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# Synthetic approaches to pallimamine and analogues using direct imine acylation

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ABSTRACT

The use of Direct Imine Acylation (DIA) methodology for the total synthesis of pallimamine is described, with three different synthetic routes examined. The construction of three advanced δ-lactam precursors, all utilising DIA, is described, along with attempts to progress these compounds further, using three distinct desymmetrisation strategies, two involving alcohol-aryl coupling, and a third involving an unusual diastereoselective lactonisation.



## 1. Introduction

Protoberberine alkaloid (±)-pallimamine **1** was isolated in 1989 from *Corrydalis pallida var sparsimamma* collected in Nan-Shan village, Taiwan, along with other known protoberberine alkaloids α-allocryptopine **2**, protopine **3** and (−)-capaurimine **4** (Fig. 1).[1] A large number of diversely functionalised protoberberines[2] have been discovered over a number of years, with the family typified by the *bis*-isoquinoline motif highlighted below in red. Many protoberberines exhibit biological activity,[3] which has helped to propagate significant research efforts towards their synthesis.[4]

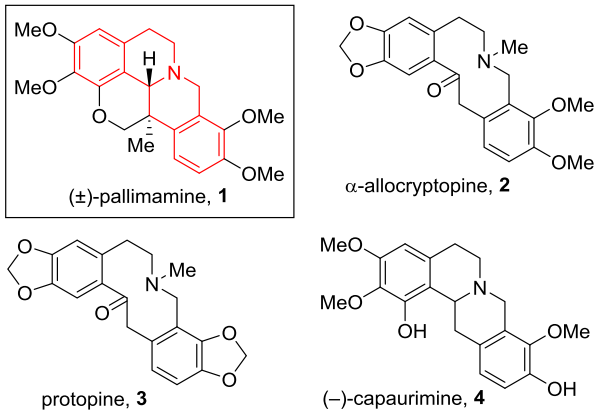


**Fig. 1.** Berberine alkaloids **1**–**4**.

To the best of our knowledge, the pentacyclic structure of pallimamine **1** with its additional tetrahydropyran ring is a unique feature amongst protoberberine alkaloids and it has not been synthesised previously. In view of these factors, as well as a long-standing interest in the application of telescoped/tandem synthetic methodology in target synthesis,[5] we were encouraged to embark upon its total synthesis. Our basic retrosynthetic analysis is shown in Fig. 2. We were confident that our recently established 'Direct Imine Acylation' (DIA) methodology[6] would facilitate the coupling of a comparatively simple imine **5** and benzoic acid derivative **6** to construct the key δ-lactam[7] ring system **7**; the viability of DIA to construct C–C bonds has been demonstrated previously in our group,[6a,6d–g] including an example in a related natural product synthesis.[6d] Following reduction (**7**→**8**) it was then planned to exploit the symmetry of the resulting diol **8** to construct the tetrahydropyran ring via a C–O coupling reaction, resulting in the desymmetrisation of the diastereotopic alcohol groups. It was expected that C–O bond formation would occur selectively via the pseudo-equatorial alcohol, rather than the alternative pseudo-axial alcohol, to form a product with the *trans*-fused ring junction required in the natural product. While we had no evidence to support this prediction when starting this work, intuitively we felt that the *trans*-fused product (and the associated transition state for its

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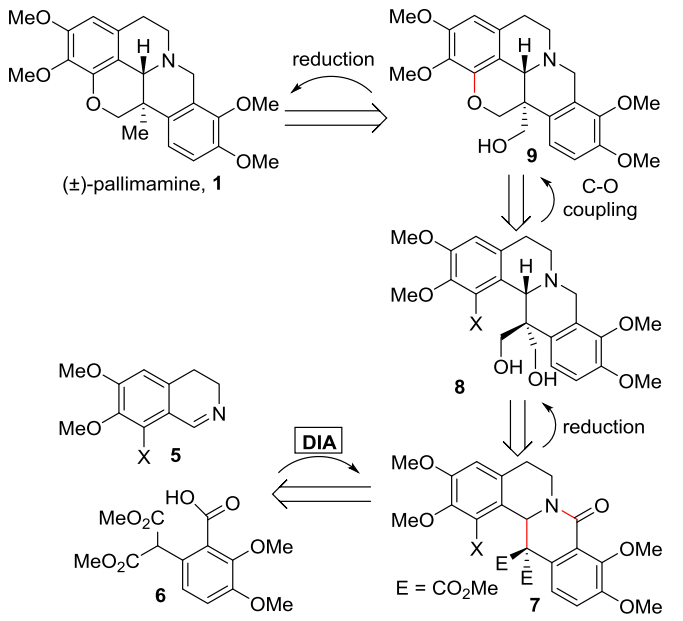
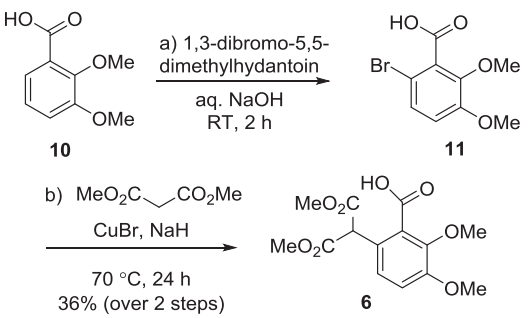



**Fig. 2.** Retrosynthetic strategy.

formation) would be more thermodynamically stable than the *cis*-variant and therefore form more easily. Indeed, it is plausible that similar thermodynamic factors are at play during its biosynthesis, giving rise to the observed *trans*-configuration in the natural product; the fact that pallimamine was isolated in racemic form offers minor supporting evidence for this hypothesis, as this suggests that its biosynthesis may proceed via an intermediate that has undergone reversible epimerisation. This paper details our efforts to date to apply the strategy outlined in Fig. 2 to the total synthesis of pallimamine.

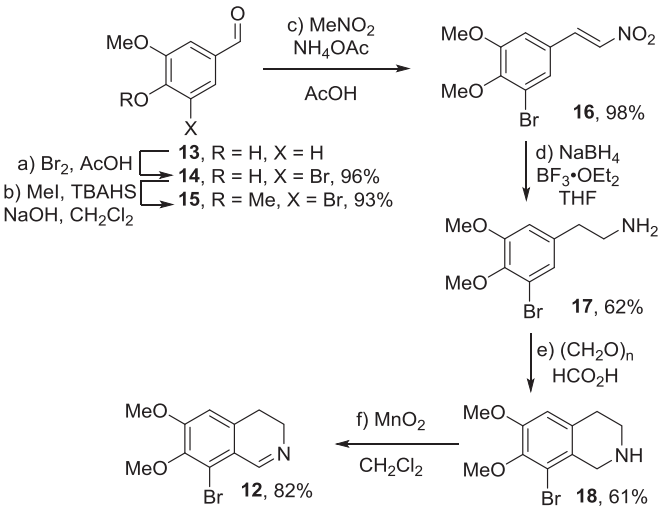
## 2. Results and discussion

The novel benzoic acid derivative **6** was prepared via a straightforward two-step protocol; commercially available 2,3-dimethoxybenzoic acid **10** was first reacted with 1,3-dibromo-5,5-dimethylhydantoin to form bromide **11** which was then converted into diester **6** via a modified Hurtley reaction (Scheme 1).[8] The overall yield for the two-step conversion of compound **10** into product **6** was relatively low (36%) but was easily performed on a large scale (7 g of **6** formed), providing ample quantities of material with which the perform the subsequent syntheses.[9]



