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A Biomimetic Phosphate Catalyzed Pictet-Spengler Reaction for the Synthesis of 1,1'-Disubstituted and Spiro-Tetrahydroisoquinoline Alkaloids

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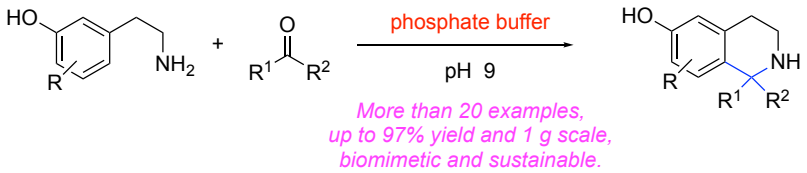
ABSTRACT



Tetrahydroisoquinoline alkaloids are an important group of compounds that exhibit a range of bioactivities. Here, a phosphate buffer catalyzed Pictet-Spengler reaction (PSR) using unreactive ketone substrates is described. A variety of 1,1'-disubstituted and spiro-tetrahydroisoquinoline alkaloids were readily prepared in one-step and high yields, highlighting the general applicability of this approach. This study features the role of phosphate in the aqueous-based PSR and provides an atom-efficient, sustainable route to new THIQs.

INTRODUCTION

Tetrahydroisoquinolines (THIQs) are an important group of pharmacologically active compounds exhibiting for example, anticancer, antimalarial, analgesic, antithrombotic, and central nervous system (CNS)-related activities. A sub-group of THIAs, the benzylisoquinoline alkaloids (BIAs) are a key family of natural products found in higher plants and mammals.[1] The BIAs in particular have attracted the attention of many researchers in recent years, giving rise to a range of patents and publications.[2-8] Amongst the THIAs, 1,1'-spiro compounds have proven to be synthetically challenging to synthesize, and they include the antiplasmodial compound **1**, natural product ochotensines **2** and **3**, and trabectedin **4** (Figure 1).[9-11]

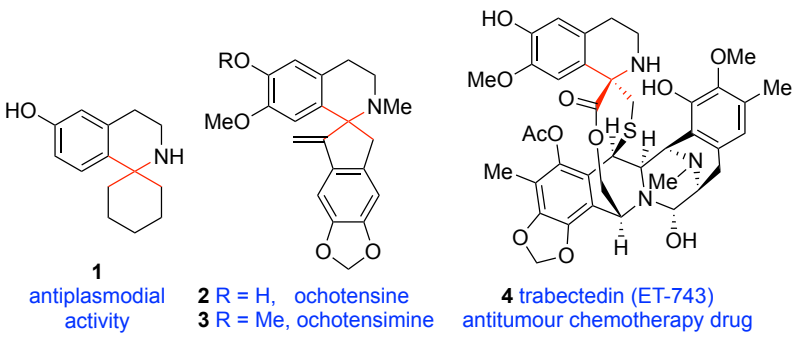


Figure 1. Selected 1,1'-spiro tetrahydroisoquinoline alkaloids

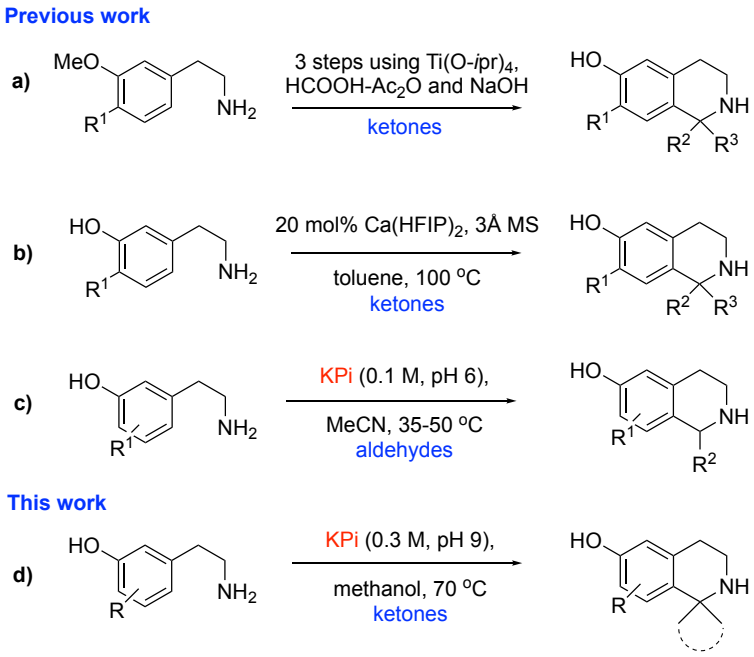
Different strategies have been used to access THIAs, including natural product extraction from plant sources, affording the desired alkaloids in low yields. In recent years, efforts have also been focused on the expression of biocatalysts for use in the stereoselective synthesis of these alkaloids. For example, in plants norcoclaurine synthases (NCSs) catalyze the first committed step in the BIA biosynthetic pathway, between dopamine **5** and 4-hydroxyphenyl acetaldehyde (4-HPAA) and this has been used in synthesis.[12-15]

The Pictet Spenglerase NCS has proven to be particularly tolerant towards a range of aldehydes and more recently has been reported to accept ketones.[16-20] While the use of NCS to generate 1,1'-

substituted THIQs is a particularly powerful strategy in stereoselective synthesis, a complementary method to access achiral compounds, or an approach that does not necessitate the production of biocatalysts would also be highly valuable.

Many methods have been reported to synthesize THIQs including the Pictet-Spengler or Bischler-Napieralski reactions,[21,22] but typically for these reactions, particularly when using ketones, high temperatures, strong acids or superacids are required.[23,24] An example includes the reaction of 1-(3-hydroxyphenyl)-2-aminoethanol with cyclohexanone to give a spiro-oxazolidine which when fused at 150 °C gave the 1,1'-spiro-hexanotetrahydroisoquinoline.[25,26] Such reaction conditions are however incompatible with less stable phenethylamines such as catechols. To overcome some of these problems, Lewis Acids catalysts such as *o*-benzenedisulfonamide,[27] titanium(IV) isopropoxide[28] or calcium *bis*-1,1,1,3,3,3-hexafluoroisopropoxide[29] have been used (Scheme 1a and 1b), but there are inherent limitations associated with the preparation of such catalysts including high costs or the requirement of a drybox.[29] In addition, the key phenolic groups must be protected or side products can be formed. Phosphate salts are a useful alternative due to the lower costs and milder reaction conditions that can be used.[30] Indeed, we have previously reported the use of aqueous phosphate in a Pictet-Spengler reaction (PSR) for the synthesis of THIQs (Scheme 1c).[30] The reaction was extended to a range of aromatic, aliphatic and heterocyclic aldehydes, but not with ketone substrates which are more sterically challenging and less reactive.

Here, we describe the discovery that aqueous phosphate reaction conditions can also be used to synthesize THIQs. The reaction conditions were optimized and applied to variously decorated phenethylamines and a wide range of cyclic and acyclic ketones in high yield (Scheme 1d). Some of the THIQs synthesized have also been reported to possess interesting bioactivities, including anti-parasitic properties.[10]



Scheme 1. a,b) Reported Lewis acid catalysed PSRs with ketones; c) Previous aqueous phosphate-mediated PSRs with aldehydes; d) PSRs with ketones reported in this work.

