = 14.7, 4.9, C4'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  136.2 (C8), 133.3 (C3'), 125.3 (C2), 121.2 (C6H), 119.6 (C5H), 118.9 (C4H), 111.0 (C7H), 107.6 (C3), 70.5 (C10'H), 67.2 (C8'H<sub>2</sub>), 60.3 (C9'H<sub>2</sub>), 54.6 (C7'H<sub>2</sub>), 51.5 (C5'H<sub>2</sub>), 24.0 (C4'H<sub>2</sub>); *m/z* (ES+) 229 [MH<sup>+</sup>, 100%]; HRMS (ES+): MH<sup>+</sup>, found 229.1334 [100%]. C<sub>14</sub>H<sub>17</sub>N<sub>2</sub>O requires 229.1335.

### 1.7. 10-Methoxy-3,4,6,7,8,12c-hexahydro-1H-[1,4]oxazino[4',3':1,2]pyridol[4,3-b]indole (**9b**)

The title compound **9b** was prepared in 39% yield on a 500  $\mu$ mol scale [along with recovered **7b** (30%)] using the general procedure. Compound **9b** was purified by crystallisation from PhH/petrol as an off-white solid. mp (PhH/Petrol) 156–158 °C;  $\nu_{\max}$  (solid) = 3800–2500 br, s, 2956 s, 2817 s, 2762 s, 1626 s, 1568 s, 1499 s, 1464 s cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (1H, s, NH), 7.31 (1H, d, *J* = 8.7, C4H), 6.80 (1H, d, *J* = 2.1, C7H), 6.73 (1H, dd, *J* = 8.7, 2.2, C5H), 4.62 (2H, dd, *J* = 10.9, 2.6, C10'H<sub>2</sub>), 3.96–3.91 (1H, m, C8'H<sub>A</sub>H<sub>B</sub>), 3.87–3.81 (1H, m, C8'H<sub>A</sub>H<sub>B</sub>), 3.81 (3H, s, OCH<sub>3</sub>), 3.62 (1H, dd, *J* = 10.2, 1.8, C9'H<sub>A</sub>H<sub>B</sub>), 3.51 (1H, t, *J* = 10.6, C9'H<sub>A</sub>H<sub>B</sub>), 3.17–3.09 (1H, m,

C4'H<sub>A</sub>H<sub>B</sub>), 3.03 (1H, dd, *J* = 11.1, 6.1, C5'H<sub>A</sub>H<sub>B</sub>), 2.81 (1H, dd, *J* = 10.1, 5.2, C7'H<sub>A</sub>H<sub>B</sub>), 2.78–2.70 (1H, m, C5' H<sub>A</sub>H<sub>B</sub>), 2.67–2.61 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD) δ 155.8 (C6), 137.1 (C8), 132.0 (C3'), 119.6 (C2), 119.4 (C4H), 109.0 (C5H), 107.3 (C3H), 95.1 (C7H), 70.5 (C10'H), 67.2 (C8'H<sub>2</sub>), 60.3 (C9'H<sub>2</sub>), 55.7 (OCH<sub>3</sub>), 54.6 (C7'H<sub>2</sub>), 51.7 (C5'H<sub>2</sub>), 23.9 (C4'H<sub>2</sub>); *m/z* (ES<sup>+</sup>) 259 [MH<sup>+</sup>, 100%]; HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 259.1445. C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> requires 259.1441.