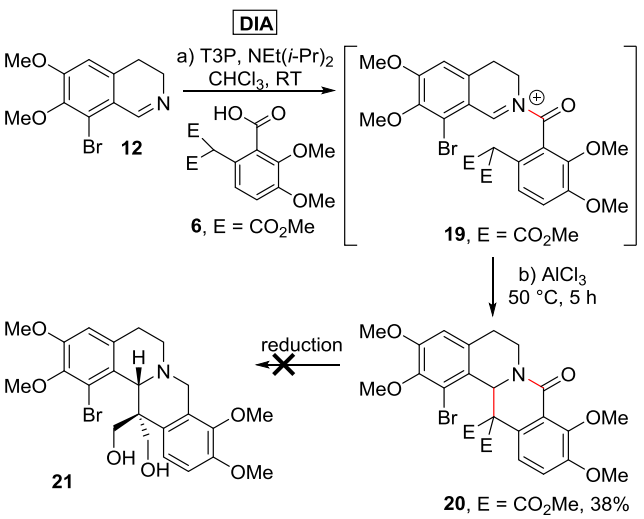

**Scheme 1.** Synthesis of benzoic acid derivative **6**.

Next, attention turned to the synthesis of brominated imine **12**; this substrate was chosen as the bromo-substituent was thought to be a useful synthetic handle with which to install the tetrahydropyran ring later in the synthesis. First, vanillin **13** was converted into amine **17** by a sequence of known procedures (bromination, alkylation, Henry reaction and reduction),[10] and was then reacted with paraformaldehyde and formic acid in a Pictet–Spengler reaction to form tetrahydroisoquinoline **18** in good overall yield. Finally, the synthesis was completed by oxidation using manganese(IV) oxide to furnish imine **12** (Scheme 2).




**Scheme 2.** Synthesis of imine **12**. TBAHS = tetrabutylammonium hydrogen sulfate.

The DIA coupling of imine **12** and acid **6** was performed by stirring both components in chloroform at rt with NEt(*i*-Pr)$_2$ and propylphosphonic acid anhydride (T3P), which led to in situ activation of the carboxylic acid and nucleophilic attack by the imine to form intermediate *N*-acyliminium ion **19** (Scheme 3). In line with the majority of the previous DIA reactions reported by our group involving C–C bond formation, it was necessary to add a Lewis acid into the reaction mixture and increase the temperature, in this case $AlCl_3$ at 50 °C, in order to promote the ring-closing step. Using this one-pot telescoped procedure, lactam **20** was isolated in 38% unoptimised yield from imine **12**. It was then planned to reduce the ester and amide groups to form diol **21**, with a view towards forming the key tetrahydropyran ring via a palladium-catalysed C–O coupling reaction, as described above (i.e., **21** → **9**, see Fig. 2).




**Scheme 3.** Synthesis of lactam **20**.

However, repeated attempts to reduce lactam **20** were unsuccessful[11] leading either to no reaction, or complex product mixtures.

The potential for the aryl bromide moiety in compound **20** to undergo unwanted reduction was postulated to be a factor in our failure to form diol **21**, and in view of this, an alternative synthetic strategy was devised in which this bromo-group is not required. It was planned instead to synthesise triol **22**, using a similar strategy to that described earlier, before constructing the tetrahydropyran ring using an oxidative coupling process,[12] as outlined in Fig. 3.

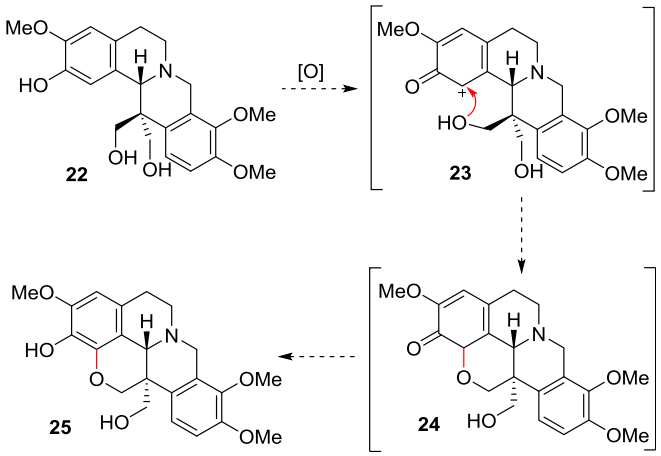
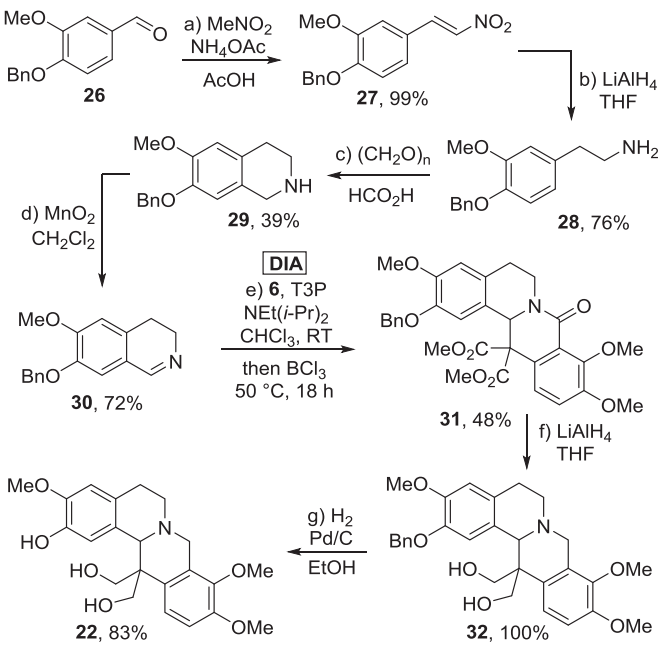


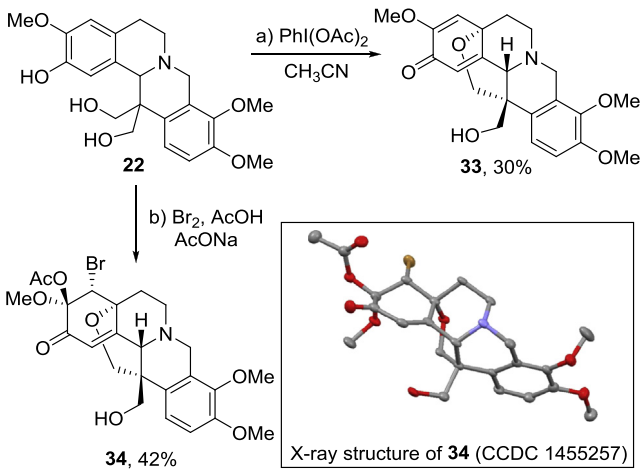

**Fig. 3.** Planned synthesis of tetrahydropyran **25**.

The synthesis of triol **22** was completed in seven steps from vanillin derivative **26**. First, based on literature precedent,[13] sequential Henry condensation, reduction, Pictet–Spengler and oxidation reactions delivered the key imine coupling partner **30**. This imine was then coupled with carboxylic acid **6** via the same DIA procedure used to synthesise lactam **20**, but with $BCl_3$ being used rather than $AlCl_3$ to promote the ring-closure. This delivered lactam **31** in reasonable overall yield, and it was then converted into the requisite triol **22** via successive reduction with $LiAlH_4$ and hydrogenolysis (Scheme 4).