RESULTS AND DISCUSSION

Aqueous phosphate media has previously been used to produce norcoclaurine from dopamine **5** and 4-HPAA via a Pictet-Spengler reaction and the reaction was extended to a range of aldehyde substrates.[30] Despite this facile approach of using catechols to generate THIAs, an extension to ketone substrates has received little attention, other than work by Tono *et al* who noted that acetone might couple with dopamine in phosphate buffer (0.1 M, pH 7.2), although the product was not characterized.[31] In addition, the extraction of dopamine from the Chinese yam with acetone was believed to form a THIA and characterization of plant acetone extracts from *Aristolochia arcuata* highlighted a THIA formed from dopamine and acetone.[32,33] The main challenge with the PSR reaction using ketones is the relatively low reactivity, which combined with the sensitivity of catechols can lead to the formation of many side products. However, inspired by the interesting NCS

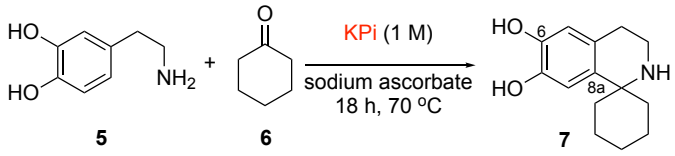
mediated PSR reaction with ketones it was decided to investigate whether an aqueous biomimetic phosphate-based approach could also be developed.[19]

Firstly, to avoid side-reactions due to the oxidation of catechols such as dopamine **5**, the antioxidant sodium ascorbate was added to reactions.[20] Cyclohexanone **6** was then used in a reaction with potassium phosphate (KPi, 1 M) with acetonitrile as co-solvent at pH 6 and 70 °C and surprisingly, the PSR product **7** was formed in 11% yield (Table 1， entry 1). Since different phosphate anions predominate at different pHs, at pH 6 the major ion is $H_2PO_4^-$, alternative pHs were explored. Unsuprisingly, no product **7** was observed at pH 4, due to dopamine protonation, and pH 12 due to the oxidation of dopamine which is prevalent at high basic pHs. However, at pH 9 the yield increased to 16% (Table 1, entry 4; see SI Figure S1 for further data on the effect of pH). A pH of 9 was then used as a suitable starting point for further reaction optimization. DFT and MP2 methods have been used in a theoretical study exploring the phosphate-mediated PSR with 3-hydroxypehenethylamine and formaldehyde, which suggested that at the lowest energy pathway required both HPO_4^{2-} and $H_2PO_4^-$ for optimal catalysis in the phosphate biomimetic reaction.[34] At pH 9, HPO_4^{2-} is the predominant anion present (with some $H_2PO_4^-$) and can facilitate both the deprotonation of the *meta*-phenolic OH and abstraction of 8a-H in the isoquinolone intermediate.

Typically, a co-solvent was required when developing the phosphate PSR reaction with aldehydes where aldehyde solubility was poor so other co-solvents were investigated, also with a view to enhancing yields. The polar aprotic solvents DMSO, DMF, and 1,4-dioxane together with the polar protic solvents methanol, ethanol and isopropanol were investigated (Table 1 and SI Figure S2). While DMSO and had little effect on the yield, it decreased when using DMF, 1,4-dioxane and isopropanol. However, the reaction yields were higher with ethanol and in particular methanol (Table 1, Entry 6) which was superior to other co-solvents (Table 1, Entry 6), giving a 43% yield of **7**. Further

studies established that lower proportions of methanol (10%-40% v/v, data not shown) generated similar yields of **7** and in the absence of co-solvent 36% of **7** was formed. This presumably reflects the fact that in the case of **6** there were no solubility issues in water.

Table 1. Initial optimization of the model reaction using **5** and **6** to give **7**[a]



5 6 7

Entry	6 (equiv.)	KPi pH	Co-solvent	Yield 7 (%)[b]
1	1.3	6	MeCN	11
2	1.3	4	MeCN	0
3	1.3	12	MeCN	0
4	1.3	9	MeCN	16
5	1.3	9	DMSO	14
6	1.3	9	EtOH	21
7	1.3	9	MeOH	43
8	1.3	9	None	36
9	2.0	9	MeOH	46
10	5.0	9	MeOH	81
11	10.0	9	MeOH	97

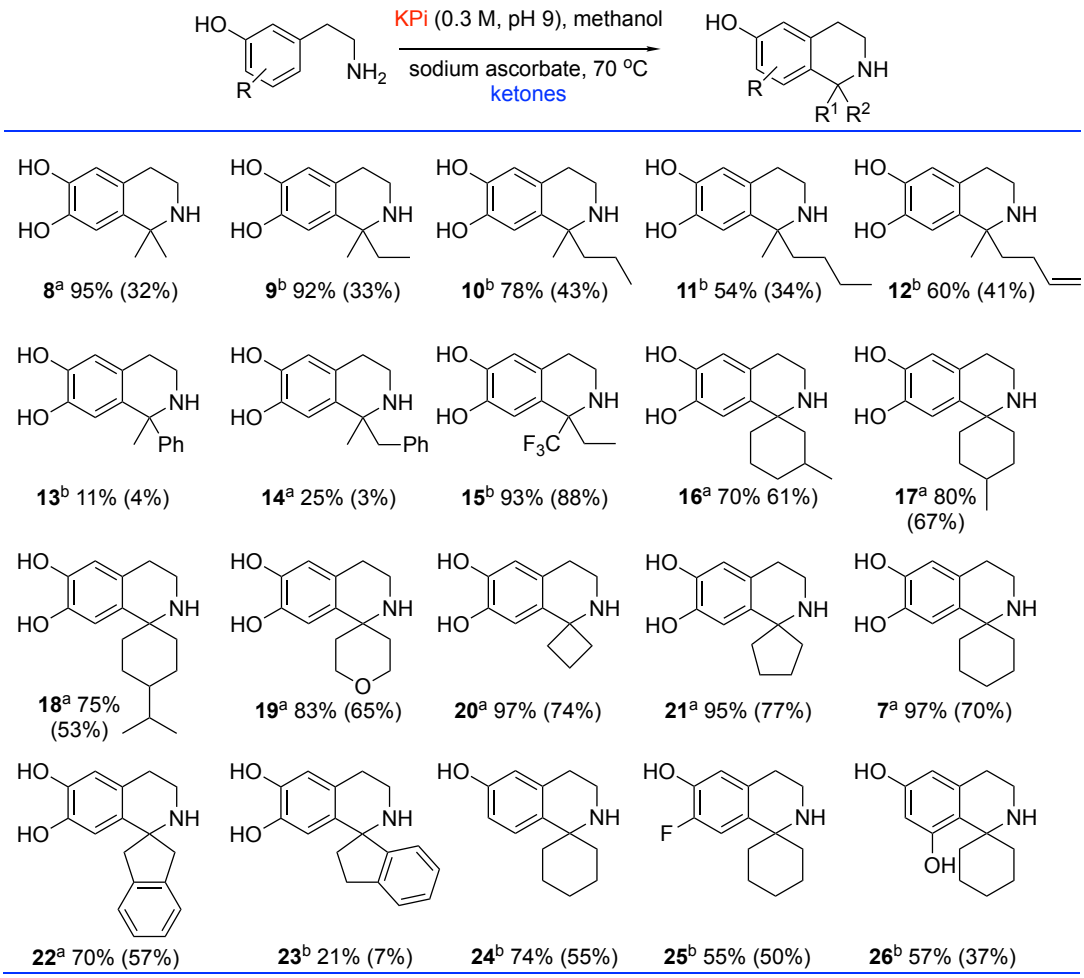
[a]*Reactions conditions*: dopamine **5** (15-25 mM), cyclohexanone **6** (20-150 mM) and sodium ascorbate (1.0 equiv. relative to dopamine) on a 1 mL scale in 1 M KPi, pH 9 and 50% co-solvent (v/v) at 70 °C; [b]Yields were determined by analytical HPLC.

