

**A convenient biomimetic synthesis of optically active putative neurotoxic metabolites of MDMA (“ecstasy”) from *R*-(–)- and *S*-(+)-*N*-methyl- $\alpha$ -methyldopamine precursors†**

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Received 2nd February 2012, Accepted 8th March 2012

DOI: 10.1039/c2ob25245g

(±)-3,4-Methylenedioxymethamphetamine (MDMA, also known as “ecstasy”) is a psychoactive drug with selective neurotoxic potential toward brain serotonin (5-HT) neurons. One hypothesis holds that MDMA neurotoxicity may at least partially be a consequence of its metabolism. In most species (including primates), *O*-demethylenated MDMA metabolites such as *N*-methyl- $\alpha$ -methyldopamine (HHMA) have been postulated to serve as precursors for toxic thioether conjugates. As yet, chirality of MDMA was not considered in previously reported *in vivo* studies because HHMA was used as the racemate. Since the stereochemistry of this chiral drug needs to be considered, the total synthesis of enantiomerically pure precursors, *R*-(–)-HHMA and *S*-(+)-HHMA, was envisioned with the ultimate goal to prepare substantial amounts of optically active thioether conjugates. Recently, we reported the first total synthesis of the *R*-enantiomer. In this paper, a novel synthesis of the *S*-enantiomer is described, in 45% overall yield (six steps) and 99% ee, using commercially available L-Boc-alanine (99% ee) as the chiral source. Having at our disposal suitable amounts of *R*-(–)-HHMA and *S*-(+)-HHMA precursors, a straightforward one-pot electrochemical procedure has been further developed for the synthesis of several catechol–thioether conjugates in acceptable yields (40–53%) and high degree of purity (99%), with complete diastereoselectivity. The availability of these newly synthesized optically active catechol–thioether conjugates is crucial for ongoing future *in vivo* studies about their role in MDMA neurotoxicity.

**Introduction**

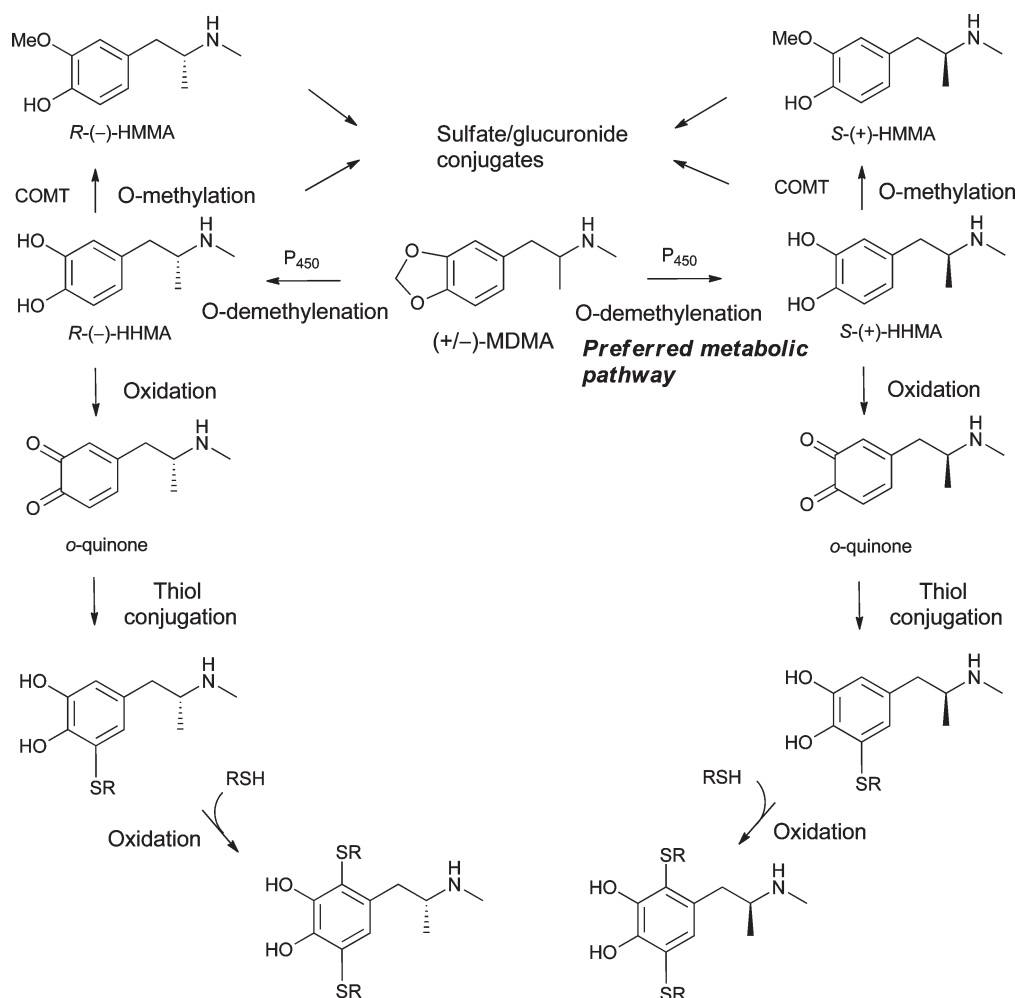
(±)-3,4-Methylenedioxymethamphetamine (MDMA, also known as “ecstasy”) is a psychoactive drug with selective neurotoxic potential toward brain serotonin (5-HT) neurons.<sup>1</sup> Despite intensive research, the precise mechanism by which MDMA selectively damages brain 5-HT neurons in most species (including primates) remains unknown.<sup>2</sup> One hypothesis holds that MDMA neurotoxicity may at least partially be a consequence of its metabolism (Scheme 1), because direct injection of the drug into specific brain area (especially cortex, hippocampus and striatum) of the rat fails to reproduce the 5-HT neurotoxic effects of

peripherally administered MDMA.<sup>3</sup> In particular, *O*-demethylenated MDMA metabolites such as *N*-methyl- $\alpha$ -methyldopamine (HHMA) or  $\alpha$ -methyldopamine (HHA), have been postulated to serve as precursors for toxic catechol–thioether conjugates.<sup>4</sup> Recently, the catechol–thioether conjugate of HHMA, 5-(*N*-acetylcystein-*S*-yl)-*N*-methyl- $\alpha$ -methyldopamine (5-NAC-HHMA) has been strongly implicated in MDMA neurotoxicity,<sup>5</sup> but efforts to replicate these findings have been unsuccessful.<sup>6</sup> So, the specific neurotoxicity profile of thioether conjugates of HHMA is controversial and remains to be well established.