**Scheme 4.** Synthesis of triol **22**.

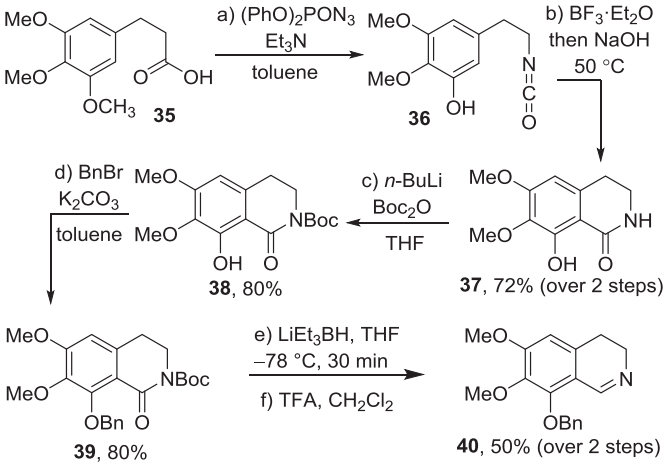
As mentioned above, it was next planned to convert triol **22** into tetrahydropyran **25** using the oxidative coupling strategy outlined in Fig. 3. First, triol **22** was treated with $PhI(OAc)_2$ in acetonitrile at rt. Encouragingly, these conditions did indeed promote oxidation and cyclisation, but unfortunately the cyclisation took place at the *para*-position of the phenol ring, furnishing the unusual bridged polycyclic compound **33**.[14] Alternative oxidative coupling conditions were therefore examined, but the use of bromine in acetic acid also led to oxidation and cyclisation onto the undesired *para*-position, along with concomitant acetate and bromide addition, furnishing bridged polycyclic **34** as a single diastereoisomer, with its structure confirmed by X-ray crystallography (see Scheme 5).[15]




**Scheme 5.** Synthesis of bridged polycyclic compounds **33** and **34**.

This strategy was ultimately unsuccessful as a route to generate pallimamine, due to the apparent bias for cyclisation into the phenol *para*-position. Nonetheless, both oxidative coupling processes are certainly interesting, especially as both products were isolated as single diastereoisomers.

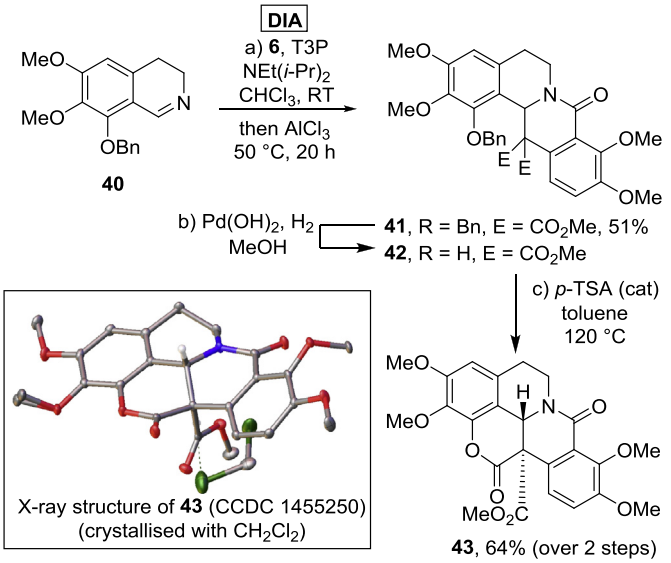
Attention then switched to a third synthetic strategy, in which it was planned to perform the final ring-closure via a lactonisation reaction. For this route, an imine with a protected oxygen substituent was required, prompting us to synthesise imine **40** in five steps. First, lactam **37** was formed in good yield from carboxylic acid **35** using Canniago's published method[16] and this was then converted into compound **39** by the sequential installation of Boc




**Scheme 6.** Synthesis of imine **40**.

and benzyl protecting groups. The synthesis of imine **40** was then completed following partial reduction of the lactam carbonyl with Super-Hydride™ and treatment with TFA, as has been demonstrated for the synthesis of related imines in our earlier work (Scheme 6).[6a]

The DIA reaction of imine **40** with acid **6** proceeded well, furnishing lactam **41** in 51% unoptimised yield, with $AlCl_3$ used as an additive in this case. Subsequent cleavage of the benzyl protecting group via hydrogenolysis revealed phenol **42**, which was then heated at reflux in toluene with catalytic *p*-TSA, furnishing lactone **43** in good yield over the two step sequence. Crucially, lactone **43** was formed as a single diastereoisomer, validating our earlier proposed desymmetrisation strategy. The product was found to possess the correct relative stereochemistry required in pallimamine, with this structural assignment confirmed by X-ray crystallographic data as shown (see Scheme 7).[15]




**Scheme 7.** Synthesis of lactone **43**.

## 3. Conclusion

Preliminary studies indicated that the reduction of pentacyclic pallimamine analogue **43** is not straightforward and the total synthesis of pallimamine **1** has therefore not yet been completed. Nonetheless, three contrasting synthetic strategies have been developed to form advanced intermediates **20**, **31** and **41**, with each utilising a direct imine acylation reaction as a key step. Lactam **41** was progressed further to give lactone **43** as a single diastereoisomer, a compound in which the complete pallimamine skeleton has been installed. In future work, we will examine a range of reduction/protection strategies to complete the synthesis of pallimamine **1** from advanced pentacyclic precursors related to **43**.

## 4. Experimental section

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous dichloromethane and toluene were obtained from an Innovative Technology Pure Solv solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. Flash column chromatography was carried out using slurry packed silica gel ($SiO_2$), 35–70 μm, 60 Å, under light positive pressure eluting with the specified solvent system. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 $F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Jeol ECX-400 NMR or Jeol ECS400 spectrometer operating 400 MHz and 100 MHz, respectively, or on a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz, respectively. All spectra were acquired at 295 K. Chemical shifts ($\delta$) are quoted in parts per million (ppm). The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad or combinations of these. The residual solvent peaks, $\delta_H$ 7.26 and $\delta_C$ 77.0 for $CDCl_3$ were used as references. Infrared spectra (IR) were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either $CH_2Cl_2$ or $CDCl_3$. High Resolution Mass Spectra (HRMS) were obtained by University of York Mass spectrometer Service, using ionisation (ESI) on a Bruker Daltonics, MicrOTOF spectrometer. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected.

### 4.1. 6-Bromo-2,3-dimethoxybenzoic acid (11)

In an ice bath, 2,3-dimethoxybenzoic acid **10** (10.0 g, 54.9 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (8.63 g, 30.2 mmol) were added to 0.7 M aq NaOH (86 mL). The reaction mixture was stirred at rt for 1 h, then 1 M aq HCl (150 mL) was added and the aqueous layer was extracted with ethyl acetate (3×200 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give compound **10** as a solid (14.3 g, quantitative), which was used without further purification in the next step; $\delta_H$ (400 MHz, $CDCl_3$) 11.46 (1H, br s), 7.21 (1H, d, $J$=8.9 Hz), 6.81 (1H, d, $J$=8.9 Hz), 3.88 (3H, s), 3.82 (3H, s); HRMS (ESI$^+$) 282.9575 [M+Na]$^+$, $C_9H_9^{79}BrNaO_4$ requires 282.9576 (0.6 ppm error). The obtained data were in accord with those reported in the literature.[17]