To improve the synthetic utility, the reaction temperature was increased to 80 °C and 90 °C with little effect. Upon increasing the number of equivalents of **6** from 1.3 equiv. to 2, 5, and 10 equiv., in the latter case, **7** was formed in quantitative yield (Table 1, entry 11), so this was used in further experiments. The effect of using lower KPi concentrations was also investigated using **5** and **6** (SI, Table S1). Concentrations of 0.1 to 1 M KPi gave **7** in 97% yield, and below 0.1 M the yield of **7** decreased. To ensure sufficient KPi was present, a 0.3 to 0.5 M KPi concentration was therefore selected. The effect of the dopamine **5** concentration in the reaction was also explored (SI, Table S2). The yield remained constant with concentrations of up to 0.3 M, decreasing to 48% at 1 M of **5** when solubility issues were encountered.

With optimized reaction conditions in hand we were curious to understand the requirement for phosphate in the reaction. Alternative buffers or bases were used at pH 9 including KOH, $KHCO_3$-K_2CO_3 (0.5 M), Na_3BO_3 (0.5 M) and Na_2SO_3 (saturated) together with water alone (SI, Table S3). When water, water adjusted to pH 9 with KOH, or Na_3BO_3 solution were used, **7** was formed in trace amounts in reactions with 10 mM of **5** (SI, Table S3). These increased to 8-15% yields in reactions using 50 mM of **5** (SI, Table S4). Interestingly, with $KHCO_3$-K_2CO_3 and Na_2SO_3 at pH 9 yields of 24% and 43% with 10 mM **5** were noted, increasing to 63% and 89% with 50 mM **5**, respectively. At both dopamine concentrations the highest yields were still observed with KPi. The role of phosphate in previous experiments for aldehyde-PSRs has been probed using DFT and MP2 methods in a theoretical study.[34] The proposed reaction scheme for 3-hydroxyphenethylamine and formaldehyde involved both HPO_4^{2-} and $H_2PO_4^-$ having a role in the formation of a complex with the iminium intermediate, and after cyclisation, $H_2PO_4^-$ assisting in the deprotonation at 8a-H of the isoquinolone, while also being complexed to the amine proton. The lower yields observed with $KHCO_3$-K_2CO_3 of 24% (10 mM **5**) and 63% (50 mM **5**) may reflect that the trigonal planar geometry of carbonate is

unlikely to be able to perform a similar role of deprotonation and amine proton complexation as readily as $H_2PO_4^-$ (or potentially HPO_4^{2-}) in the re-aromatization step, compared to tetrahedral phosphate. The relatively high yields with Na_2SO_3 were interesting and may be due to its trigonal pyramidal structure, enabling the re-aromatization step in a similar fashion to KPi, combined with the reducing environment it provides. Overall, KPi gave rise to the highest yields so was used in further experiments. It was also noted that in the reaction between **5** and **6** for the KPi concentrations used, no *ortho*-regioisomer was detected presumably due to steric reasons.[35]

With suitable reaction conditions established, the general applicability of the reaction was explored for the synthesis of a range of 1,1'-disubstituted and spiro-THIQ alkaloids (Scheme 2). Reactions were monitored by ^{1}H NMR spectroscopy, due to the reported challenges with product isolation.[29] In addition, to confirm the NMR data, for several reactions, yields were confirmed by HPLC analysis. The phosphate mediated PSR could tolerate a range of methyl ketones, giving **8**-**12** in 54-95% yield when using aliphatic ketones. The reaction yields were greater for **8** and **9**, reflecting the influence of the increasing alkyl chain length and associated steric effects in the intermediates and subsequent cyclizations to give products **10**-**12**. For the aromatic ketones acetophenone or phenyl acetone giving **13** and **14**, respectively, again poor reactivities were observed, reflecting unfavorable steric interactions in the cyclization step to generate the THIQs. The introduction of a trifluoromethyl group however was readily achieved giving **15** in 93% yield.



Scheme 2. Application of the phosphate catalyzed PSR to synthesize 1,1'-disubstituted and spiro-THIQ alkaloids. *Typical reactions conditions*: dopamine **5** (15-25 mM), ketone (20-150 mM) and sodium ascorbate (1.0 equiv. relative to dopamine or the corresponding phenethylamine) were reacted together on a 1 mL scale in 0.3 M KPi, pH 9 and methanol (50% v/v of methanol and ketone combined) at 70 °C. Small scale reactions were performed in duplicate or triplicate. Yields were determined by ^{1}H NMR spectroscopy with an internal standard (maleic acid), and also by HPLC analysis (see SI, Table S5 for HPLC retention times) for several examples to confirm the data; [a] 10 equiv. of the corresponding ketones were used; [b]50 equiv. of the corresponding ketones were used. All products were isolated (yields are in brackets) either from these small-scale reactions or larger reactions and purified, using the acid-base extraction method or preparative HPLC, for characterization purposes.

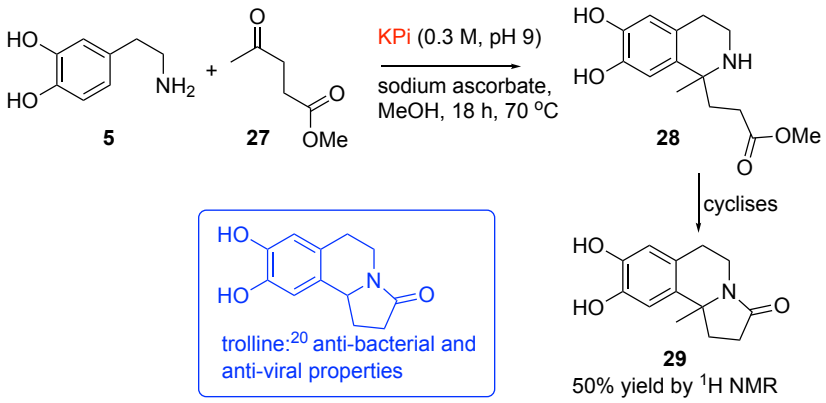
The introduction of a third cyclic or heterocyclic ring could more widely be introduced into the THIA scaffold, following the model reaction to give **7**. Using 3- or 4-methyl cyclohexanone readily gave **16** and **17** in 70% and 80% yield, respectively. Similarly, with 4-isopropyl cyclohexanone, **18** was generated in 75% yield and using tetrahydro-4*H*-pyran-4-one **19** was formed 83% yield. When using cyclobutanone and cyclopentanone THIAs **20** and **21** were formed in 97% and 95% yield, comparable yields to when using **6**, highlighting that other ring sizes can readily be used in the phosphate catalyzed Pictet-Spengler condensation. Furthermore, the use of 1- or 2-indanone afforded the tetracyclic ochotensine[9] derivatives **22** and **23** in 70% and 21% yields, respectively.

In addition to using alternative ketone substrates, selected substituted phenethylamines were investigated (Scheme 2). 2-(3-Hydroxyphenyl)ethylamine[20] was used with **6** to synthesize **24**, a compound previously synthesized in 2 steps and 10% yield and reported to possess anti-malarial properties.[10] A yield of 74% was achieved and the product was isolated by preparative HPLC in 53% yield. The fluorinated analogue 4-fluoro-3-hydroxy phenethylamine was also used to give **25** in 55% yield. A regioisomer of dopamine, 5-(2-aminoethyl)benzene-1,3-diol,[36] which will provide more unfavorable steric interactions was investigated and gave **26** in a reasonable 57% yield.