As yet, chirality of MDMA was not considered in previously reported *in vivo* studies, because HHMA, the precursor of catechol–thioether conjugates, was used as the racemate. However, both MDMA enantiomers show different pharmacological and pharmacokinetic profiles.<sup>7</sup> Enantioselective metabolism is the most likely explanation for the enantioselective pharmacokinetics of MDMA and was observed for the cytochrome P450-mediated phase I metabolism into HHMA (Scheme 1),<sup>8</sup> for the catechol-*O*-methyltransferase (COMT)-catalyzed methylation of HHMA to HMMA<sup>9</sup> and for HHMA sulfation,<sup>10</sup> with a preference for the *S*-enantiomers. In contrast, recent findings have indicated that *O*-glucuronidation of HMMA *in vivo*<sup>11</sup> as well as HMMA sulfation<sup>10</sup> are not expected to be enantioselective.

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† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra of *S*-(+)-HHMA **7** and its synthetic intermediates **1–6**, together with optically active catechol–thioether conjugates **8–15**; analytical HPLC chromatograms of *S*-(+)-HHMA **7** and of optically active catechol–thioether conjugates **8–15**. See DOI: 10.1039/c2ob25245g



**Scheme 1** Stereochemistry of the hepatic metabolism of MDMA in humans including the postulated conjugate formation. Only, *O*-demethylation leading to *R*-(-)-HHMA and *S*-(+)-HHMA is presented.

HHMA, which is a major metabolite in humans,<sup>12</sup> is the precursor of thioether conjugates. Because HHMA exists as a pair of enantiomers (Scheme 1), its thioether conjugates exist as a mixture of diastereoisomers as they possess several chiral centers: that of HHMA present in the alkylamino side chain (carbon atom  $\alpha$  to the amine function), together with those present in the thiol moieties. Because MDMA enantiomers have different pharmacological properties, one would also predict that the thioether conjugates of the HHMA enantiomers similarly display distinct neurotoxicity profiles. The preparation of such diastereoisomers requires the tedious synthesis of enantiomerically pure precursors *R*-(-)-HHMA and *S*-(+)-HHMA. To overcome this limitation, analytical and semipreparative methodologies for the diastereoisomeric separation of HHMA thioether conjugates have been recently reported, but this separation method only furnished small quantities of both diastereoisomers.<sup>13</sup>

This prompted us to realize the total synthesis of enantiomerically pure precursors, *R*-(-)-HHMA and *S*-(+)-HHMA, with the ultimate goal to prepare large amounts of optically active thioether conjugates and to further determine if these conjugates play a role in MDMA neurotoxicity. Recently, we reported the first total synthesis of *R*-(-)-HHMA. Using *L*-DOPA as the

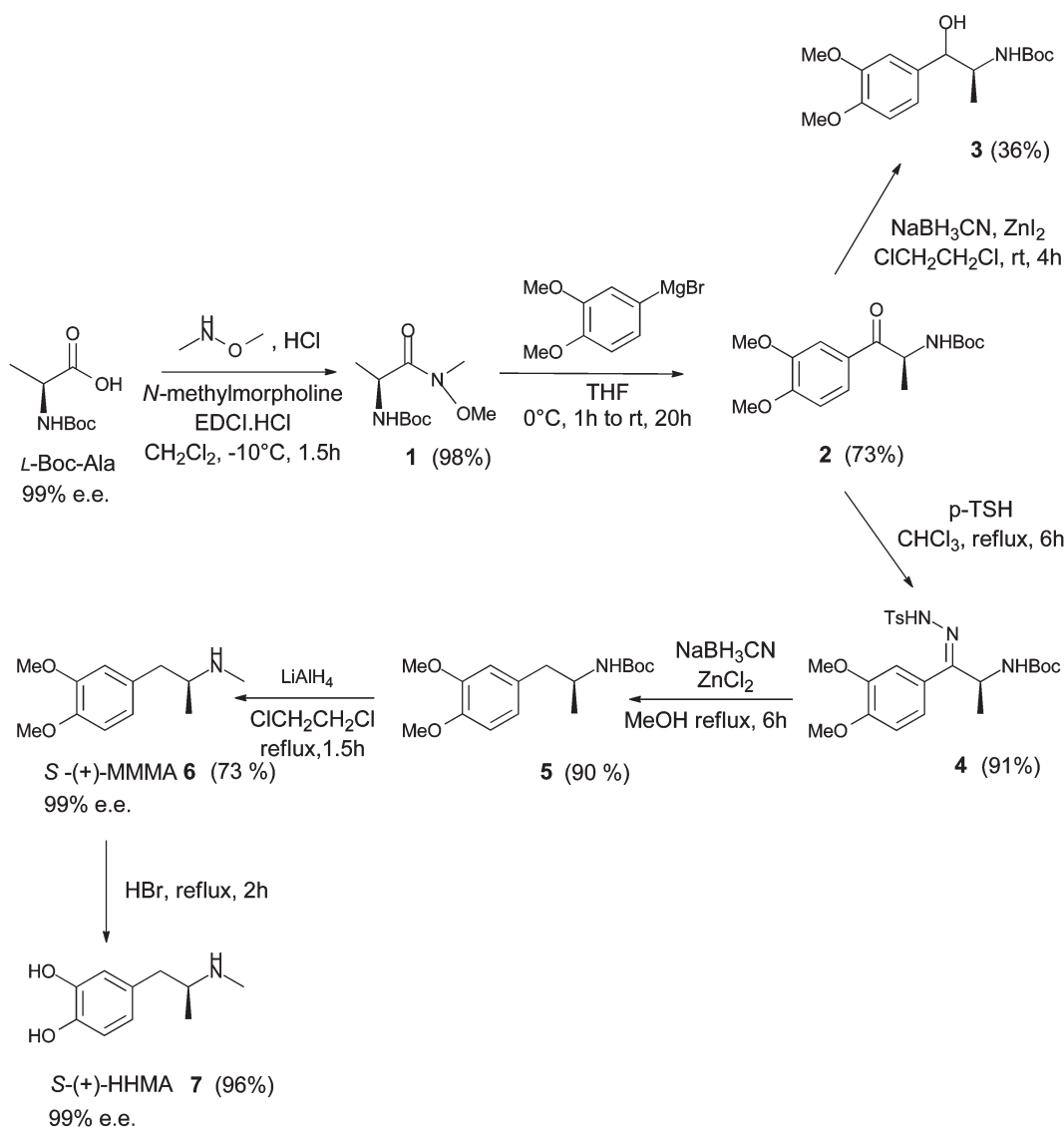
inducer of chirality, the preparation of *R*-(-)-HHMA was achieved through seven steps, in 30% overall yield and 99.5% enantiomeric excess (ee).<sup>14</sup>

In this paper, we describe the first total synthesis of *S*-(+)-HHMA in 45% overall yield (six steps) and 99% ee, using commercially available *L*-Boc-alanine (99% ee) as the chiral source. To the best of our knowledge, the only synthesis of enantiomerically enriched *S*-(+)-HHMA (80% ee), performed through resolution of *N*-methyl- $\alpha$ -methyl-dopamine with dibenzoyl-*L*-(-)-tartaric acid, is known.<sup>15</sup> Having at our disposal large amounts of *R*-(-)-HHMA and *S*-(+)-HHMA precursors, we have further prepared several optically active catechol-thioether mono- and bis-conjugates, following the straightforward one-pot procedure we have recently developed starting from ( $\pm$ )-HHMA racemate,<sup>16</sup> using anodic oxidation as a mimic of P450-mediated enzymatic oxidation.