### 4.2. 6-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)-2,3-dimethoxybenzoic acid (6)

Sodium hydride (6.16 g, 165 mmol, 60% in mineral oil) was added portionwise to a rapidly stirred cold suspension (0 °C) of 6-bromo-2,3-dimethoxybenzoic acid **11** (18.0 g, 68.8 mmol), copper(I) bromide (987 mg, 6.88 mmol) and dimethyl malonate (240 mL) [note: a solid crust formed on top of the reaction during the addition of sodium hydride]. After the addition of the sodium hydride was complete, the mixture was stirred for 10 min at rt and then for 20 h at 70 °C. The resulting suspension was then quenched with water (800 mL), washed with ether (3×1500 mL) and then acidified with 10% hydrochloric acid. The acidic aqueous residues were then extracted with ethyl acetate (3×1000 mL) and the organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 2:1→1:1 petrol:ethyl acetate→ethyl acetate) afforded compound **6** as a white solid (7.74 g, 36%); $R_f$ 0.47 ($CH_2Cl_2$/MeOH, 50:1); mp 104–108 °C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3223, 2955, 1735, 1581, 1494, 1438, 1264, 1150, 1055; $\delta_H$ (400 MHz, $CDCl_3$) 7.22 (1H, d, $J$=8.7 Hz), 7.08 (1H, d, $J$=8.7 Hz), 5.36 (1H, s), 3.99 (3H, s), 3.91 (3H, s), 3.78 (6H, s); $\delta_C$ (100 MHz, $CDCl_3$) 169.0, 167.3, 152.3, 147.6, 126.5, 125.5, 124.8, 115.2, 62.2, 56.0, 54.2, 52.9; HRMS (ESI$^+$) 335.0728 [M+Na]$^+$, $C_{14}H_{16}NaO_8$ requires 335.0737.

### 4.3. 6,7-Dimethoxy-8-bromo-1,2,3,4-tetrahydroisoquinoline (18)

A solution of 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine **17**[10] (498 mg, 1.91 mmol) and paraformaldehyde (58 mg, 1.91 mmol) in formic acid (1 mL) was heated to 50 °C for 15 h. After this time, the solvent was removed in vacuo, and 1 M aq NaOH was

added (10 mL). The aqueous solution was extracted with dichloromethane (3×10 mL), and the combined organic layers dried ($Na_2SO_4$), concentrated in vacuo and purified by flash chromatography ($SiO_2$, ethyl acetate→5% MeOH/ethyl acetate) to afford the *title compound* as an off-white solid (317 mg, 61%). Mp 62–64 °C; $R_f$ 0.12 ($CH_2Cl_2$/MeOH, 9:1); $\nu_{max}$ (thin film)/cm$^{-1}$ 3336, 2934, 2831, 1598, 1563, 1484, 1429, 1325, 1304, 1261, 1110, 1035, 1003, 806; $\delta_H$ (400 MHz, $CDCl_3$) 6.60 (s, 1H), 3.90 (s, 2H), 3.83 (s, 3H). 3.81 (s, 3H), 3.05 (t, *J*=5.9 Hz, 2H), 2.72 (t, *J*=5.9 Hz, 2H), 2.10 (br s, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 151.6, 144.6, 132.3, 127.7, 118.1, 112.4, 60.6, 56.2, 48.8, 43.3, 29.4; MS (ESI$^+$) *m*/*z* (rel %) 272 ([M+H]$^+$, 100), 286 ([M+Na]$^+$, 20); HRMS (ESI$^+$) 272.0269 [M+H]$^+$, $C_{11}H_{15}BrNO_2$ requires 272.0291.

### 4.4. 6,7-Dimethoxy-8-bromo-3,4-dihydroisoquinoline (12)

Amine **18** (285 mg, 1.05 mmol) was dissolved in dichloromethane (10.5 mL) and $MnO_2$ (1.82 g, 20.9 mmol) was added. The resulting suspension was stirred for 16 h at rt, before being filtered through a short pad of Celite and concentrated in vacuo, affording the *title compound* **12** as a pale brown solid which was used without further purification (283 mg, 84%). Mp 95–96 °C (lit.[12] 102 °C); $R_f$ 0.44 ($CH_2Cl_2$/MeOH, 9:1); $\nu_{max}$ (thin film)/cm$^{-1}$ 2938, 1616, 1593, 1551, 1484, 1404, 1309, 1278, 1222, 1118, 1032, 1011, 989, 813, 611; $\delta_H$ (400 MHz, $CDCl_3$) 8.59 (s, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.72–3.66 (m, 2H), 2.68–2.61 (m, 2H); $\delta_C$ (100 MHz, $CDCl_3$) 158.6, 155.5, 145.3, 135.5, 120.5, 119.4, 110.5, 60.8, 56.3, 46.8, 25.6; MS (ESI$^+$) *m*/*z* (rel %) 270 ([M+H]$^+$, 100), 299 ([M+Na]$^+$, 10); HRMS (ESI$^+$) 270.0134 [M+H]$^+$, $C_{11}H_{13}^{79}BrNO_2$ requires 270.0124.

### 4.5. Dimethyl 12-bromo-3,4,10,11-tetramethoxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (20)

Imine **12** (225 mg, 0.83 mmol) and carboxylic acid **6** (390 mg, 1.25 mmol) were dissolved in $CHCl_3$ (12 mL), and *N*,*N*-diisopropylethylamine (198 mg, 1.53 mmol) was added, followed by T3P (50% in THF, 796 mg, 1.25 mmol). The resulting solution was stirred at room temperature for 40 min before the addition of $AlCl_3$ (221 mg, 1.66 mmol), and heating to 50 °C for 5 h. After this time, the mixture was poured onto a rapidly stirring mixture of satd aq Rochelle's salt and $Et_2O$ (1:1, 80 mL) and stirred for 1 h. The aqueous layer was extracted with $Et_2O$ (3×40 mL), and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by successive flash chromatography ($SiO_2$, 1→2% MeOH/$CH_2Cl_2$), affording the *title compound* **20** as a colourless oil (178.7 mg, 38%). $R_f$ 0.42 (ethyl acetate); $\nu_{max}$ (thin film)/cm$^{-1}$ 2943, 1736, 1658, 1595, 1484, 1451, 1425, 1395, 1311, 1272, 1258, 1119, 1031, 941, 812, 772, 733; $\delta_H$ (400 MHz, $CDCl_3$) 7.25 (d, *J*=8.6 Hz, 1H), 7.07 (d, *J*=8.6 Hz, 1H), 6.76 (s, 1H), 5.90 (s, 1H), 4.89 (ddd, *J*=12.7, 5.0, 1.5 Hz, 1H), 4.04 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.67–3.61 (m, 1H), 3.54 (s, 3H), 2.81 (td, *J*=12.7, 3.3 Hz, 1H), 2.64–2.56 (m, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 168.1, 166.9, 162.5, 153.7, 152.9, 149.9, 144.4, 138.8, 129.7, 125.2, 124.0, 123.2, 120.9, 114.9, 111.6, 64.5, 61.8, 60.5, 60.4, 56.2, 56.0, 53.4, 53.0, 39.3, 30.3; MS (ESI$^+$) *m*/*z* (rel %) 564 ([M+H]$^+$, 10), 586 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 586.0674 [M+Na]$^+$, $C_{25}H_{26}^{79}BrNNaO_9$ requires 586.0683.

