Supporting Information

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

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**Figure S1.** Influence of pH on the phosphate catalysed PSR.

\[
\begin{align*}
\text{HO} & \quad \text{NH}_2 \\
\text{HO} & \quad \text{O} \\
\text{KPi} \ (1 \text{ M}) & \quad \text{MeCN} \ (50\% \ \text{v/v}) \\
18 \text{ h}, \ 70 ^\circ \text{C} & 
\end{align*}
\]

\[
\begin{align*}
\text{5} & \quad + \quad \text{6} \\
\xrightarrow{\text{KPi} \ (1 \text{ M})} & \\
\text{7} & 
\end{align*}
\]

**pH affects yields of KPi catalyzed PSR**

| pH | Yield (%) |
|----|-----------|
| 4.2 | 0         |
| 5.1 | 1         |
| 6.1 | 5         |
| 7.0 | 10        |
| 8.0 | 15        |
| 9.0 | 16        |
| 10.0 | 15       |
| 11.0 | 10       |
| 12.3 | 5         |

**Reaction conditions:** dopamine 5 (17-27 mM), cyclohexanone 6 (19 mM) and sodium ascorbate (1.0 equiv. to dopamine) on a 1 mL scale in KPi (1 M) and 50% MeCN (v/v). Yields were determined using analytical HPLC based on the formation of 7.
**Figure S2.** Influence of co-solvent on the phosphate catalysed PSR.

![Chemical structure](image)

**Reaction conditions:** dopamine 5 (15 mM), cyclohexanone 6 (19 mM) and sodium ascorbate (1.0 equiv. to dopamine) on a 1 mL scale in KPi (1 M, pH 9) and 50% co-solvent (v/v). Yields were determined using analytical HPLC based on the formation of 7.
**Table S1.** Influence of KPi concentration on the PSR

![Chemical reaction](image)

| [KPi] mM | Yield a |
|----------|---------|
| 5        | 15      |
| 12.5     | 28      |
| 25       | 64      |
| 50       | 92      |
| 100      | 97      |
| 300      | 97      |
| 500      | 97      |
| 1000     | 97      |

Reaction conditions: 5 (15 mM), 6 (150 mM) and sodium ascorbate (1.0 equiv. to dopamine) with 50% v/v methanol at 70 °C for 18 h (1 mL scale). aYields were determined by analytical HPLC based on the formation of 7.
Table S2. Influence of dopamine concentration on the PSR.

\[
\begin{align*}
\text{HO} & \text{HO} \\
\text{NH}_2 & \rightarrow \text{HO} \\
\text{KPi (0.3 M, pH 9)} & \text{Sodium Ascorbate} \\
\text{MeOH (50% v/v)} & \text{18 h, 70 °C}
\end{align*}
\]

| [Dopamine] mM | Yield\textsuperscript{a} |
|---------------|------------------|
| 15            | 97               |
| 25            | 97               |
| 50            | 97               |
| 100           | 97               |
| 300           | 97               |
| 500           | 90               |
| 1000          | 48               |

\textit{Reaction conditions:} 5, 6 (10 equiv. to dopamine) and sodium ascorbate (1.0 equiv. to dopamine) with 50% v/v methanol at 70 °C for 18 h (1 mL scale). \textsuperscript{a} Yields were determined by analytical HPLC based on the formation of 7.
Table S3. Influence of buffer or base on the PSR (10 mM dopamine 5).

![Chemical structure of dopamine 5, ketone 6, and product 7]

| Buffer                                      | Yield<sup>a</sup> |
|---------------------------------------------|-------------------|
| K<sub>2</sub>HPO<sub>4</sub>-K<sub>3</sub>PO<sub>4</sub> (0.5 M, pH 9)<sup>b</sup> | 91%               |
| KHCO<sub>3</sub>-K<sub>2</sub>CO<sub>3</sub> (0.5 M, pH 9)                  | 24%               |
| KOH (pH 9)<sup>c</sup>                                                          | <1%               |
| H<sub>2</sub>O                                                                 | <1%               |
| Na<sub>3</sub>BO<sub>3</sub> (0.5 M, pH 9)<sup>d</sup>            | <1%               |
| Na<sub>2</sub>SO<sub>3</sub> (saturated, pH 9)<sup>e</sup> | 43%               |

<sup>a</sup>Yields were determined by <sup>1</sup>H NMR (600 MHz) spectroscopy. <sup>b</sup>K<sub>3</sub>PO<sub>4</sub> (0.5 M) and K<sub>2</sub>HPO<sub>4</sub> (0.5 M) were mixed and adjusted to pH 9. <sup>c</sup>Dilute KOH (aq.) was added to water until a pH of 9 was reached; <sup>d</sup>NaOH (aq.) was added to H<sub>3</sub>BO<sub>3</sub> to pH 9 and then diluted to 0.5 M with water; <sup>e</sup>Na<sub>2</sub>SO<sub>3</sub> (0.5 M, pH 9) was prepared initially and some precipitation observed when mixed with methanol.