## Results and discussion

### Synthesis of *S*-(+)-HHMA

Inexpensive *N*-protected amino-acids are attractive starting materials for the preparation of optically active arylalkylamines.



**Scheme 2** Synthetic procedure for the total synthesis of *S*-(+)-HHMA **7**.

This is the reason why we chose *L*-Boc-alanine, commercially available with high optical purity (99%), as the chiral source. At the outset, our synthetic strategy for the preparation of *S*-(+)-HHMA (Scheme 2) involved the common synthesis of the Weinreb amide **1** that was achieved in 98% yield, followed by condensation with lithiated 4-bromoveratrol for producing the arylketone intermediate **2**. Although it was reported that close Weinreb amides coupled with lithiated bromobenzene derivatives in good to high yields,<sup>17</sup> in our case the yield of arylketone **2** did not exceed 15%. We also attempted to employ the very attractive Merck procedure which afforded large quantities of  $\alpha$ -Boc-amino ketones from  $\alpha$ -Boc-amino Weinreb amides through a pre-deprotonation protocol using a stoichiometric amount of a simple aryl Grignard reagent.<sup>18</sup> However, when applied to the Weinreb amide **1**, the expected arylketone **2** was synthesized in moderate yield (51%). Finally, treatment of the Weinreb amide **1** with 3 equivalents of the Grignard reagent (3,4-dimethoxyphenylmagnesium bromide)<sup>19</sup> allowed us to markedly improve the yield in arylketone **2** which reached 73%.

Different methods could be then utilized to reduce the arylketone **2** into the corresponding methylene derivative **5** including catalytic hydrogenation,<sup>20</sup> Clemensen reduction,<sup>21</sup> reduction with hydride reagents such as lithium aluminum hydride (LiAlH<sub>4</sub>) in combination with strong Lewis acids,<sup>22</sup> or use of triethylsilane in trifluoroacetic acid or in BF<sub>3</sub>·Et<sub>2</sub>O.<sup>23</sup> Unfortunately, most of these reduction methods necessitate the use of strongly acidic reagents which can lead to undesired side reactions such as Boc protecting group cleavage. So, we focused on the reduction system using sodium cyanoborohydride in the presence of zinc iodide (NaBH<sub>3</sub>CN–ZnI<sub>2</sub>) in dichloroethane, earlier reported to reduce arylketones into arylalkanes with a high degree of selectivity.<sup>24</sup> However, under these experimental conditions, only the corresponding alcohol **3** was isolated in 36% yield. Since sterically hindered ketones are often resistant to reduction even under forcing conditions,<sup>25</sup> we envisioned an indirect method *via* the intermediacy of a tosylhydrazone derivative **4**.<sup>26</sup> Accordingly, the arylketone **2** was transformed into the corresponding tosylhydrazone **4** in almost quantitative yield

(91%), in refluxing chloroform in the presence of *p*-toluenesulfonylhydrazine (*p*-TSH). As can be seen below, the choice of chloroform as the solvent was crucial for a perfect control of enantioselectivity. Further, reduction using the NaBH<sub>3</sub>CN–ZnI<sub>2</sub> system failed to produce arylalkane **5** because tosylhydrazone **4** decomposed under these experimental conditions. Finally, replacing ZnI<sub>2</sub> with ZnCl<sub>2</sub> allowed the reduction of the tosylhydrazone **4** to the expected arylalkane **5** in high yield (90%). Upon optimization, we found that a combination of 1 mmol of tosylhydrazone with 8 mmol of NaBH<sub>3</sub>CN and 4 mmol of ZnCl<sub>2</sub> in refluxing methanol gave the best results. Reduction of Boc group was accomplished using LiAlH<sub>4</sub> in dichloroethane, leading to *S*(+)-MMMA **6** in 73% yield, with high optical purity (99%), as determined by HPLC analysis of the Mosher amide. The latter could be easily compared with the Mosher amide previously obtained from enantiomerically pure *R*(–)-HHMA, previously prepared in our laboratory.<sup>14</sup> Finally, complete demethylation of *S*(+)-MMMA **6** using hydrobromic acid heated at reflux, afforded *S*(+)-HHMA **7** in 96% yield. As earlier observed, no racemisation occurred in the course of the deprotection step.<sup>14</sup> Finally, using *L*-Boc-alanine (99% ee) as the chiral source, the preparation of *S*(+)-HHMA **7** was achieved through six steps, in 45% overall yield and 99% ee.

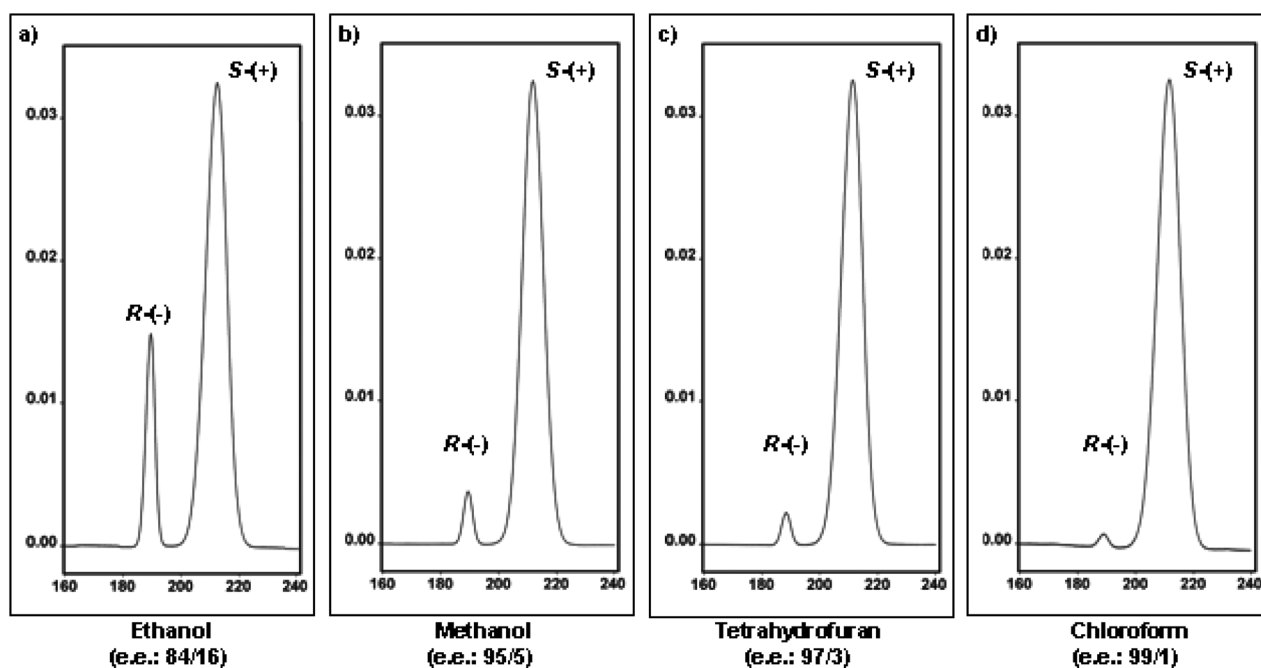
The tosylhydrazone synthesis constituted the critical step for the enantioselectivity of the overall synthetic procedure, because of the occurrence of a keto–enol displacement at the origin of racemisation. Indeed, heating arylketone **2** in refluxing protic solvents such as methanol, in the presence of hydrazine, favored the keto–enol displacement and then the racemisation of the stereocenter.<sup>27</sup> This was confirmed by using ethanol, another protic solvent which possesses a higher boiling point. Then, the ee dramatically failed to 84% (Fig. 1). Conversely, using aprotic