### 4.6. 1-(Benzyloxy)-2-methoxy-4-[(*E*)-2-nitroethenyl]benzene (27)

4-Benzyloxy-3-methoxybenzaldehyde **26** (1.00 g, 4.13 mmol) was dissolved in AcOH (5 mL), and $NH_4OAc$ (477 mg, 6.20 mmol) and $MeNO_2$ (756 mg, 12.4 mmol) were added successively. The resulting mixture was heated to 90 °C for 19 h. After this time, the reaction mixture was cooled to rt, quenched with $H_2O$ (20 mL) and filtered. The filtrate was extracted with ethyl acetate (3×20 mL), and the organic extracts combined with the filtrant, dried ($MgSO_4$) and concentrated in vacuo to afford the *title compound* **27** which was used without further purification (1.17 g, 99%). Mp 119–120 °C (lit.[13a] 119–121 °C); $\delta_H$ (400 MHz, $CDCl_3$) 7.95 (d, *J*=13.6 Hz, 1H), 7.51 (d, *J*=13.6 Hz, 1H), 7.45–7.30 (m, 5H), 7.10 (dd, *J*=8.3, 2.0 Hz, 1H), 7.02 (d, *J*=2.0 Hz, 1H), 6.92 (d, *J*=8.3 Hz, 1H), 5.22 (s, 2H), 3.93 (s, 3H $\delta_C$ (100 MHz, $CDCl_3$) 152.0, 150.1, 139.4, 136.2, 135.4, 128.9, 128.3, 127.3, 124.5, 123.2, 113.5, 110.9, 71.0, 56.2.

### 4.7. 2-[4-(Benzyloxy)-3-methoxyphenyl]ethan-1-amine (28)

A solution of nitrostyrene **27** (5.00 g, 17.5 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.00 g, 52.5 mmol) in dry THF (60 mL) at 0 °C. After complete addition, the reaction mixture was heated 70 °C for 2 h, before being cooled to 0 °C and quenched by addition of ethyl acetate (50 mL) followed by $H_2O$ until evolution of gas ceased. $Na_2SO_4$ was added and the mixture stirred for 30 min before being filtered and concentrated in vacuo. The residue was taken up in 1 M aq HCl (100 mL), washed with $Et_2O$ (2×100 mL), basified to pH 10 with 1 M NaOH and extracted with $Et_2O$ (3×100 mL). the combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuo to afford the *title compound* **28** as an off-white solid which was used without further purification (3.43 g, 76%). Mp 59–61 °C (lit.[13a] 63–65 °C); $\delta_H$ (400 MHz, $CDCl_3$) 7.47–7.40 (m, 2H), 7.39–7.33 (m, 2H), 7.32–7.27 (m, 1H), 6.81 (d, *J*=8.1 Hz, 1H), 6.74 (d, *J*=1.9 Hz, 1H), 6.67 (dd, *J*=8.1, 1.9 Hz, 1H), 5.13 (s, 2H), 3.88 (s, 3H), 2.93 (t, *J*=6.8 Hz, 2H), 2.68 (t, *J*=6.8 Hz, 2H); $\delta_C$ (100 MHz, $CDCl_3$) 149.7, 146.7, 137.5, 133.2, 128.7, 127.9, 127.4, 120.9, 114.3, 112.7, 71.3, 56.1, 43.7, 39.7; MS (ESI$^+$) *m*/*z* (rel %) 241 ([M−NH$_2$]$^+$, 95), 258 ([M+H]$^+$, 90), 280 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 258.1492 [M+H]$^+$, $C_{16}H_{20}NO_2$ requires 258.1489.

### 4.8. 6-Methoxy-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (29)

Amine **28** (3.34 g, 13.0 mmol) and paraformaldehyde (390 mg, 13.0 mmol) were dissolved in formic acid (6.5 mL) and heated to 50 °C for 17 h. After this time, 1 M aq NaOH (100 mL) was added and the aqueous solution extracted with $CH_2Cl_2$ (3×100 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The crude residue was purified by flash chromatography ($SiO_2$, 5→10% MeOH/$CH_2Cl_2$) to afford the *title compound* **29** as a brown solid (1.38 g, 39%). Mp 71–73 °C ($CHCl_3$) (lit.[13b] 124–126 °C); $R_f$ 0.07 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 7.45–7.41 (m, 2H) 7.38–7.33 (m, 2H), 7.32–7.27 (m, 1H), 6.60 (s, 1H), 6.53 (s, 1H), 5.10 (s, 2H), 3.88 (s, 2H), 3.85 (s, 3H), 3.11 (t, *J*=6.0 Hz, 2H), 2.72 (t, *J*=6.0 Hz, 2H), 1.92 (br s, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 148.3, 146.6, 137.4, 128.7, 127.9, 127.6, 127.4, 127.3, 112.7, 112.1, 71.3, 56.2, 47.9, 44.0, 28.7; MS (ESI$^+$) *m*/*z* (rel %) 270 ([M+H]$^+$, 100); HRMS (ESI$^+$) 270.1482 [M+H]$^+$, $C_{17}H_{20}NO_2$ requires 270.1489.

### 4.9. 6-Methoxy-7-(benzyloxy)-3,4-dihydroisoquinoline (30)

Amine **29** (1.38 g, 5.12 mmol) was dissolved in dichloromethane (50 mL) and $MnO_2$ (8.90 g, 103 mmol) was added. The resulting suspension was stirred for 16 h at rt, before being filtered through a short pad of Celite and concentrated in vacuo, affording the *title compound* **30** as a pale brown solid which was used without further purification (980 mg, 72%). Mp 93–94 °C ($CHCl_3$) (lit.[13c] 101–101.5 °C); $R_f$ 0.11 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 8.15 (t, *J*=2.0 Hz, 1H), 7.44 (d, *J*=7.3 Hz, 2H), 7.42–7.35 (m, 2H), 7.34–7.29 (m, 1H), 6.82 (s, 1H), 6.69 (s, 1H), 5.15 (s, 2H), 3.92 (s, 3H), 3.71 (ddd, *J*=8.2, 6.5, 2.2 Hz, 2H), 2.70–2.64 (m, 2H); $\delta_C$ (100 MHz, $CDCl_3$) 159.8, 152.1, 147.0, 137.0, 130.6, 128.8, 128.1, 127.5, 121.6, 113.4, 110.9,

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71.5, 56.2, 47.4, 25.0; MS ($ESI^+$) *m*/*z* (rel %) 268 ($[M+H]^+$, 100); HRMS ($ESI^+$) 268.1332 $[M+H]^+$, $C_{17}H_{18}NO_2$ requires 268.1332.

### 4.10. Dimethyl 3,4,10-trimethoxy-11-(benzyloxy)-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (31)

Imine **30** (48.5 mg, 0.180 mmol) and carboxylic acid **6** (85 mg, 0.270 mmol) were dissolved in $CHCl_3$ (2.5 mL) and *N*,*N*-diisopropylethylamine (43 mg, 0.33 mmol) and T3P (50% in THF, 172 mg, 0.270 mmol) were added successively. The resulting solution was stirred at rt for 40 min before the addition of $BCl_3$ (1 M in $CH_2Cl_2$, 0.36 mL, 0.36 mmol), and heated to 50 °C for 4 h. After this time, the reaction was quenched with $NaHCO_3$ (10 mL), and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude residue by flash chromatography ($SiO_2$, 50%→60%, ethyl acetate/hexane) afforded the *title compound* **31** as a yellow oil (49 mg, 48%). $R_f$ 0.48 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2941, 1733, 1656, 1515, 1487, 1453, 1422, 1311, 1250, 1228, 1120, 1019, 912, 732; $\delta_H$ (400 MHz, $CDCl_3$) 7.45–7.40 (m, 2H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 1H), 7.04 (d, *J*=8.6 Hz, 1H), 6.87 (s, 1H), 6.77 (d, *J*=8.6 Hz, 1H), 6.72 (s, 1H), 5.48 (s, 1H), 5.08 (d, *J*=12.2 Hz, 1H), 5.02 (d, *J*=12.2 Hz, 1H), 4.95–4.89 (m, 1H), 4.03 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.54 (s, 3H), 2.92–2.84 (m, 2H), 2.72–2.64 (m, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 170.2, 167.4, 162.4, 154.0, 150.1, 149.3, 146.5, 137.2, 132.5, 130.7, 128.7, 128.0, 127.6, 123.4, 123.3, 122.4, 115.2, 114.1, 111.7, 71.6, 66.5, 61.8, 60.9, 56.2, 56.0, 53.1, 53.0, 39.1, 29.2; MS ($ESI^+$) *m*/*z* (rel %) 562 ($[M+H]^+$, 10), 584 ($[M+Na]^+$, 100); HRMS ($ESI^+$) 584.1874 $[M+Na]^+$, $C_{31}H_{31}NNaO_9$ requires 584.1891.