Reaction conditions: 5 (10 mM), 6 (100 mM) and sodium ascorbate (1.0 equiv. to dopamine) with 50% v/v methanol under 70 °C for 21 h (1 mL scale).
Table S4. Influence of buffer or base on the PSR (50 mM dopamine 5).

![Chemical structures](image)

| Buffer                                      | Yielda |
|---------------------------------------------|--------|
| K$_2$HPO$_4$-K$_3$PO$_4$ (0.5 M, pH 9)$^b$  | 94%    |
| KHCO$_3$-K$_2$CO$_3$ (0.5 M, pH 9)          | 63%    |
| KOH (pH 9)$^c$                              | 15%    |
| H$_2$O                                      | 11%    |
| Na$_3$BO$_3$ (0.5 M, pH 9)$^d$              | 8%     |
| Na$_2$SO$_3$ (saturated, pH 9)$^e$          | 89%    |

*Reaction conditions: 5 (50 mM), 6 (500 mM) and sodium ascorbate (1.0 equiv. to dopamine) with 50% v/v methanol under 70 °C for 21 h (1 mL scale). *Yields were determined by $^1$H NMR (300 MHz) spectroscopy. $^b$K$_3$PO$_4$ (0.5 M) and K$_2$HPO$_4$ (0.5 M) were mixed and adjusted to pH 9. $^c$Dilute KOH (aq.) was added to water until a pH of 9 was reached; $^d$NaOH (aq.) was added to H$_3$BO$_3$ to pH 9 and then diluted to 0.5 M with water; $^e$Na$_2$SO$_3$ (0.5 M, pH 9) was prepared initially and some precipitation observed when mixed with methanol.*
Table S5. HPLC retention times of substrates and PSR products.

| Compound | Retention time (min) | Compound | Retention time (min) | Compound | Retention time (min) |
|----------|----------------------|----------|----------------------|----------|----------------------|
| 5        | 2.4                  | 7        | 4.9                  | 8        | 2.5                  |
| 9        | 2.9                  | 10       | 5.2                  | 11       | 5.4                  |
| 12       | 5.1                  | 13       | 5.5                  | 14       | 5.7                  |
| 15       | 4.8                  | 16       | 5.4                  | 17       | 5.4                  |
| 18       | 6.3                  | 19       | 3.1                  | 20       | 4.0                  |
| 21       | 4.5                  | 22       | 4.9                  | 23       | 5.4                  |
| 24       | 5.5                  | 25       | 5.8                  | 26       | 5.3                  |
| 29       | 5.3                  |          |                      |          |                      |

*Retention times were determined following the analytical HPLC method described.*
NMR Spectra

$^1$H NMR of compound 7

$^{13}$C NMR of compound 7
\(^1\)H NMR of compound 8

\(^{13}\)C NMR of compound 8
$^1$H NMR of compound 9

$^{13}$C NMR of compound 9
$^1$H NMR of compound 10

$^{13}$C NMR of compound 10
\textbf{\textsuperscript{1}H NMR of compound 11}

\textbf{\textsuperscript{13}C NMR of compound 11}
$^1$H NMR of compound 12

$^{13}$C NMR of compound 12
$^1$H NMR of compound 13

$^{13}$C NMR of compound 13
$^1$H NMR of compound 14

$^{13}$C NMR of compound 14
$^1$H NMR of compound 15

$^{13}$C NMR of compound 15
$^1$H NMR of compound 16

$^{13}$C NMR of compound 16
$^1$H NMR of compound 17

$^{13}$C NMR of compound 17
$^1$H NMR of compound 18

$^{13}$C NMR of compound 18
**$^1$H NMR of compound 19**

**$^{13}$C NMR of compound 19**
$^1$H NMR of compound 20

$^{13}$C NMR of compound 20
**1H NMR of compound 21**

![1H NMR spectrum of compound 21](image)

**13C NMR of compound 21**

![13C NMR spectrum of compound 21](image)
$^1$H NMR of compound 22

$^{13}$C NMR of compound 22
\(^1\)H NMR of compound 23

\(^{13}\)C NMR of compound 23
$^1$H NMR of compound 24

$^{13}$C NMR of compound 24
$^1$H NMR of compound 25

$^{13}$C NMR of compound 25
$^{1}H$ NMR of 5-(2-aminoethyl)benzene-1,3-diol.HBr

$^{13}C$ NMR of 5-(2-aminoethyl)benzene-1,3-diol.HBr
$^{1}H$ NMR of compound 26

$^{13}C$ NMR of compound 26
$^1$H NMR of compound 29

$^{13}$C NMR of compound 29