solvents, the ee increased to 97% in tetrahydrofuran, while no detectable racemisation was found in chloroform as the ee was equivalent to that of the starting *L*-Boc-alanine (99%).

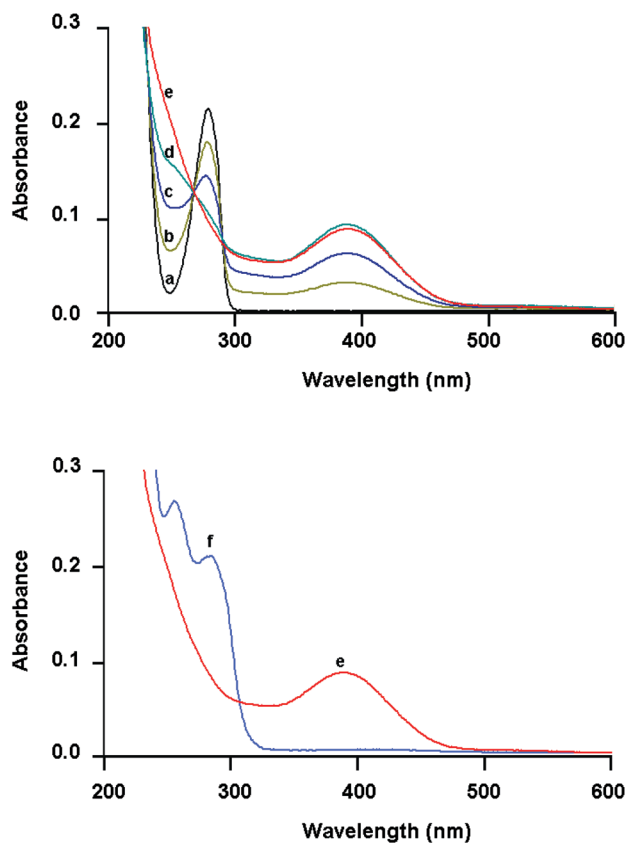
#### Synthesis of optically active catechol–thioether mono-conjugates **8–11**

In the racemic series, the most utilized method for synthesizing a thioether mono-conjugate involves the oxidation of (±)-HHMA with mushroom tyrosinase in the presence of a thiol.<sup>4f,h,5a,28</sup> The reaction proceeds *via* the formation of the *o*-quinone intermediate, followed by a 1,6-Michael addition reaction of thiol. However, this enzymatic procedure is not adapted for routine synthesis because it is too expensive and not suitable for yielding substantial amounts of catechol–thioether mono-conjugates. For a long time, electrochemical oxidation has proved to be an efficient tool for the generation of highly electrophilic *o*-quinone species, which can be further scavenged by diverse nucleophilic entities.<sup>29</sup> In particular, unstable *o*-quinone species have been electrogenerated from catecholamines such as dopamine,<sup>30</sup> nor-epinephrine,<sup>31</sup> or *N*-acetyldopamine<sup>32</sup> and then scavenged by thiol residues to afford the corresponding catechol–thioether adducts.

Recently, we reported a straightforward one-pot electrochemical synthesis of catechol–thioether mono-conjugates of (±)-HHMA, which proved to be especially attractive for routine synthesis because of acceptable yields, high degree of purity and environmentally friendly conditions.<sup>16a</sup> This methodology was found to be much more efficient than the enzymatic procedure for producing a thioether mono-conjugate of (±)-2,4,5-trihydroxy-methamphetamine.<sup>33</sup> So, we decided to adapt our electrochemical procedure to the synthesis of optically active thioether



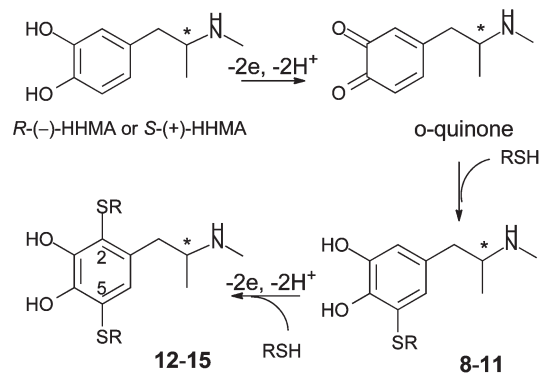
**Fig. 1** HPLC chromatograms for the analytical resolution of Mosher amide diastereoisomers prepared from *S*(+)-MMMA **6**. Tosylhydrazone intermediate **4** was prepared in different refluxing solvents: (a) ethanol; (b) methanol; (c) tetrahydrofuran; (d) chloroform. Conditions of HPLC: column Kromasil C18, 250 × 4.6 mm–5 μm; eluent (H<sub>2</sub>O + 1% TFA)/MeCN 55/45; flow rate, 0.4 mL min<sup>-1</sup>.



**Fig. 2** Spectrophotometric changes accompanying the electrochemical synthesis of optically active catechol–thioether mono-conjugate **8**. (Spectra a–e): electrochemical oxidation of *S*(+)-HHMA (1 mM), at a platinum anode ( $E = +1.0$  V versus Ag/AgCl), in deaerated 0.2 M HCl aqueous solution; (a) 0 (before electrolysis), (b) 0.5, (c) 1.0, (d) 1.5, (e) 2.0 mol of electrons, (Spectrum f): after addition of 2 equiv of *N*-acetylcysteine to the two electron-oxidized solution. Cell thickness is 0.1 cm.

mono-conjugates starting from *S*(+)-HHMA and *R*(–)-HHMA precursors. The anodic oxidation of *S*(+)-HHMA or *R*(–)-HHMA was realized through controlled potential electrolysis, under acidic conditions, in the absence of the thiol substrate because the thioether conjugate was also electroactive at the applied potential.