### 4.11. 13,13-Bis(hydroxymethyl)-3,4,10-trimethoxy-11-(benzyloxy)-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (32)

Lithium aluminium hydride (31.0 mg, 0.817 mmol) was added to a solution of diester **31** (91.5 mg, 0.16 mmol) in dry THF (4 mL) at 0 °C. The cooling was removed after 5 min, and the reaction mixture allowed to stir for 6 h at rt before being quenched by successive addition of ethyl acetate, $H_2O$ and $Na_2SO_4$. The mixture was stirred for 30 min, filtered and evaporated to afford the *title compound* **32** as a brown oil which was used without further purification (78.6 mg, 100%). $R_f$ 0.38 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 3337, 2935, 2836, 1730, 1608, 1515, 1496, 1454, 1330, 1257, 1282, 1227, 1098, 1022, 995, 911, 805, 733; $\delta_H$ (400 MHz, $CDCl_3$) 7.44 (d, *J*=7.0 Hz, 2H), 7.38–7.32 (m, 2H), 7.32–7.27 (m, 1H), 7.13 (d, *J*=8.7 Hz, 1H), 6.92 (s, 1H), 6.90 (d, *J*=8.7 Hz, 1H), 6.68 (s, 1H), 5.24 (d, *J*=13.1 Hz, 1H), 5.12 (d, *J*=13.1 Hz, 1H), 4.17 (s, 1H), 4.13 (d, *J*=15.8 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 3.71 (d, *J*=12.2 Hz, 1H), 3.66 (d, *J*=15.5 Hz, 1H), 3.32–3.20 (m, 2H), 3.18 (d, *J*=10.1 Hz, 1H), 3.16–3.10 (m, 1H), 3.04 (dd, *J*=10.1, 1.7 Hz, 1H) 2.63–2.54 (m, 2H); $\delta_C$ (100 MHz, $CDCl_3$) 150.5, 148.3, 145.7, 145.1, 137.7, 131.8, 131.2, 131.0, 128.6, 127.9, 127.3, 124.7, 120.8, 115.1, 112.0, 111.8, 71.0, 67.3, 64.6, 63.1, 60.2, 56.1, 55.9, 54.8, 51.0, 49.0, 30.5; MS ($ESI^+$) *m*/*z* (rel %) 492 ($[M+H]^+$, 100); HRMS ($ESI^+$) 492.2367 $[M+H]^+$, $C_{29}H_{34}NO_6$ requires 492.2381.

### 4.12. 13,13-Bis(hydroxymethyl)-11-hydroxy-3,4,10-trimethoxy-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene (22)

Diol **32** (73.6 mg, 0.150 mmol) was dissolved in ethyl acetate (5 mL), Pd/C (15 mg, 10 wt. %) was added, and the reaction mixture placed under an atmosphere of hydrogen. The reaction was stirred for 20 h, before being filtered through a short plug of Celite™ and evaporated. The crude residue was then re-suspended in EtOH (5 mL), Pd/C (15 mg) was added, the reaction mixture placed under an atmosphere of hydrogen and stirred for another 5 h before being filtered through a short plug of Celite™ and evaporated to afford the *title compound* **22** as a colourless oil (53.5 mg, 83%). $\nu_{max}$ (thin film)/$cm^{-1}$ 3275, 2938, 1719, 1677, 1610, 1517, 1497, 1454, 1283, 1231, 1090, 1004, 815; $\delta_H$ (400 MHz, $CD_3OD$) 8.42 (s, 1H), 7.35 (d, *J*=8.7 Hz, 1H), 7.13 (d, *J*=8.7 Hz, 1H), 7.04 (s, 1H), 6.83 (s, 1H), 4.84 (s, 1H), 4.51 (d, *J*=15.3 Hz, 1H), 4.18 (d, *J*=15.3 Hz, 1H), 4.06 (d, *J*=11.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 6H), 3.81 (d, *J*=11.9 Hz, 1H), 3.58 (d, *J*=11.0 Hz, 1H), 3.41 (d, *J*=9.1 Hz, 1H), 3.29–3.21 (m, 2H), 3.05 (td, *J*=11.6, 2.3 Hz, 1H), 2.80 (d, *J*=16.1 Hz, 1H); $\delta_C$ (100 MHz, $CD_3OD$) 150.7, 147.2, 144.9, 144.6, 130.0, 127.3, 127.2, 122.1, 122.0, 114.8, 112.8, 111.6, 65.7, 65.2, 62.4, 59.4, 55.0, 55.0, 53.4, 50.9, 49.0, 27.8; MS ($ESI^+$) *m*/*z* (rel %) 402 ($[M+H]^+$, 100); HRMS ($ESI^+$) 402.1897 $[M+H]^+$, $C_{22}H_{28}NO_6$ requires 402.1911.

### 4.13. 4-(Hydroxymethyl)-8,9,17-trimethoxy-2-oxa-12-azapentacyclo[10.6.2.0$^{1,14}$.0$^{4,13}$.0$^{5,10}$]icosa-5,7,9,14,17-pentaen-16-one (33)

Phenol **22** (43.4 mg, 0.108 mmol) was dissolved in MeCN (5 mL) and diacetoxyiodobenzene (41.7 mg, 0.129 mmol) was added in one portion. The resulting solution was stirred for 1 h, before being quenched with $NaHCO_3$ (20 mL). The aqueous solution was extracted with ethyl acetate (3×20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude residue by flash chromatography ($SiO_2$, MeOH/$CH_2Cl_2$, 25:1) afforded the *title compound* **33** as a yellow oil (13.1 mg, 30%). $R_f$ 0.43 ($CH_2Cl_2$/MeOH, 9:1); $\nu_{max}$ (thin film)/$cm^{-1}$ 3356, 2928, 2855, 1681, 1656, 1626, 1493, 1454, 1273, 1209, 1175, 1063, 1020, 732; $\delta_H$ (400 MHz, $CDCl_3$) 7.06 (d, *J*=8.6 Hz, 1H), 6.92 (d, *J*=8.6 Hz, 1H), 6.41 (s, 1H), 5.68 (s, 1H), 4.22 (d, *J*=16.6 Hz, 1H), 4.17 (s, 1H), 4.03 (d, *J*=12.1 Hz, 1H), 3.92 (d, *J*=16.6 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.41 (d, *J*=11.0 Hz, 1H), 3.37–3.32 (m, 2H), 3.03 (td, *J*=11.7, 3.9 Hz, 1H), 2.61 (dd, *J*=11.7, 5.1 Hz, 1H), 2.12 (dd, *J*=13.0, 3.4, 1H), 1.65 (td, *J*=13.0, 5.4 Hz, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 181.2, 158.3, 151.4, 151.2, 146.6, 129.5, 128.7, 124.4, 122.0, 116.7, 111.5, 71.8, 70.5, 67.9, 61.2, 60.8, 55.8, 55.3, 48.8, 45.2, 43.3, 39.6; MS ($ESI^+$) *m*/*z* (rel %) 400 ($[M+H]^+$, 100); HRMS ($ESI^+$) 400.1746 $[M+H]^+$, $C_{22}H_{26}NO_6$ requires 400.1755.