To highlight the utility of this methodology, the synthesis of **7** and **20** as selected compounds were then performed on a 1 g scale. The reaction yields by ^{1}H NMR spectroscopy were 97% and at this larger scale it was possible to isolate the materials using an acid-base extraction method to give **7** in 40% yield and **20** in 51% yield.

The use of a ketone possessing an ester functionality for subsequent ring cyclisation was also investigated to establish a reaction cascade to form an additional ring, as this strategy with an aldehyde has been successfully used to generate the anti-bacterial trolline.[20] Using the ketone KPi

reaction conditions established, **5** was reacted with commercially available methyl levulinate **27** to form a linear intermediate **28** with a C-1 quaternary carbon. Spontaneous cyclisation by amine nucleophilic attack at the ester carbonyl, following the favored 5-*exo-trig* mode, afforded lactam **29** in 50% yield (by ^{1}H NMR spectroscopy) (Scheme 3).



Scheme 3. Application of the KPi catalysed PSR with **27** in a cascade reaction.

CONCLUSION

In summary a biomimetic approach for the synthesis of 1,1'-disubstituted and spiro-THIQs has been established using a Pictet-Spengler reaction with unactivated ketones. The reaction is readily performed in methanol/phosphate buffer at pH 9 and 70 °C: these are significantly milder reaction conditions than those previously reported. The reaction successfully used methyl ketones, cyclic ketones and aromatic ketones with phenethylamines bearing a *meta*-hydroxyl group. Overall, this study provides a low-cost and sustainable way of making C-1,1' disubstituted THIQ alkaloids using phosphate buffer, to afford a range of products in high yields using a facile procedure.

EXPERIMENTAL

General Information. All chemicals were obtained from commercial suppliers and used as received. Small- scale reactions were heated using a BIOER Mixing block MB-102, and the scale-up

reactions were heated using Heidolph MR Hei-Tec type heating mantle. Thin layer chromatography was carried out using Merck TLC Silica gel 60 F_{254} plates and products were visualized using combinations of UV light (254 nm), potassium permanganate and phosphomolybdic acid staining solutions. Column chromatography was carried out using silica gel (particle size 40–60 μm). Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum 100 FT-IR Spectrometer or a Bruker Alpha Platinum-ATR, operating in ATR mode. ^{1}H NMR spectra were recorded on Bruker Avance 400, 500, 600 and 700 MHz spectrometers at 25 °C, using the residual protic solvent stated as the internal standard. Chemical shifts are quoted in ppm to the nearest 0.01 ppm using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sext (sextet), dd (doublet of doublets), dt (doublet of triplets), m (multiplet) defined as all multi-peak signals where overlap or complex coupling of signals make definitive descriptions of peaks difficult. The coupling constants are defined as *J* and quoted in Hz. ^{13}C{^{1}H} NMR spectra were recorded at 100, 125, 150 or 175 MHz on Bruker Avance 400, 500, 600 and 700 MHz spectrometers at 25 °C using the stated solvent as standard. Chemical shifts are reported to the nearest 0.1 ppm. Melting points were measured with a Gallenkamp apparatus and were uncorrected.

Mass spectra were obtained using a Waters Acquity UPLC SQD (using a linear gradient of 5-95% of acetonitrile over 5 min, with a C8 column, and flow rate of 0.6 mL/min) and Waters LCT Premier XE ESI Q-TOF mass spectrometer in the Department of Chemistry, UCL.

Determination of yields using ^{1}H NMR spectroscopy. Reactions were set up in duplicate (1 mL scale) in eppendorf tubes which were shaken at 70 °C for 20 h. The reaction mixture was transferred to a round-bottomed flask and evaporated to remove the methanol. Water was then removed on a freeze-drier to obtain a solid, which was dissolved in a solution of maleic acid (CD_3OD:D_2O = 1:3, 1

mL) and characterized by ^{1}H NMR spectroscopy. The concentration of the maleic acid was half of the starting material dopamine. The peak integration of maleic acid proton (δ = 5.89 ppm) was calibrated as 1.00, and the integration (×100%) of one of the product aromatic protons was used to determine the NMR yield.

HPLC methods

Analytical HPLC methods. HPLC analysis was carried out on an Agilent 1260 Infinity HPLC with mobile phase (A: water with 0.1% TFA; B: acetonitrile) in a gradient of A/B = 90%/10% at 0-1 min, A/B = 90%/10% to A/B = 30%/70% at 1-6 min, 100% B at 6-6.5 min, A/B = 90%/10% at 6.5-10 min. Each injection volume was 10 μL. The column was an ACE 5 C_{18} reverse phase column (150 mm × 4.6 mm). The flow rate was 1 mL/min and detection wavelength was 280 nm. The retention time of each compound is given in the SI, Table S5.

Preparative HPLC methods. Preparative HPLC was carried out on a Dionex 580 HPLC system, including P580 Pump, ASI-100 Automated Sample Injector and PDA-100 Photodiode Array Detector. A C_{18} reverse phase column, Agilent ZORBAX 300SB-C18 (250 mm × 9.4 mm, 5 μm) was used for purifications. The detection wavelength was 280 nm and the flow rate was 2 mL/min. Chromeleon Client Program software was used to monitor the HPLC traces.

Method I Mobile phase (A: water with 0.1% TFA; B: acetonitrile with 0.1% TFA) in a gradient of A/B = 95%/5% at 0-6 min, A/B = 95%/5% to A/B = 55%/45% at 6-10 min, A/B = 55%/45% at 10-15 min, A/B = 55%/45% to A/B = 10%/90% at 15-16 min, A/B = 10%/90% at 16-18 min, A/B = 10%/90% to A/B = 95%/5% at 18-20 min, A/B = 95%/5% at 20-25 min.

Method II Mobile phase (A: water with 0.1% TFA; B: acetonitrile with 0.1% TFA) in a gradient of A/B = 95%/5% at 0-10 min, A/B = 95%/5% to A/B = 5%/95% at 10-12 min, A/B = 5%/95% at 12-13 min, A/B = 5%/95% to A/B = 95%/5% at 13-14 min, A/B = 95%/5% at 14-30 min.

Method III Mobile phase (A: water with 0.1% TFA; B: acetonitrile with 0.1% TFA) in a gradient of A/B = 85%/15% at 0-30 min.

3',4'-Dihydro-2*H*-spiro[cyclohexane-1,1'-isoquinoline]-6',7'-diol hydrochloride.[19] (**7.HCl**)

To a solution of dopamine hydrochloride (19 mg, 0.10 mmol) and sodium ascorbate (20 mg, 0.10 mmol) in KPi buffer (0.3 M, pH 9, 0.5 mL) and methanol (0.5 mL) was added cyclohexanone (104 µL, 1.0 mmol). The reaction mixture was shaken at 70 °C for 18 h and monitored by analytical HPLC. The reaction mixture was diluted to ~7 mL with water and directly purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and evaporated to obtain **7**.HCl (19 mg, 70%) as a solid. The NMR yield of the reaction (97%) was determined following the general procedure described. The reaction was scaled-up using **5**.HCl (1.00 g, 5.27 mmol) sodium ascorbate (1 equiv. with respect to dopamine) in KPi buffer (0.3 M, pH 9, 52.7 mL) and methanol (52.7 mL), and **6** was added (5.48 mL, 52.7 mmol). The reaction mixture was shaken at 70 °C for 20 h, then the pH adjusted to 3 by the addition of HCl (2 M). The solvent was removed *in vacuo*, and the residue suspended in acetonitrile at 0 ºC. Finally, the mixture was filtered and solvent removed *in vacuo* to give **7**.HCl (0.491 g, 40%). ^{1}H NMR (600 MHz; CD_3OD) δ 6.76 (s, 1H), 6.57 (s, 1H), 3.41 (t, J = 6.4 Hz, 2H), 2.96 (t, J = 6.4 Hz, 2H), 2.10–1.97 (m, 4H), 1.88–1.77 (m, 3H), 1.70–1.60 (m, 2H), 1.52–1.42 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz; CD_3OD) δ 146.4, 146.0, 129.9, 123.1, 116.1, 113.3, 61.0, 38.6, 36.8, 26.2, 25.3, 21.7; *m/z* [ES+] 234 ($[MH]^+$, 100%).