When the controlled potential of the platinum anode was fixed at +1.0 V versus Ag/AgCl, which is at a potential for which *S*(+)-HHMA (or *R*(–)-HHMA) could be oxidized to the *o*-quinone species, a coulometric value of  $2.0 \pm 0.1$  was found for the number ( $n$ ) of electrons involved in the oxidation of one molecule of *S*(+)-HHMA (or *R*(–)-HHMA) into the transient *o*-quinone species. The latter was rather stable in aqueous 0.2 M HCl, as shown by monitoring the UV absorption spectrum in the course of the electrolysis (Fig. 2). After the application of the potential, a decrease in the UV absorption band shown by *S*(+)-HHMA (or *R*(–)-HHMA) at 280 nm ( $\epsilon = 2190 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ ) was observed, while a new band at 391 nm developed. Spectral changes showed two isosbestic points at 268 and 290 nm, indicating that a simple equilibrium between two species was shifted (Fig. 2, spectra a–e). Subsequent addition of 2 equiv of thiol such as *N*-acetylcysteine (NAC) or glutathione resulted in the immediate discoloration of the yellow solution,



**Scheme 3** Multi-step one-pot electrochemical synthesis of optically active catechol–thioether bis-conjugates **12–15**.

**Table 1** One-pot synthesis of optically active catechol–thioether mono- and bis-conjugates **8–15**<sup>a</sup>

Series	RSH	Product	Yield <sup>b</sup> (%)
Mono-conjugates			
<i>S</i> (+)-	NAC	<b>8</b>	51
<i>S</i> (+)-	Glutathione	<b>9</b>	48
<i>R</i> (–)-	NAC	<b>10</b>	52
<i>R</i> (–)-	Glutathione	<b>11</b>	48
Bis-conjugates			
<i>S</i> (+)-	NAC	<b>12</b>	46 <sup>c</sup>
<i>S</i> (+)-	Glutathione	<b>13</b>	40
<i>R</i> (–)-	NAC	<b>14</b>	53
<i>R</i> (–)-	Glutathione	<b>15</b>	40 <sup>c</sup>

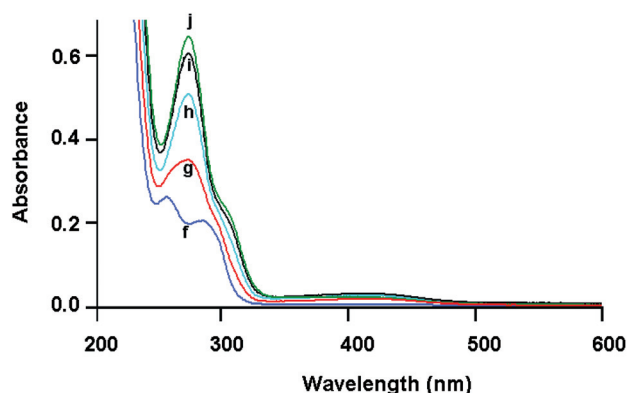
<sup>a</sup> Reagents and conditions: *R*(–)-HHMA or *S*(+)-HHMA = 1 mM; RSH = 2 mM (mono-conjugate) and RSH = 5 mM (bis-conjugate); 0.2 M HCl; 10 °C; Pt anode ( $E = +1.0$  V vs. Ag/AgCl); 30 min. <sup>b</sup> Yields refer to isolated products (after semi-preparative reversed-phase HPLC, degree of purity: 99%). NAC: *N*-acetylcysteine. <sup>c</sup> Mono-conjugate was also recovered (5–17%).

due to the formation of the catechol–thioether mono-conjugate, which was identified by the change in the UV absorption spectrum (Fig. 2, spectrum f), showing new absorption maxima around 256 and 285 nm. Treatment of the electrolysis solution afforded, after semipreparative reversed-phase HPLC (see the Experimental section), optically active catechol–thioether mono-conjugates **8–11** (Scheme 3) in yields ranging from 48 to 52% (Table 1).

### Synthesis of optically active catechol–thioether bis-conjugates **12–15**

For the synthesis of optically active catechol–thioether bis-conjugates **12–15**, we used our multi-step one-pot electrochemical procedure first reported for the preparation of thioether bis-conjugates of ( $\pm$ )-HHMA.<sup>16b</sup> The undeniable benefits of this method, which uses *R*(–)-HHMA or *S*(+)-HHMA as the starting material without the need to isolate the optically active thioether mono-conjugate intermediate, include atom economy, as well as economies of time, resource management, and waste generation (Scheme 3).

For the synthesis of catechol–thioether bis-conjugate **12**, for example, the first experimental step consisted of the generation of the *o*-quinone species and consecutive addition of 2 equiv of



**Fig. 3** Spectrophotometric changes accompanying the multi-step one-pot electrocatalysis of *S*-(+)-catechol-thioether bis-conjugate **12**. (Spectrum f): after addition of 3 equiv of *N*-acetylcysteine to the two electron-oxidized solution of *S*-(+)-HHMA (1 mM), at a platinum anode ( $E = +1.0$  V versus Ag/AgCl), in deaerated 0.2 M HCl aqueous solution; (Spectra g–j): spectra recorded after the consumption of additional 3.5 mol of electrons: (g) 1.0, (h) 2.0, (i) 3.0, (j) 3.5 (end of the process). Cell thickness is 0.1 cm.

NAC, under the aforementioned experimental conditions. After the electrolysis solution became colorless, catechol-thioether mono-conjugate **8** was not isolated but a third equiv of NAC was added. In a second step, the resulting solution was oxidized again at +1.0 V versus Ag/AgCl, which is at a potential for which **8** could be oxidized to the corresponding *o*-quinone-thioether species. Then, the solution became pale yellow, while a new band at 274 nm, with a shoulder around 305 nm (Fig. 3, spectrum j), developed at the expense of both UV absorption bands at 256 and 285 nm (Fig. 3, spectrum f). At the end of the electrolysis, a coulometric value of 3.5 was found for *n* and the recorded spectrum j corresponded to that of optically active catechol-thioether bis-conjugate **12**, as corroborated after recording the UV absorption of the isolated product. To maintain a reducing medium during work-up, two additional equiv of NAC were then added. Finally, treatment of the electrolysis solution afforded, after semi-preparative reversed-phase HPLC (see the Experimental section), the catechol-thioether bis-conjugate **12** in 46% yield.

The same one-pot procedure allowed the isolation of catechol-thioether bis-conjugate **13–15** in yields ranging from 40 to 53% (Table 1). As expected, the electrochemical procedure proceeded with complete diastereoselectivity (see the ESI†).