### 4.14. 18-Bromo-4-(hydroxymethyl)-8,9,17-trimethoxy-16-oxo-2-oxa-12-azapentacyclo[10.6.2.0$^{1,14}$.0$^{4,13}$.0$^{5,10}$]icosa-5,7,9,14-tetraen-17-yl acetate (34)

Phenol **22** (12.6 mg, 0.031 mmol) and AcONa (5.0 mg, 0.062 mmol) were dissolved in AcOH (1 mL) and cooled to 0 °C. Bromine (7.5 mg, 0.047 mmol) was added dropwise and the solution stirred for 45 min at the same temperature. After this time, the reaction was quenched by addition of satd aq $Na_2S_2O_3$ (5 mL), basified to pH 8 with $NaHCO_3$, and the aqueous solution was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and the resulting crude residue was purified by flash chromatography ($SiO_2$, 1→5% MeOH/$CH_2Cl_2$), affording the title compound **34** as a white solid (7.0 mg, 42%). Mp 90–92 °C ($CHCl_3$); $R_f$ 0.44 ($CH_2Cl_2$/MeOH, 9:1); $\nu_{max}$ (thin film)/$cm^{-1}$ 3514, 2940, 1745, 1700, 1492, 1370, 1273, 1240, 1073, 1025, 914, 790, 729; $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (d, *J*=8.6 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 6.27 (s, 1H), 5.17 (s, 1H), 4.17 (d, *J*=16.2 Hz, 1H), 4.14 (s, 1H), 4.13 (d, *J*=12.0 Hz, 1H), 3.91–3.85 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.60 (d, *J*=12.4 Hz, 1H), 3.38 (d, *J*=10.5 Hz, 1H), 3.38 (s, 3H), 3.31 (d, *J*=10.5 Hz, 1H), 2.96 (td, *J*=12.2, 3.6 Hz, 1H), 2.57–2.50 (m, 1H), 2.33 (dd, *J*=13.6, 2.0 Hz, 1H), 2.21 (s, 3H), 1.73–1.63 (m, 1H); $\delta_C$ (100 MHz, $CDCl_3$) 186.7, 169.8, 158.8, 151.4, 146.5, 129.2, 128.5, 122.1, 121.9, 111.5, 99.2, 72.0, 70.6, 67.9, 62.2, 60.8, 55.9, 55.8, 52.3, 49.1, 46.2, 43.1, 38.6, 21.3; MS ($ESI^+$) *m*/*z* (rel %) 478 ($[M-OAc]^+$, 90), 538 ($[M+H]^+$, 100) 560 ($[M+Na]^+$, 90); HRMS ($ESI^+$) 538.1073 $[M+H]^+$, $C_{24}H_{29}^{79}BrNO_8$ requires 538.1071.

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### 4.15. 8-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-one (37)[16]

Diphenylphosphorylazide (8.96 mL, 0.0420 mol) was added dropwise to a stirred solution of carboxylic acid **35** (10.0 g, 0.0420 mol) and triethylamine (5.80 mL, 0.0420 mol) in toluene (125 mL) at rt. The reaction was then stirred at 90 °C for 1.5 h. Most of the solvent was removed in vacuo to afford a mobile oil. The flask was cooled to 0 °C under nitrogen atmosphere and $BF_3{\cdot}OEt_2$ (20.8 mL, 0.169 mol) was added dropwise. The reaction mixture was stirred for 20 h at rt before it was quenched with 1 M NaOH to pH 10. Ethyl acetate (300 mL) was added and the rapidly stirred mixture was heated for 1 h at 50 °C solvating all the crude material. The mixture was cooled to rt, the layers separated and the aqueous fraction further extracted with ethyl acetate (2×300 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$ and the solvent removed in vacuo to give the crude product. Column chromatography ($SiO_2$, 1:1 petrol:ethyl acetate→pure ethyl acetate) afforded the *title compound* **37** (7.34 g, 80%) as a white solid; $R_f$ 0.40 (ethyl acetate); $\delta_H$ (400 MHz, $CDCl_3$) 12.37 (1H, s), 6.45 (1H, br s), 6.25 (1H, s), 3.88 (3H, s), 3.86 (3H, s), 3.52 (2H, dt, $J$=6.7, 2.7 Hz), 2.90 (2H, t, $J$=6.7 Hz); HRMS (ESI$^+$) 246.0736; $C_{11}H_{13}NNaO_4$ ($MNa^+$) requires: 246.0737 (0.2 ppm error); Elemental Analysis: calculated for $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.20; H, 5.95; N, 6.17. The obtained data were in accord with those reported in the literature.[16]

### 4.16. *tert*-Butyl-8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (38)

*n*-BuLi (11.0 mL, 27.6 mmol, 2.5 M in hexanes) was added in a stirred solution of lactam **37** (2.05 g, 9.18 mL) in dry THF (110 mL) at −78 °C. After 10 min a solution of $Boc_2O$ (2.21 g, 10.1 mmol) in THF (28 mL) was transferred via syringe at −78 °C. The reaction mixture was then allowed to warm to rt and left to stir for 20 h. The reaction was quenched with satd aq $NH_4Cl$ (100 mL) at rt. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic extracts dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and purified by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate→pure ethyl acetate) to afford the title compound **38** as colorless crystals (2.35 g, 80%); $R_f$ 0.60 (1:1 petrol:ethyl acetate); mp 115–117 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3007, 2977, 2941, 1711, 1643, 1575, 1450, 1420, 1368, 1291, 1254, 1228; $\delta_H$ (400 MHz, $CDCl_3$) 12.24 (1H, s), 6.23 (1H, s), 3.90 (2H, t, $J$=6.3 Hz), 3.88 (3H, s), 3.83 (3H, s), 2.90 (2H, t, $J$=6.3 Hz), 1.55 (9H, s); $\delta_C$ (100 MHz, $CDCl_3$) 169.3, 157.5, 157.2, 152.0, 136.1, 135.2, 106.3, 101.6, 83.6, 60.6, 55.9, 44.6, 28.4, 27.9; HRMS (ESI$^+$) 346.1248; $C_{16}H_{21}NNaO_6$ ($MNa^+$) requires: 346.1261; Elemental Analysis: calculated for $C_{16}H_{21}NO_6$ requires C, 59.43; H, 6.55; N, 4.33; found C, 59.66; H, 6.46; N, 4.25.

### 4.17. *tert*-Butyl-8-(benzyloxy)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (39)

Lactam **38** (115 mg, 0.355 mmol) and benzyl bromide (0.063 mL, 0.532 mmol) were dissolved in toluene (3 mL). $K_2CO_3$ (98.1 mg, 0.710 mmol) was added and the reaction mixture was stirred at 120 °C for 20 h. The reaction was cooled to rt before it was quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic extracts dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and purified by column chromatography ($SiO_2$, 4:1 petrol:ethyl acetate) to afford the *title compound* **39** as colourless oil (118 mg, 80%); $R_f$ 0.50 (1:1 petrol:ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2977, 2936, 1761, 1708, 1592, 1489, 1454, 1423, 1379, 1309, 1279, 1248, 1146, 1121; $\delta_H$ (400 MHz, $CDCl_3$) 7.59–7.57 (2H, m), 7.36–7.26 (3H, m), 6.47 (1H, s), 5.16 (2H, s), 3.98 (3H, s), 3.83 (3H, s), 3.81 (2H, t, $J$=6.2 Hz), 2.84 (2H, t, $J$=6.2 Hz), 1.57 (9H, s); $\delta_C$ (100 MHz, $CDCl_3$) 161.2, 156.4, 154.3, 152.6, 142.4, 137.4, 137.0, 129.0, 128.1, 127.8, 117.7, 105.6, 82.6, 75.8, 61.0, 56.0, 44.1, 29.5, 28.0; HRMS (ESI$^+$) 436.1728; $C_{23}H_{27}NNaO_6$ ($MNa^+$) requires: 436.1731.