1,1-Dimethyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride.[33] (**8.HCl**)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 963 μL) in a capped Eppendorf tube. Acetone (37 μL, 0.50 mmol) was then added and the reaction mixture was shaken under argon at 70 °C. After 18 h, the acetone was removed *in vacuo*. The remaining solution was freeze-dried and the NMR yield (95%) determined following the general procedure described. The reaction was also performed in duplicate to confirm the NMR yield and these two reaction products were combined and purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and evaporated at 55 °C to obtain **8**.HCl as a white solid (7.4 mg, 32%). ^{1}H NMR (400 MHz; CD_3OD) δ 6.70 (s, 1H), 6.57 (s, 1H), 3.46 (t, J = 6.4 Hz, 2H, 3-H_2), 2.96 (t, J = 6.4 Hz, 2H, 4-H_2), 1.67 (s, 6H, 2 × CH_3); ^{13}C{^{1}H} NMR (100 MHz; CD_3OD) δ 146.5, 146.2, 129.6, 122.3, 116.1, 112.7, 58.1, 38.8, 28.5, 26.0; *m/z* [ES+] 194 ($[MH]^+$, 100%).

1-Ethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride. (9.HCl)

To a solution of dopamine hydrochloride (19 mg, 0.10 mmol) and sodium ascorbate (20 mg, 0.10 mmol) in KPi buffer (0.3 M, pH 9, 1 mL) and methanol (0.55 mL) was added butanone (0.45 mL, 5.0 mmol). The reaction mixture was shaken at 70 °C for 18 h and monitored by analytical HPLC. The reaction mixture was diluted to 25 mL with water, washed with ethyl acetate (3 × 20 mL) and evaporated *in vacuo* to remove residual ethyl acetate, then directly purified using preparative HPLC method II. Fractions were combined, exchanged with HCl (1 M) and evaporated to give **9**.HCl (8.0 mg, 33%) as a white solid. The NMR yield of the reaction (92%) was determined following the general procedure described. Mp. 129-133 °C (H_2O); ν_{max} (film) 2970, 2792, 1591, 1523 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 6.64 (s, 1H), 6.58 (s, 1H), 3.50–3.36 (m, 2H), 3.03–2.84 (m, 2H), 2.02 (q, J = 7.2 Hz, 2H), 1.63 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz; CD_3OD) δ 146.5,

146.1, 128.7, 122.9, 116.2, 113.0, 61.2, 39.0, 34.5, 26.0, 25.9, 8.1; *m/z* [ES+] 208 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{12}H_{18}NO_2$ 208.1332 $[MH]^+$, found 208.1332.

1-Methyl-1-propyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride. (10.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (235 μL) in a capped Eppendorf tube. 2-Pentanone (265 μL, 2.50 mmol) was then added and the reaction mixture was shaken under argon at 70 °C. After 20 h the methanol was removed *in vacuo* and the NMR yield (78%) determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and evaporated at 55 °C to give **10**.HCl (11 mg, 43%) as a white solid. Mp. 237-239 °C (H_2O); ν_{max} (film) 3341, 3127, 2958, 1593, 1530 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.65 (s, 1H), 6.58 (s, 1H), 3.49–3.37 (m, 2H), 3.03–2.83 (m, 2H), 1.98–1.90 (m, 2H), 1.64 (s, 3H), 1.49–1.41 (m, 1H), 1.33–1.25 (m, 1H), 0.98 (t, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 146.5, 146.1, 128.9, 122.8, 116.2, 113.0, 60.9, 44.1, 39.0, 26.4, 26.0, 17.8, 14.4; *m/z* [ES+] 222 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{13}H_{20}NO_2$ 222.1489 $[MH]^+$, found 222.1489.

1-Butyl-1-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride. (11.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (191.6 μL) in a capped Eppendorf tube. 2-Hexanone (308.4 μL, 2.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (54%) was determined following the general procedure described. Two further duplicate reactions were performed and these two reaction products were combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **11**.HCl (4.6 mg, 34%) as a white solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3255,

2957, 1599, 1392 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 6.65 (s, 1H), 6.58 (s, 1H), 3.49–3.38 (m, 2H), 3.04–2.93 (m, 1H), 2.89 (dt, *J* = 17.0, 5.4 Hz, 1H), 2.00–1.93 (m, 2H), 1.63 (s, 3H), 1.45–1.32 (m, 3H), 1.29–1.19 (m, 1H), 0.94 (t, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (151 MHz; CD_3OD) δ 146.5, 146.1, 128.9, 122.8, 116.2, 113.0, 60.9, 41.7, 39.0, 26.5, 26.4, 25.9, 23.9, 14.2; *m/z* [ES+] 236 ([MH]$^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{14}H_{22}NO_2$ 236.1648 [MH]$^+$, found 236.1645.

1-(But-3-en-1-yl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol. (12.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (210.4 μL) in a capped Eppendorf tube. 5-Hexen-2-one (289.6 μL, 2.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (60%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **12**.HCl (5.4 mg, 41%) as a white solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3196, 2957, 1672, 1616, 1369 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 6.67 (s, 1H), 6.59 (s, 1H), 5.82 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.09 (dd, *J* = 16.9, 1.5 Hz, 1H), 5.01 (br d, *J* = 10.3 Hz, 1H), 3.48–3.42 (m, 2H), 2.99–2.96 (m, 1H), 2.95–2.89 (m, 1H), 2.24–2.15 (m, 1H), 2.08–2.01 (m, 3H), 1.67 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz; CD_3OD) δ 146.6, 146.2, 137.9, 128.5, 122.9, 116.24, 116.18, 113.0, 60.8, 41.1, 39.1, 28.8, 26.4, 25.9; *m/z* [ES+] 234 ([MH]$^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{14}H_{20}NO_2$ 234.1489 [MH]$^+$, found 234.1490.

1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride. (13.HCl)

To a solution of dopamine hydrochloride (95 mg, 0.50 mmol) and sodium ascorbate (100 mg, 0.50 mmol) in KPi buffer (0.3 M, pH 9, 5 mL) and methanol (2.08 mL) was added acetophenone (2.92 mL, 25 mmol). The reaction mixture was heated at 70 °C for 20 h and the methanol removed *in vacuo*.

The product was extracted with ethyl acetate (3 × 15 mL) and the organic phases combined, dried, and evaporated. The residue was suspended in dimethyl carbonate (10 mL) and HCl (10 mL, 1 M) and the aqueous phase washed with dimethyl carbonate (3 × 5 mL) then evaporated to obtain the crude product. This was dissolved in water-acetonitrile (1:1) and directly purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and evaporated to give **13**.HCl (6.0 mg, 4.1%) as a pale yellow solid. The NMR yield of the reaction (11%) was determined following the general procedure described. Mp. > 200 °C decomposed (H_2O); ν_{max} (film) 3208, 2961, 2783, 1585 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 7.45–7.39 (m, 3H), 7.35–7.30 (m, 2H), 6.69 (s, 1H), 6.47 (s, 1H), 3.42–3.35 (m, 1H), 3.15–3.05 (m, 2H), 2.98–2.92 (m, 1H), 2.13 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 147.2, 146.2, 142.0, 130.4, 130.1, 129.1, 128.0, 123.9, 116.0, 114.6, 63.3, 39.1, 27.3, 25.8; *m/z* [ES+] 256 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{16}H_{18}NO_2$ 256.1332 $[MH]^+$, found 256.1332.