## Conclusions

For years, the potential role of metabolites in MDMA neurotoxicity has been a topic of interest. Recently, 5-NAC-HHMA has been strongly suspected to be involved in MDMA neurotoxicity,<sup>5a</sup> but efforts to replicate these findings have been unsuccessful.<sup>6</sup> The reasons for this discrepancy is not clear, but it is important to note that 5-NAC-HHMA used in these studies was prepared through different methods yielding a different ratio of 5-NAC-HHMA diastereoisomers.<sup>13</sup> This raised the question of the chirality of MDMA which was not considered in previously reported *in vivo* studies, because HHMA, the precursor of 5-NAC-HHMA metabolite, was used as the racemic mixture.

Since the stereochemistry of MDMA needed to be considered, we recently accomplished the first total synthesis of *R*-(–)-HHMA enantiomer.<sup>14</sup> However, the synthesis of optically pure *S*-enantiomer was also required for comparison. This is the reason why we have developed an efficient and stereocontrolled route for the total synthesis of *S*-(+)-HHMA through six steps, in 45% overall yield and 99% ee, using *L*-Boc-alanine (99% ee) as the inducer of chirality. Having at our disposal suitable amounts of both enantiomers, we have further used anodic oxidation as a mimic of P450 enzymatic oxidation for the synthesis of several optically pure catechol-thioether mono- and bis-conjugates. To the best of our knowledge, no optically active catechol-thioether metabolites of MDMA have never been prepared as yet. Then, using *S*-(+)-HHMA and *R*-(–)-HHMA as the starting materials, the straightforward one-pot electrochemical procedure we have developed allows the synthesis of diastereomerically pure conjugates **8–15**, in acceptable yields (40–53%) and high degree of purity (99%), under environmentally friendly conditions. The availability of these newly synthesized optically active thioether conjugates is crucial for ongoing future *in vivo* studies about their exact role in the neurotoxic effects of MDMA.

## Experimental section

All reagents and solvents (HPLC grade) were commercial products of the highest available purity and were used as supplied.

Analytical thin-layer chromatography was carried out on silica gel Macherey-Nagel Polygram SIL G/UV 254 (0.25 mm). Column chromatography was performed on Macherey-Nagel Si 60 M silica gel (40–63 μm).

HPLC was carried out using a Waters system consisting of a 600E multi-solvent delivery system, a Rheodyne-type loop injector, and a 2487 dual-channels UV-visible detector set at 254 and 278 nm. A mixture of two solvents A and B constituted the mobile phase. Solvent A was prepared by adding 1% concentrated trifluoroacetic acid (TFA) to deionized water. Solvent B was prepared by adding 0.5% TFA to a 1 : 1 (v/v) mixture of methanol and deionized water. Semipreparative reversed-phase HPLC was performed using a 250 × 20 mm, 5 μm Kromasil C18 column and a 2 mL loop injector, whereas for the analytical reversed-phase HPLC, a 250 × 4.6 mm, 5 μm Kromasil C18 column, together with a 50 μL loop injector, were used.

Melting points were measured on a Kofler apparatus. Optical rotations were measured at 25 °C using a Perkin-Elmer 341 polarimeter.  $[\alpha]_D$  values are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>.

UV absorption spectra were recorded on a Varian Cary 100 spectrophotometer. IR absorption spectra were recorded on a Shimadzu FT IRAffinity-1 spectrometer equipped with PIKE Gladi-Diam ATR.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were performed on a Bruker AC-300 spectrometer operating at 300 and 75 MHz, respectively. Chemical shifts are expressed as δ units (part per million) downfield from TMS (tetramethylsilane). The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds are included in the ESI† as a proof of their identity.

Low-resolution mass spectra (LRMS) were recorded on a Waters ZQ 2000 operating in positive ion mode. High-resolution

mass spectra (HRMS) were recorded on a LTQ-Orbitrap spectrometer operating in positive or negative ion mode.

Controlled-potential electrolyses were carried out in a cylindrical three-electrode divided cell (9 cm diameter), using a Voltalab 32 electrochemical analyser (Radiometer, Copenhagen). In the main compartment, a cylindrical platinum grid (area = 47 cm<sup>2</sup>) served as the anode (working electrode). A platinum sheet was placed in the concentric cathodic compartment (counter-electrode), which was separated from the main compartment with a glass frit. The reference electrode was an Ag–AgCl electrode, to which all potentials quoted are referred.

(*R*)-*N*-Methyl- $\alpha$ -methyl-dopamine hydrobromide, [*R*-(–)-HHMA, HBr] was synthesized in seven steps from commercially available L-DOPA, using our previously reported procedure.<sup>14</sup>

#### (*S*)-*tert*-Butyl 1-[(methoxy-methyl)amino]-1-oxopropan-2-ylcarbamate (1)

*N,O*-Dimethylhydroxylamine hydrochloride (1.06 g, 10.9 mmol, 1.03 equiv) and *N*-methylmorpholine (1.2 mL, 10.9 mmol, 1.03 equiv) were added to a solution of L-Boc-alanine (2 g, 10.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (17 mL) at –10 °C, followed by addition of small portions of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (2.08 g, 10.9 mmol, 1.03 equiv). After stirring at the same temperature for 1.5 h, the reaction was quenched with ice cold 1 M HCl (6.4 mL). The organic phase was separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The combined organic phases (27 mL) were washed with saturated aqueous NaHCO<sub>3</sub> (6 mL). The saturated aqueous NaHCO<sub>3</sub> phase was back extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> phases were then dried over MgSO<sub>4</sub>. Filtration and evaporation of the solvent under reduced pressure afforded Weinreb amide **1** as a white solid (2.4 g, 10.33 mmol) in 98% yield. mp 150–152 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 25.6 (*c* 0.04, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.32 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 3.22 (s, 3H), 3.78 (s, 3H), 4.69 (m, 1H), 5.29 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  18.6, 28.4, 32.1, 46.5, 61.6, 79.5, 155.2, 173.6. HRMS (ESI) *m/z* calcd for [M + Na]<sup>+</sup> 255.1321; found, 255.1321.

#### (*S*)-*tert*-Butyl-1-oxo-1-(3,4-dimethoxy)phenylpropan-2-ylcarbamate (2)

To a solution of Weinreb amide **1** (0.75 g, 3.21 mmol) in dry THF (33 mL) at 0 °C was added dropwise a 0.5 M solution of 3,4-dimethoxyphenylmagnesium bromide in THF (19.5 mL, 9.63 mmol, 3 equiv). The mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred for 20 h. Then, the reaction mixture was quenched with 1 M HCl (39 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with a saturated NaCl aqueous solution (30 mL), dried over MgSO<sub>4</sub> and filtered off, and the solvent was evaporated under reduced pressure. Column chromatography (toluene–acetone 95 : 5), afforded arylketone **2** in 73% yield (0.72 g, 2.33 mmol) as a white solid. mp 88–90 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 13.3 (*c* 0.04, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.41 (d, *J* = 7.0 Hz, 3H), 1.46 (s, 9H), 3.95 (s, 3H), 3.96 (s, 3H), 5.27 (m, 1H), 5.59 (d, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 7.53 (s, *J* = 1.9 Hz, 1H), 7.64 (dd, *J* = 7.0 and 1.9 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.3, 28.4,

50.5, 56.0, 56.1, 79.6, 110.2, 110.6, 123.4, 127.1, 149.2, 153.8, 155.2, 197.9; HRMS (ESI) *m/z* calcd for [M + Na]<sup>+</sup> 332.1474; found, 332.1476.