#### 1.8. 2-Methyl-1,2,3,4,6,7,8,12c-octahydropyrazino[1',2':1,2]pyrido[4,3-b]indole (8c)

The title compound **8c** was prepared in 54% yield on a 400 μmol scale [along with recovered **6c** (24%)] using the general procedure. Compound **8c** was purified by crystallisation from PhH/petrol as an off-white solid. mp (PhH/Petrol) 182–184 °C; *v*<sub>max</sub> (solid) 3800–2500 br, m, 2937 m, 2793 m, 1905 w, 1868 w, 1655 m, 1619 m, 1492 m, 1452 s cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.06 (1H, s, NH), 7.53 (1H, d, *J* = 7.5, C4H), 7.25–7.28 (1H, m, C7H), 7.10 (1H, t, *J* = 7.3, C6H), 7.06 (1H, t, *J* = 7.1, C5H), 3.70 (1H, d, *J* = 10.3, C10'H), 3.64 (1H, d, *J* = 10.3, C9'H<sub>A</sub>H<sub>B</sub>), 3.05–3.12 (2H, m, C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>), 2.99–2.91 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 2.91–2.83 (1H, m, C8'H<sub>A</sub>H<sub>B</sub>), 2.82–2.60 (4H, m, C4'H<sub>A</sub>H<sub>B</sub>/C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>/C8'H<sub>A</sub>H<sub>B</sub>), 2.41 (3H, s, NCH<sub>3</sub>), 2.15 (1H, t, *J* = 10.3, C9'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 136.4 (C8), 133.1 (C3'), 125.5 (C2), 121.1 (C4H), 119.4 (C6H), 119.0 (C5H), 111.0 (C7H), 109.5 (C3), 59.7 (C10'H), 59.5 (C8'H<sub>2</sub>), 55.1 (C9'H<sub>2</sub>), 54.4 (C7'H<sub>2</sub>), 51.3 (C5'H<sub>2</sub>), 46.4 (NCH<sub>3</sub>), 24.2 (C4'H<sub>2</sub>); *m/z* (ES<sup>+</sup>) 242 [MH<sup>+</sup>, 100%]; HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 242.1658. C<sub>15</sub>H<sub>20</sub>N<sub>3</sub> requires 242.1652.

#### 1.9. 10-Methoxy-2-methyl-1,2,3,4,6,7,8,12c-octahydropyrazino[1',2':1,2]pyrido[4,3-b]indole (9c)

The title compound **9c** was prepared in 49% yield on a 523 μmol scale [along with recovered **7c** (22%)] using the general procedure. Compound **9c** was purified by crystallisation from PhH/petrol as an off-white solid. mp (PhH/Petrol) 145–147 °C; *v*<sub>max</sub> (solid) 3800–2500 br s, 2897 s, 1620 m, 1454 m cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.84 (1H, s, NH), 7.39 (1H, d, *J* = 8.6, C4H), 6.79 (1H, s, C7H), 6.73 (1H, d, *J* = 8.6, C5H), 3.80 (3H, s, OCH<sub>3</sub>), 3.64 (1H, d, *J* = 11.2, C10'H), 3.60 (1H, d, *J* = 10.5, C9'H<sub>A</sub>H<sub>B</sub>), 3.04–3.12 (2H, m, C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>), 2.96–2.90 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 2.89–2.84 (1H, m, C8'H<sub>A</sub>H<sub>B</sub>), 2.61–2.79 (4H, m, C4'H<sub>A</sub>H<sub>B</sub>/C5'H<sub>A</sub>H<sub>B</sub>/C7'H<sub>A</sub>H<sub>B</sub>/C8'H<sub>A</sub>H<sub>B</sub>), 2.40 (3H, s, NCH<sub>3</sub>), 2.13 (1H, t, *J* = 10.5, C9'H<sub>A</sub>H<sub>B</sub>); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD) δ 156.8 (C6), 138.8 (C8), 132.7 (C3'), 120.7 (C2), 119.8 (C4H), 109.4 (C5H), 108.3 (C3), 95.7 (C7H), 60.7 (C10'H), 59.8 (C8'H<sub>2</sub>), 55.9 (OCH<sub>3</sub>), 55.3 (C9'H<sub>2</sub>), 52.2 (C7'H<sub>2</sub>), 49.9 (C5'H<sub>2</sub>), 46.1 (NCH<sub>3</sub>), 24.5 (C4'H<sub>2</sub>); *m/z* (ES<sup>+</sup>): 272 [MH<sup>+</sup>, 100%]; HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 272.1762. C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O requires 272.1757.