1-Benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride.[19] (**14.HCl**)

To a solution of dopamine hydrochloride (56 mg, 0.30 mmol) and sodium ascorbate (60 mg, 0.30 mmol) in KPi buffer (0.3 M, pH 9, 10 mL) and methanol (10 mL) was added phenyl acetone (400 μL, 3.0 mmol). The reaction mixture was heated at 70 °C for 18 h and the methanol removed *in vacuo*. The product was extracted with ethyl acetate (3 × 20 mL) and the organic phases combined, dried and evaporated. The residue was resuspended in dimethyl carbonate (10 mL) and HCl (10 mL, 1 M) and the aqueous phase washed with dimethyl carbonate (4 × 5 mL) then evaporated to obtain the crude product. This was dissolved in water-acetonitrile (1:1) and was purified (twice) using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and evaporated to give **14**.HCl (2.4 mg, 3%). The NMR yield of the reaction (25%) was determined following the general procedure described. ^1H NMR (700 MHz; CD_3OD) δ 7.36–7.29 (m, 3H), 7.18–7.15 (m, 2H),

6.63 (s, 1H), 6.60 (s, 1H), 3.36–3.32 (m, 3H), 3.25 (d, J = 14.0 Hz, 1H), 2.93 (t, J = 6.3 Hz, 2H), 1.67 (s, 3H); $^{13}C\{^{1}H\}$ NMR (176 MHz; CD_3OD) δ 146.6, 145.8, 135.3, 131.8, 129.6, 128.7, 127.9, 122.9, 116.0, 113.5, 60.8, 47.1, 39.0, 26.5, 25.6; *m/z* [ES+] 270 ($[MH]^+$, 100%).

1-Ethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride. (15.HCl)

To a solution of dopamine hydrochloride (19 mg, 0.10 mmol) and sodium ascorbate (20 mg, 0.10 mmol) in KPi buffer (0.3 M, pH 9, 1 mL) and methanol (0.32 mL) was added 1,1,1-trifluoro-2-butanone (0.68 mL, 5.0 mmol). The reaction mixture was heated at 70 °C for 18 h and monitored by analytical HPLC. The reaction mixture was directly purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and evaporated to give **15**.HCl (26 mg, 88%) as a white solid. The NMR yield of the reaction (93%) was determined following the general procedure described. Mp. 115-117 °C (H_2O); ν_{max} (film) 3130, 3042, 1526 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 6.81 (s, 1H), 6.70 (s, 1H), 3.60–3.45 (m, 2H), 3.04 (dt, J = 17.4, 6.3 Hz, 1H), 2.96 (dt, J = 17.4, 6.0, 1H), 2.45–2.35 (m, 2H), 1.06 (t, J = 7.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz; CD_3OD) δ 148.4, 146.6, 126.2 ($^{1}J_{CF}$ = 285 Hz, CF_3), 126.1, 117.4, 116.7, 113.9, 65.9 ($^{2}J_{CF}$ = 26.7 Hz, CCF_3), 41.6, 28.7, 25.6, 7.8; *m/z* [ES+] 262 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{12}H_{15}F_3NO_2$ 262.1049 $[MH]^+$, found 262.1049.

3-Methyl-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinoline]-6',7'-diol hydrochloride.[19] **(16.HCl)**

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (438.7 μL) in a capped Eppendorf tube. 3-Methylcyclohexanone (61.3 μL, 0.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (70%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined

and purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **16**.HCl (8.7 mg, 61%) as a solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3196, 2947, 1594, 1394 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.73 (s, 1H), 6.57 (s, 1H), 3.42–3.39 (m, 2H), 2.96–2.94 (m, 2H), 2.08–1.99 (m, 2H), 1.93 (td, *J* = 14.6, 4.4 Hz, 1H), 1.88–1.81 (m, 2H), 1.78–1.69 (m, 1H), 1.68–1.60 (m, 2H), 1.13 (dq, *J* = 12.6, 4.2 Hz, 1H), 1.00 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 146.5, 146.1, 129.6, 123.0, 116.1, 113.2, 61.7, 45.3, 38.7, 36.3, 34.1, 28.3, 26.2, 22.5, 21.6; *m/z* [HRMS ES+] calcd for $C_{15}H_{22}NO_2$ 248.1651 $[MH]^+$, found 248.1664.

4-Methyl-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinoline]-6',7'-diol hydrochloride.[19] (**17.HCl**)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (438.7 μL) in a capped Eppendorf tube. 4-Methylcyclohexanone (61.3 μL, 0.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (80%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **17**.HCl (9.5 mg, 67%) as a solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3196, 2947, 1594, 1394 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.73 (s, 1H), 6.57 (s, 1H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.10–2.05 (m, 4H), 1.78 (dd, *J* = 15.0, 1.8 Hz, 2H), 1.69–1.60 (m, 1H), 1.36–1.22 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 146.5, 146.1, 129.5, 123.2, 116.1, 113.2, 60.6, 38.7, 36.9, 32.4, 30.1, 26.2, 22.2; *m/z* [HRMS ES+] calcd for $C_{15}H_{22}NO_2$ 248.1651 $[MH]^+$, found 248.1661.

4-Isopropyl-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinoline]-6',7'-diol hydrochloride. (**18.HCl**)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (463 μL) in a capped Eppendorf tube. 4-Isopropylcyclohexanone (70 mg, 0.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (75%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **18**.HCl (8.3 mg, 53%) as a white solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3223, 2931, 1652, 1524 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.73 (s, 1H), 6.57 (s, 1H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.08 (m, 4H), 1.91–1.84 (m, 2H), 1.57–1.48 (m, 1H), 1.34–1.25 (m, 3H), 0.97 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz; CD_3OD) δ 146.5, 146.1, 129.5, 123.2, 116.1, 113.2, 60.9, 44.1, 38.8, 37.2, 33.9, 26.3, 25.5, 20.3; *m/z* [ES+] 276 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{17}H_{26}NO_2$ 276.1958 $[MH]^+$, found 276.1960.

2',3,3',4,5',6'-Hexahydro-2*H*-spiro[isoquinoline-1,4'-pyran]-6,7-diol hydrochloride. (19.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (453.8 μL) in a capped Eppendorf tube. Tetrahydro-4*H*-pyran-4-one (46.2 μL, 0.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (83%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **19**.HCl (8.9 mg, 65%) as a white solid. Mp. 200 °C decomposed (H_2O); ν_{max} (film) 3223, 2969, 1591, 1525 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.79 (s, 1H), 6.59 (s, 1H), 3.97 (dd, *J* = 12.6, 4.5 Hz, 2H), 3.76 (td, *J* = 12.6, 2.0 Hz, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.35 (ddd, *J* = 15.4, 12.6, 4.5 Hz, 2H), 2.00 (m, 2H); $^{13}C\{^1H\}$ NMR

(151 MHz; CD_3OD) δ 146.9, 146.3, 128.5, 123.4, 116.2, 113.4, 63.3, 58.7, 39.0, 36.8, 26.1; *m/z* [ES+] 236 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{13}H_{18}NO_3$ 236.1281 $[MH]^+$, found 236.1282.