#### (*S*)-*tert*-Butyl-1-hydroxy-1-(3,4-dimethoxy)phenylpropan-2-ylcarbamate (3)

Zinc iodide (239 mg, 0.75 mmol, 1.5 equiv) and NaBH<sub>3</sub>CN (236 mg, 3.75 mmol, 7.5 equiv) were added to a solution of arylketone **2** (154 mg, 0.5 mmol) in dry dichloroethane (2.5 mL). The resulting mixture was stirred at room temperature for 4 h, and filtered through Celite®. The white solid was then washed with 100 mL of dichloromethane, and the combined filtrates were evaporated to dryness. Column chromatography (dichloromethane–methanol–triethylamine 89 : 10 : 1) afforded alcohol **3** as a colorless oil (57 mg, 0.18 mmol) in 36% yield (mixture of diastereoisomers). UV  $\lambda_{\text{max}}$  (MeOH)/nm 279 ( $\epsilon$ /dm<sup>3</sup> mol<sup>–1</sup> cm<sup>–1</sup> 2495), 300sh; IR (neat) 3356, 2974, 2934, 1682, 1514, 1452, 1365, 1254, 1232, 1157, 1140, 1024 cm<sup>–1</sup>; Major diastereoisomer: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.96 (d, 3H), 1.44 (s, 9H), 3.51 (broad s, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.94 (m, 1H), 4.77 (m, 2H), 6.82 (m, 2H), 6.88 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.8, 28.3, 51.9, 55.8, 55.9, 76.3, 79.7, 109.4, 110.7, 118.5, 133.5, 148.2, 148.7, 156.3; LRMS (ES+) *m/z* 334 [M + Na]<sup>+</sup>.

#### (*S*)-Methyl-*N'*-[1-(3,4-dimethoxyphenyl)-(2-*tert*-butoxycarbonylamino)propylidene] benzenesulfonylhydrazide (4)

To a solution of arylketone **2** (562 mg, 1.82 mmol) in chloroform (4.0 mL) were added 406 mg of *para*-toluenesulfonylhydrazine (2.18 mmol, 1.2 equiv). The resulting solution was heated to reflux for 6 h, and stirred at room temperature during the night. After evaporation of the solvent under reduced pressure, the resulting yellow solid was purified by column chromatography (petroleum ether–ethyl acetate 65 : 35) leading to tosylhydrazone **4** as a white solid (790 mg, 1.65 mmol) in 91% yield. mp 96–98 °C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 4.85 (*c* 0.04, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.20 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 9H), 2.45 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.54 (m, 1H), 5.38 (d, 1H), 6.65 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.58 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.0, 21.6, 28.4, 50.9, 56.0 (×2), 79.4, 109.9, 111.6, 120.4, 122.4, 128.0, 129.6, 135.0, 144.2, 149.7, 150.4, 155.0, 157.1; HRMS (ESI) *m/z* calcd for [M + Na]<sup>+</sup> 500.1831; found, 500.1835.

#### (*S*)-*tert*-Butyl-1-(3,4-dimethoxy)phenylpropan-2-ylcarbamate (5)

Zinc chloride (681 mg, 5 mmol, 4 equiv) and NaBH<sub>3</sub>CN (628 mg, 10 mmol, 8 equiv) were added to a solution of tosylhydrazone **4** (595 mg, 1.25 mmol) in methanol (10 mL). The reaction mixture was heated to reflux for 6 h, and stirred at 56 °C during the night. After addition of 20 mL of 0.1 M NaOH, the resulting mixture was extracted with diethyl ether (3 × 80 mL). The organic phase was then dried over MgSO<sub>4</sub> and filtered off, and the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography (petroleum ether–ethyl acetate 65 : 35) to afford compound **5** as a white

solid in 90% yield (333 mg, 1.13 mmol). mp 98–100 °C;  $[\alpha]_{\text{D}}^{25} + 6.5^\circ$  (*c* 0.04, methanol);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.08 (d,  $J = 6.6$  Hz, 3H), 1.43 (s, 9H), 2.59 (m,  $J = 13.4$  Hz, 1H), 2.79 (m,  $J = 13.4$  Hz, 1H), 3.86 and 3.87 (2 s, 7H), 4.40 (broad s, 1H), 6.71 (m, 2H), 6.79 (d,  $J = 8.6$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.1, 28.4, 42.5, 47.4, 55.7, 55.8, 79.0, 111.0, 112.5, 121.5, 130.8, 147.5, 148.7, 155.2; HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{Na}]^+$  318.1681; found, 318.1678.

#### (S)-3,4-Dimethoxymethamphetamine (S)-MMMA (6)

$\text{LiAlH}_4$  solution in THF (2.4 M, 1.02 mL) was added dropwise to a solution of compound **5** (480 mg, 1.625 mmol) in dry dichloroethane (20 mL) at 0 °C. The resulting solution was heated to reflux for 1.5 h, quenched successively with 0.55 mL of water, 0.55 mL of 5 M NaOH and 1.55 mL of water, stirred for 45 min and filtered through Celite®. The white solid was then washed with 100 mL of dichloromethane, and the combined filtrates were evaporated to dryness. After purification by column chromatography (dichloromethane–methanol–triethylamine 87 : 10 : 3), (S)-MMMA **6** was obtained as a colorless oil in 73% yield (249 mg, 1.19 mmol).  $[\alpha]_{\text{D}}^{25} + 12.2^\circ$  (*c* 0.04, MeOH); note  $[\alpha]_{\text{D}}^{25}$  was found to be  $-12.4^\circ$  for the *R* enantiomer when measured under the same experimental conditions; UV  $\lambda_{\text{max}}$  (MeOH)/nm 280 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2600), 285sh;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.08 (d,  $J = 6.2$  Hz, 3H), 1.69 (broad s, 1H), 2.40 (s, 3H), 2.63 (m, 2H), 2.77 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 6.74 (m, 2H), 6.82 (d,  $J = 8.7$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  19.6, 33.9, 43.1, 55.8 ( $\times 2$ ), 56.4, 111.1, 112.3, 121.1, 131.9, 147.4, 148.7. HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{H}]^+$  210.1494; found, 210.1496.