#### 1.10. 2-Ethyl-1-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8d)

The title compound **8d** was prepared in 41% yield on a 462 μmol scale [along with recovered **6d** (23%)] using the general procedure. The mixture was purified by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] to give **8d** as a pale yellow oily solid. *v*<sub>max</sub> (liquid film) 3401 s, 3152 s, 3056 s, 2968 s, 2929 s, 2834 s, 1623 w, 1590 w, 1454 m, 1429 w, 1369 w, 1329 w cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.88 (1H, s, NH), 7.26 (1H, d, *J* = 7.9, C4H), 7.12–7.09 (1H, m, C7H), 7.11 (1H, t, *J* = 7.0, C6H), 7.07 (1H, t, *J* = 7.0, C5H), 4.12 (1H, q, *J* = 6.5, C10'H), 3.16 (1H, ddd, *J* = 12.6, 8.6, 4.4, C5'H<sub>A</sub>H<sub>B</sub>), 2.95–2.82 (2H, m, C5'H<sub>A</sub>H<sub>B</sub>/C4'H<sub>A</sub>H<sub>B</sub>), 2.73–2.66 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 2.64–2.57 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 2.73–2.66 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 1.43 (3H, d, *J* = 6.6, C9'H<sub>3</sub>), 1.19 (3H, t, *J* = 7.1, C8'H<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 136.1 (C8), 131.7 (C3'), 126.4 (C2), 121.2 (C6H),

119.3 (C5H), 118.2 (C4H), 113.6 (C7H), 110.8 (C3), 51.4 (C10'H), 47.2 (C7'H<sub>2</sub>), 44.0 (C5'H<sub>2</sub>), 22.0 (C4'H<sub>2</sub>), 17.9 (C9'H<sub>3</sub>), 13.2 (C8'H<sub>3</sub>); *m/z* (ES<sup>+</sup>) 215 [MH<sup>+</sup>, 100%], 158 (25%); HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 215.1549. C<sub>14</sub>H<sub>19</sub>N<sub>2</sub> requires 215.1543.

#### 1.11. 2-Ethyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (9d)

The title compound **9d** was prepared in 42% yield on a 292 μmol scale [along with recovered **7d** (23%)] using the general procedure. The mixture was purified by column chromatography [SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5:1)] to give **9d** as a pale brown oily solid. *v*<sub>max</sub>(solid) 3600–2500 br, s, 2926 s, 2851 s, 1738 m, 1624 s, 1457 s cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (1H, s, NH), 7.30 (1H, d, *J* = 8.5, C4H), 6.79 (1H, s, C7H), 6.74 (1H, d, *J* = 8.5, C5H), 4.14 (1H, q, *J* = 5.8, C10'H), 3.77 (3H, s, OCH<sub>3</sub>), 3.20–3.13 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 2.99–2.92 (1H, m, C4'H<sub>A</sub>H<sub>B</sub>), 2.90–2.77 (2H, m, C7'H<sub>A</sub>H<sub>B</sub>/C5'H<sub>A</sub>H<sub>B</sub>), 2.77–2.69 (1H, m, C7'H<sub>A</sub>H<sub>B</sub>), 2.67–2.59 (1H, m, C5'H<sub>A</sub>H<sub>B</sub>), 1.44 (3H, d, *J* = 6.4, C9'H<sub>3</sub>), 1.21 (3H, t, *J* = 7.0, C8'H<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 156.0 (C6), 136.9 (C8), 130.0 (C3'), 120.7 (C2), 118.6 (C4H), 108.7 (2C, C3/C5H), 95.2 (C7H), 55.9 (OCH<sub>3</sub>), 51.7 (C10'H), 47.1 (C7'H<sub>2</sub>), 44.0 (C4'H<sub>2</sub>), 21.8 (C5'H<sub>2</sub>), 18.0 (C9'H<sub>3</sub>), 12.8 (C8'H<sub>3</sub>); *m/z* (ES<sup>+</sup>) 245 [MH<sup>+</sup>, 100%], 188 (60%). HRMS (ES<sup>+</sup>): MH<sup>+</sup>, found 245.1651. C<sub>15</sub>H<sub>20</sub>N<sub>4</sub> requires 245.1648.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgment

We thank EPSRC (EP/F038321/1 and EP/F0376431/1) for funding.

#### Supplementary material

Supplementary material (experimental details for preparation of starting materials and copies of <sup>1</sup>H/<sup>13</sup>C NMR for compounds **2**, **3**, **6a-d**, **7a-d**, **8a-d** and **9a-d**) is available.

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