3',4'-Dihydro-2'*H*-spiro[cyclobutane-1,1'-isoquinoline]-6',7'-diol hydrochloride. (20.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (463 μL) in a capped Eppendorf tube. Cyclobutanone (37 μL, 0.50 mmol) was then added and the reaction mixture shaken under argon at 70 °C. After 20 h the NMR yield (97%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **20**.HCl (8.9 mg, 74%) as a white solid. The reaction was scaled-up using **5**.HCl (1.00 g, 5.27 mmol) sodium ascorbate (1 equiv. with respect to dopamine) in KPi buffer (0.3 M, pH 9, 52.7 mL) and methanol (52.7 mL), and cyclobutanone was added (3.92 mL, 52.7 mmol). The reaction mixture was shaken at 70 °C for 20 h, then the pH adjusted to 3 by the addition of HCl (2 M). The solvent was removed *in vacuo*, and the residue suspended in acetonitrile at 0 ºC. Finally, the mixture was filtered and solvent removed *in vacuo* to give **20**.HCl (0.646 g, 51%). Mp. > 250 °C (H_2O); ν_{max} (film) 3155, 2947, 1578, 1398 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 7.03 (s, 1H), 6.57 (s, 1H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.93 (t, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 8.3 Hz, 4H), 2.22 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 146.9, 146.4, 128.5, 122.8, 115.8, 112.4, 61.3, 39.5, 35.1, 26.1, 14.2; *m/z* [ES+] 206 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{12}H_{16}NO_2$ 206.1176 $[MH]^+$, found 206.1176.

3',4'-Dihydro-2'*H*-spiro[cyclopentane-1,1'-isoquinoline]-6',7'-diol hydrochloride. (21.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (456 μL) in a capped Eppendorf tube. Cyclopentanone (44 μL, 0.50 mmol) was then added and the reaction mixture shaken under argon at

70 °C. After 20 h the NMR yield (95%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method III. Fractions were combined, exchanged with HCl (1 M) and freeze dried to give **21**.HCl (9.8 mg, 77%) as a solid. Mp. >200 °C decomposed (H_2O); ν_{max} (film) 3223, 2970, 1592 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 6.66 (s, 1H), 6.55 (s, 1H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.24–2.12 (m, 4H), 2.0 –1.98 (m, 2H), 1.98–1.90 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 146.5, 146.3, 129.6, 123.1, 115.8, 112.8, 68.8, 42.0, 40.3, 26.0, 25.9; *m/z* [ES+] 220 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{13}H_{18}NO_2$ 220.1332 $[MH]^+$, found 220.1329.

1,3,3',4'-Tetrahydro-2'*H*-spiro[indene-2,1'-isoquinoline]-6',7'-diol hydrochloride. (22.HCl)

Dopamine hydrochloride (56 mg, 0.30 mmol), sodium ascorbate (60 mg, 0.30 mmol), and 2-indanone (396 mg, 3.0 mmol) were mixed in KPi buffer (0.3 M, pH 9, 10 mL) and methanol (10 mL) The reaction mixture was stirred at 70 °C for 18 h, and then diluted to 50 mL with water. The brown insoluble precipitate was removed by filtration and the filtrate extracted with ethyl acetate (4 × 20 mL). The organic phase was washed with brine (2 × 20 mL), dried, filtered and evaporated to obtain the crude product. The residue was washed with cold ethanol, stirred in HCl (1 M) for 4 h and the solvent removed *in vacuo* (< 55 °C) to give **22**.HCl (38 mg, 57%) as a white solid. The NMR yield (70%) was determined following the general procedure described. Mp. >240 °C decomposed (H_2O); ν_{max} (film) 3396 (br), 1621, 1590, 1524 cm^{-1}; ^1H NMR (600 MHz; CD_3OD) δ 7.35–7.27 (m, 4H), 6.60 (s, 1H), 6.56 (s, 1H), 3.60 (d, *J* = 17.1 Hz, 2H), 3.56 (d, *J* = 17.1 Hz, 2H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.03 (t, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz; CD_3OD) δ 147.0, 146.3, 140.0, 129.1, 128.9, 125.9, 122.9, 116.0, 112.1, 67.8, 48.1, 40.5, 26.0; *m/z* [ES+] 268 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{17}H_{18}NO_2$ 268.1332 $[MH]^+$, found 268.1332.

2,3,3',4'-Tetrahydro-2'*H*-spiro[indene-1,1'-isoquinoline]-6',7'-diol hydrochloride. (23.HCl)

Dopamine hydrochloride (9.5 mg, 0.050 mmol), sodium ascorbate (10 mg, 0.050 mmol) and 1-indanone (66 mg, 0.5 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (500 μL) in a capped Eppendorf tube. The reaction mixture was shaken under argon at 70 °C. After 20 h the NMR yield (21%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and solvent removed *in vacuo* (< 55 °C) to give **23**.HCl (2.1 mg, 7%) as a white solid. Mp. > 240 °C decomposed (H_2O); ν_{max} (film) 3142, 2946, 2791, 1605, 1408 cm^{-1}; ^1H NMR (700 MHz; CD_3OD) δ 7.48–7.42 (m, 2H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 6.66 (s, 1H), 6.16 (s, 1H), 3.60–3.48 (m, 2H), 3.30–3.24 (m, 1H), 3.23–3.14 (m, 2H), 3.02 (dt, *J* = 16.8, 4.2 Hz, 1H), 2.81–2.72 (m, 1H), 2.60 (dt, *J* = 16.8, 8.4 Hz, 1H); ^{13}C NMR (176 MHz; CD_3OD) δ 146.9, 146.0, 145.9, 143.5, 131.3, 128.6, 127.6, 126.40, 126.36, 123.8, 115.5, 114.2, 71.8, 41.0, 40.0, 30.1, 25.6; *m/z* [ES+] 268 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{17}H_{18}NO_2$ 268.1332 $[MH]^+$, found 268.1331.

3',4'-Dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinolin]-6'-ol hydrochloride.[10] (**24.HCl**)

2-(3-Hydroxyphenyl)ethylamine hydrochloride[20] (8.7 mg, 0.050 mmol), and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (241 μL) in a capped Eppendorf tube. Cyclohexanone (259 μL, 2.5 mmol) was added and the mixture shaken under argon at 70 °C. After 20 h the NMR yield (74%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and then purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and the solvent removed *in vacuo* (< 55 °C) to give **24**.HCl (7.1 mg, 55%) as a solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3217, 2930, 2766, 1589, 1440 cm^{-1}; ^1H NMR (700 MHz; CD_3OD) δ 7.24 (d, *J* = 7.8 Hz, 1H), 6.74 (dd, *J* = 7.8, 2.1 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.06 (t, *J* = 6.3

Hz, 2H), 2.09–2.03 (m, 4H), 1.87–1.79 (m, 3H), 1.70–1.62 (m, 2H), 1.55–1.45 (m, 1H); $^{13}C\{^{1}H\}$ NMR (176 MHz; CD_3OD) δ 157.8, 133.1, 129.5, 128.1, 115.9, 115.7, 61.0, 38.2, 36.6, 26.7, 25.0, 21.5; *m/z* [ES+] 218 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{14}H_{20}NO$ 218.1539 $[MH]^+$, found 218.1539.