### 4.18. 8-(Benzyloxy)-6,7-dimethoxy-3,4-dihydroisoquinoline (40)

Lactam **39** (102 mg, 0.247 mmol) was dissolved in THF (2.6 mL) and cooled to −78 °C. Super-Hydride™ (0.371 mL, 0.371 mmol, 1 M solution in THF) was added dropwise and stirring continued for 30 min at −78 °C. The excess reducing agent was quenched at −78 °C by the sequential addition of methanol (0.213 mL), water (0.107 mL), aq $H_2O_2$ solution 30% w/v (0.107 mL) and 6 M aq NaOH (0.107 mL).[18] Stirring was continued while the mixture warmed to rt. The resulting mixture was then diluted with water (5 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ solution (10 mL), satd aq $Na_2CO_3$ solution (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$ and concentrated in vacuo. The crude material was used directly in the next step without further purification. A 1:1 mixture of $CH_2Cl_2$:TFA (2 mL), that had been pre-cooled to 0 °C, was added immediately to the crude product and the resulting solution was left to stir for 1 h at rt. The majority of the volatile organics were then removed in vacuo, before the crude residue was dissolved in dichloromethane (20 mL), washed with satd aq $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 1:1 ethyl acetate:petrol→2:1 ethyl acetate:petrol→pure ethyl acetate) afforded the *title compound* **40** as colourless oil (37.1 mg, 50%); $R_f$ 0.15 (9:1 ethyl acetate:MeOH); $\nu_{max}$ (thin film)/$cm^{-1}$ 2938, 1619, 1597, 1570, 1492, 1454, 1427, 1379, 1348, 1311, 1234, 1123, 1093, 1191; $\delta_H$ (400 MHz, $CDCl_3$) 8.49 (1H, br s), 7.44–7.42 (2H, m), 7.39–7.30 (3H, m), 6.47 (1H, s), 5.13 (2H, s), 3.89 (3H, s), 3.87 (3H, s), 3.63 (2H, t, $J$=7.8 Hz), 2.60 (2H, t, $J$=7.8 Hz); $\delta_C$ (100 MHz, $CDCl_3$) 155.8, 155.4, 150.5, 140.4, 136.8, 133.3, 128.4, 128.4, 128.2, 115.8, 106.4, 76.1, 61.0, 56.0, 46.8, 25.3; HRMS (ESI$^+$) 298.1427; $C_{18}H_{20}NO_3$ ($MH^+$) requires: 298.1438.

### 4.19. 13,13-Dimethyl 12-(benzyloxy)-3,4,10,11-tetramethoxy-5-oxo-7,8,12b,13-tetrahydro-5*H*-6-azatetraphene-13,13-dicarboxylate (41)

Imine **40** (250 mg, 0.841 mmol) and carboxylic acid **6** (315 mg, 1.01 mmol) were dissolved in $CHCl_3$ (25.2 mL), and *N*,*N*-diisopropylethylamine (0.270 mL, 1.56 mmol) was added, followed by T3P (50% in THF, 802 mg, 1.26 mmol). The resulting solution was stirred at room temperature for 20 min before the addition of $AlCl_3$ (224 mg, 1.68 mmol), and heating to 50 °C for 2 h. After this time, the mixture was diluted with ethyl acetate (300 mL), washed sequentially with sat aq $NaHCO_3$ (150 mL) and 10% aq Rochelle's salt (150 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography ($SiO_2$, 5:1→1:1 hexane:ethyl acetate), affording the *title compound* **41** as a colourless oil (255 mg, 51%); $R_f$ 0.60 (ethyl acetate); mp 70–72 °C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2949, 1740, 1654, 1602, 1580, 1453, 1487, 1424, 1308, 1272, 1236, 1124, 1068; $\delta_H$ (400 MHz, $CDCl_3$) 7.26–7.22 (1H, m), 7.18–7.11 (4H, m), 7.04 (2H, br s), 6.53 (1H, s), 5.09, (1H, s), 4.90 (1H, d, $J$=11.0 Hz), 4.81 (1H, ddd, $J$=13.3, 5.3, 2.5 Hz), 4.77 (1H, d, $J$=11.0 Hz), 4.03 (3H, s), 3.93 (3H, s), 3.89 (3H, s), 3.87 (3H, s), 3.53 (3H, s), 3.48 (3H, s), 3.33 (1H, ddd, $J$=13.3, 13.3, 4.1 Hz), 2.56–2.48 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 168.8, 166.7, 162.2, 153.2, 152.7, 150.3, 149.2, 139.6, 136.3, 136.1, 129.9, 129.5, 128.5, 128.1, 126.0, 123.3, 117.9, 114.5, 107.3, 75.7, 64.6, 61.5, 60.9, 56.2, 55.9, 55.7, 52.8, 52.6,

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39.1, 29.7; HRMS ($ESI^+$) 592.2183; $C_{32}H_{34}NO_{10}$ ($MH^+$) requires: 592.2177.

### 4.20. (6*SR*,11b*RS*)-Methyl 1,2,8,9-tetramethoxy-7,12-dioxo-4,5,6,7,11b,12-hexahydrobenzo[*g*]chromeno[3,4,5-*ija*]quinolizine-11b-carboxylate (43)

A 100-mL round bottom flask containing benzyl ether **41** (199 mg, 0.337 mmol) and methanol (3.4 mL) was purged with argon. Palladium hydroxide (35 mg, 20 wt % on carbon) was then added, and the reaction vessel was re-purged with argon, evacuated and fitted with a hydrogen balloon. The reaction was stirred at rt for 20 h, then evacuated, flushed with argon, filtered through Celite™ and concentrated in vacuo. The crude product (phenol **42**, 169 mg) was then dissolved in toluene (12 mL). *p*-Toluenesulfonic acid monohydrate (16.9 mg, 0.0888 mmol) was added and the resulting solution stirred at 120 °C for 6 h, and then concentrated in vacuo. Purification by column chromatography ($SiO_2$, 1:1 ethyl acetate:hexane→2:1 ethyl acetate:hexane) afforded the *title compound* **43** as colourless oil (101 mg, 64%); $R_f$ 0.50 (ethyl acetate); $\nu_{max}$ (thin film)/$cm^{-1}$ 2939, 1784, 1745, 1661, 1483, 1462, 1308, 1224, 1164, 1075, 731; $\delta_H$ (400 MHz, $CDCl_3$) 8.11 (1H, d, $J$=8.8), 7.13 (1H, d, $J$=8.8), 6.61 (1H, s), 5.16 (1H, s), 4.13–405 (2H, m), 4.05 (3H, s), 3.93 (6H, s), 3.90 (3H, s), 3.50 (3H, s), 2.97–2.80 (2H, m); $\delta_C$ (100 MHz, $CDCl_3$) 166.0, 162.9, 161.9, 154.5, 153.4, 150.4, 142.2, 135.4, 129.5, 124.9, 124.4, 124.3, 114.8, 110.3, 107.6, 61.6, 61.6, 56.2, 56.0, 54.9, 53.5, 52.2, 38.6, 27.4; HRMS ($ESI^+$) 492.1279; $C_{24}H_{23}NNaO_9$ ($MNa^+$) requires: 492.1265.

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