7'-Fluoro-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinolin]-6'-ol hydrochloride. (25.HCl)

To a solution of 2-(4-fluoro-3-hydroxyphenyl)ethylamine hydrobromide[20] (23.6 mg, 0.10 mmol) and sodium ascorbate (20 mg, 0.10 mmol) in KPi buffer (0.3 M, pH 9, 1 mL) and methanol (0.32 mL) cyclohexanone (518 μL, 5.0 mmol) was added. The reaction mixture was heated at 70 °C for 20 h and the methanol was removed *in vacuo*. The solution was freeze-dried, dissolved in water-acetonitrile (1:1) and centrifuged at 4000 rpm for 10 min. The supernatant was then purified by preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and evaporated (at < 55 °C) to give **25**.HCl (14 mg, 50%) as a white solid. The NMR yield of the reaction (55%) was determined following the general procedure described. Mp. > 250 °C (H_2O); ν_{max} (film) 3150, 3061, 2942, 2762, 1525 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 7.18 (d, $^{3}J_{HF}$ = 12.6 Hz, 1H), 6.74 (d, $^{4}J_{HF}$ = 8.4 Hz, 1H), 3.45 (t, *J* = 6.2 Hz, 2H), 3.03 (t, *J* = 6.2 Hz, 2H), 2.11–1.97 (m, 4H), 1.89–1.74 (m, 3H), 1.73–1.59 (m, 2H), 1.56–1.42 (m, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz; CD_3OD) δ 152.1 (d, $^{1}J_{CF}$ = 241 Hz), 145.9 (d, $^{2}J_{CF}$ = 13.4 Hz), 130.3, 128.4, 118.6 (d, J_{CF} = 3.0 Hz), 114.4 (d, J_{CF} = 21.0 Hz), 61.0, 38.4, 36.6, 26.3, 25.1, 21.6; *m/z* [ES+] 236 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{14}H_{19}FNO$ 236.1445 $[MH]^+$, found 236.1446.

5-(2-Aminoethyl)benzene-1,3-diol hydrobromide.[36]

The reaction was carried out in anhydrous condition. To a solution of 3,5-dimethoxyphenyl acetonitrile (753 mg, 4.25 mmol) in THF (10 mL) was added borane-THF solution (1 M; 13 mL, 13 mmol) at 0 °C. The reaction was stirred for 24 h at room temperature, cooled to 0 °C and methanol

(30 mL) was added. The solution was then stirred for another 24 h, concentrated under vacuum and co-evaporated with methanol (3 × 10 mL). The residue was purified by silica column chromatography (dichloromethane-methanol (containing 1% triethylamine), 9:1 to 5:1) to give 2-(3,5-dimethoxyphenyl)ethan-1-amine[37] (427 mg, 55%) as an oil. R_f = 0.13 (dichloromethane-methanol (containing 1% triethylamine), 9:1); ^{1}H NMR (600 MHz; $CDCl_3$) δ 6.36–6.34 (m, 2H), 6.32 (t, *J* = 2.4 Hz, 1H), 3.77 (s, 6H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.12 (br s, 2H); ^{13}C{^{1}H} NMR (151 MHz; $CDCl_3$) δ 161.0, 142.1, 107.0, 98.2, 55.4, 43.2, 40.0.

2-(3,5-Dimethoxyphenyl)ethan-1-amine (427 mg, 2.36 mmol) was stirred in dichloromethane (20 mL) and boron tribromide (1 M; 7.5 mL, 7.5 mmol) at room temperature for 24 h. Methanol (30 mL) was then added and the reaction stirred for another 3 h. The mixture was then concentrated under the vacuum and co-evaporated with methanol to give 5-(2-aminoethyl)benzene-1,3-diol.HBr[36] (572 mg, 100%) as the HBr salt. ^{1}H NMR (600 MHz; CD_3OD) δ 6.23 (d, *J* = 2.3 Hz, 2H), 6.19 (t, *J* = 2.3 Hz, 1H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.82 (t, *J* = 7.8 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz; CD_3OD) δ 160.0, 140.0, 108.2, 102.5, 41.9, 34.5; *m/z* [ES+] 154 ($[MH]^+$, 100%).

3',4'-Dihydro-2'*H*-spiro[cyclohexane-1,1'-isoquinoline]-6',8'-diol hydrochloride. (26.HCl)

3,5-Dihydroxyl phenethylamine hydrobromide (11.7 mg, 0.050 mmol),and sodium ascorbate (10 mg, 0.050 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (241 μL) in a capped Eppendorf tube. Cyclohexanone (259 μL, 2.5 mmol) was added and the mixture shaken under argon at 70 °C. After 20 h the NMR yield (57%) was determined following the general procedure described. Two further duplicate reactions were performed, and the two reaction products combined and then purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and the solvent removed *in vacuo* (< 55 °C) to give **26**.HCl (5.0 mg, 37%) as a solid. Mp. > 250 °C (H_2O); ν_{max} (film) 3232, 3092, 2861, 1590 cm^{-1}; ^{1}H NMR (600 MHz; CD_3OD) δ 6.23 (d, *J* = 2.4 Hz, 1H),

6.14 (d, *J* = 2.4 Hz, 1H), 3.34 (t, *J* = 6.0 Hz, 2H), 3.04–2.95 (m, 4H), 1.82–1.73 (m, 5H), 1.67–1.53 (m, 2H), 1.50–1.34 (m, 1H); $^{13}C\{^{1}H\}$ NMR (151 MHz; CD_3OD) δ 158.7, 157.1, 134.9, 116.1, 108.1, 103.8, 61.6, 38.3, 31.8, 28.0, 25.1, 21.6; *m/z* [ES+] 256 ($[MNa]^+$, 29%), 234 ($[MH]^+$, 75); *m/z* [HRMS ES+] calcd for $C_{14}H_{20}NO_2$ 234.1489 $[MH]^+$, found 234.1489.

8,9-Dihydroxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one. (**29**)

Dopamine hydrochloride (9.5 mg, 0.050 mmol) and sodium ascorbate (10.5 mg, 0.053 mmol) were mixed in KPi buffer (0.3 M, pH 9, 500 μL) and methanol (200 μL) in a capped Eppendorf tube. Methyl levulinate **28** (300 μL, 2.5 mmol) was added and the mixture shaken under argon at 70 °C for 20 h. A duplicate reaction was performed, these two reactions were combined and the methanol removed *in vacuo*. The solution was freeze-dried and the NMR yield of the reaction (50%) determined following the general procedure described. The product was then purified using preparative HPLC method I. Fractions were combined, exchanged with HCl (1 M) and the solvent removed *in vacuo* (< 55 °C) to give **29**.HCl (4.4 mg, 19%) as a white solid. Mp. > 237-238 °C (H_2O); ν_{max} (film) 3246 (br), 2966, 1644, 1520 cm^{-1}; ^{1}H NMR (700 MHz; CD_3OD) δ 6.57 (s, 1H), 6.50 (s, 1H), 4.12 (dd, *J* = 13.3, 6.3 Hz, 1H), 3.11 (td, *J* = 13.3, 4.7 Hz, 1H), 2.75–2.69 (m, 1H), 2.67–2.60 (m, 2H), 2.41–2.33 (m, 2H), 2.06–2.00 (m, 1H), 1.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (176 MHz; CD_3OD) δ 174.8, 145.4, 145.2, 134.9, 124.1, 116.0, 112.4, 62.8, 35.7, 35.4, 31.4, 28.6, 27.2; *m/z* [ES+] 234 ($[MH]^+$, 100%); *m/z* [HRMS ES+] calcd for $C_{13}H_{16}NO_3$ 234.1125 $[MH]^+$, found 234.1126.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: xxxx. Supplementary Figures and Tables and ^{1}H NMR and ^{13}C NMR spectra of all new products.

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Notes

The authors declare no competing financial interests.

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