#### (S)-N-Methyl- $\alpha$ -methyl-dopamine hydrobromide [S-(+)-HHMA, HBr] (7)

A 48% aqueous solution of HBr (3.3 mL) (18.9 mmol) was added to (S)-MMMA **6** (531 mg, 2.55 mmol). The resulting solution was heated to reflux for 2 h, under nitrogen. After evaporation under reduced pressure, the brown oil was purified by column chromatography (dichloromethane–MeOH 80 : 20) affording (S)-HHMA, HBr **7** as a colorless oil (640 mg, 2.44 mmol) in 96% yield.  $[\alpha]_{\text{D}}^{25} + 3.2^\circ$  (*c* 0.04, MeOH); UV  $\lambda_{\text{max}}$  (aqueous 0.2 M HCl)/nm 280 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2190);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.11 (d,  $J = 6.5$  Hz, 3H), 2.53 (s, 3H), 2.62 (m, 1H), 2.75 (m, 1H), 3.30 (m, 1H), 6.57 (d,  $J = 8.1$  Hz, 1H), 6.66 (s, 1H), 6.74 (d,  $J = 8.1$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  14.8, 29.9, 37.9, 56.4, 116.2, 116.9, 121.7, 128.1, 142.8, 143.9. HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{H}]^+$  182.1181; found, 182.1180.

#### (S)-5-(N-Acetylcystein-S-yl)-N-methyl- $\alpha$ -methyl-dopamine (8)

**General procedure A.** A solution of S-(+)-HHMA, HBr **7** (65.5 mg, 0.25 mmol), in 0.2 M HCl (250 mL), was oxidized under nitrogen at 10 °C at a platinum grid whose potential was fixed at +1.0 V versus Ag/AgCl. After the consumption of 2 electrons per molecule, 2 equiv of *N*-acetylcysteine (83 mg, 0.50 mmol) were added to the pale yellow solution which turned

colorless. The reaction mixture was immediately frozen at  $-80$  °C and then freeze-dried. The residue was subdivided in fractions of about 25 mg. Each fraction was dissolved in 2 mL of water, and then purified by semipreparative reversed-phase HPLC, using a mixture of solvent A–solvent B 80 : 20 as the eluent (flow rate: 14 mL  $\text{min}^{-1}$ ). Fractions containing (S)-5-NAC-HHMA **8** were collected, immediately frozen at  $-80$  °C, and then freeze-dried. Compound **8** was isolated as a white solid (44 mg, 0.13 mmol), in 51% yield. Its degree of purity (99.5%) was determined by analytical HPLC (eluent: solvent A–MeCN 93 : 7 – flow rate: 0.8 mL  $\text{min}^{-1}$ ); UV  $\lambda_{\text{max}}$  (aqueous 0.2 M HCl)/nm 255 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2640), 292 (1980);  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  1.11 (d,  $J = 6.5$  Hz, 3H), 1.78 (s, 3H), 2.55 (s, 3H), 2.60 (m, 1H), 2.78 (m, 1H), 3.04 (m, 1H), 3.28 (m, 2H), 4.23 (m, 1H), 6.65 (s, 1H), 6.75 (s, 1H).  $^{13}\text{C NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  14.7, 21.5, 29.8, 34.5, 37.8, 52.7, 56.2, 117.2, 119.4, 126.2, 128.1, 143.9, 144.3, 173.8, 174.1. HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{H}]^+$  343.1322; found, 343.1322.

#### (S)-5-(Glutathion-S-yl)-N-methyl- $\alpha$ -methyl-dopamine (9)

General procedure A, replacing *N*-acetylcysteine with glutathione (157 mg, 0.50 mmol) afforded after semipreparative reversed-phase (eluent: solvent A–solvent B 69 : 31 – flow rate: 3 mL  $\text{min}^{-1}$ ), (S)-5-Glu-HHMA **9** as a white solid (58 mg, 0.12 mmol), in 48% yield. Its degree of purity (99.5%) was determined by analytical HPLC (eluent: solvent A–MeCN 93 : 7 – flow rate: 1 mL  $\text{min}^{-1}$ ). UV  $\lambda_{\text{max}}$  (aqueous 0.2 M HCl)/nm 256 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2630), 292 (1820);  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  1.09 (d,  $J = 6.5$  Hz, 3H), 2.02 (m, 2H), 2.36 (t,  $J = 7.5$  Hz, 2H), 2.54 (s, 3H), 2.61 (m, 1H), 2.76 (m, 1H), 3.04 (m, 1H), 3.24 (m, 2H), 3.69 (s, 2H), 3.90 (m, 1H), 4.27 (m, 1H), 6.63 (s, 1H), 6.73 (s, 1H).  $^{13}\text{C NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  14.7, 25.3, 29.8, 30.7, 34.7, 37.8, 40.9, 52.1, 53.0, 56.2, 117.0, 119.3, 126.0, 128.2, 143.9, 144.4, 171.5, 172.3, 172.7, 174.0. HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{H}]^+$  487.1857; found, 487.1858.

#### (R)-5-(N-Acetylcystein-S-yl)-N-methyl- $\alpha$ -methyl-dopamine (10)

General procedure A, replacing S-(+)-HHMA, HBr by R-(–)-HHMA, HBr afforded, after semipreparative reversed-phase HPLC (eluent: solvent A–solvent B 80 : 20 – flow rate: 14 mL  $\text{min}^{-1}$ ), (R)-5-NAC-HHMA **10** as a white solid (44 mg, 0.13 mmol), in 52% yield. Its degree of purity (99%) was determined by analytical HPLC (eluent: solvent A–MeCN 93 : 7 – flow rate: 0.8 mL  $\text{min}^{-1}$ ). UV  $\lambda_{\text{max}}$  (aqueous 0.2 M HCl)/nm 255 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2640), 292 (1980);  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  1.12 (d,  $J = 6.5$  Hz, 3H), 1.79 (s, 3H), 2.55 (s, 3H), 2.62 (m, 1H), 2.78 (m, 1H), 3.04 (m, 1H), 3.28 (m, 2H), 4.23 (m, 1H), 6.66 (s, 1H), 6.76 (s, 1H).  $^{13}\text{C NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  14.7, 21.5, 29.8, 34.6, 37.9, 52.7, 56.2, 117.1, 119.4, 126.3, 128.1, 144.0, 144.4, 173.8, 174.2. HRMS (ESI)  $m/z$  calcd for  $[\text{M} + \text{H}]^+$  343.1322; found, 343.1321.

#### (R)-5-(Glutathion-S-yl)-N-methyl- $\alpha$ -methyl-dopamine (11)

General procedure A replacing S-(+)-HHMA, HBr by R-(–)-HHMA, HBr and *N*-acetylcysteine by glutathione (157 mg, 0.5 mmol) afforded, after semipreparative reversed-phase HPLC



(eluent: solvent A–solvent B 69 : 31 – flow rate: 3 mL min<sup>-1</sup>), (*R*)-5-Glu-HHMA **11** as a pale pink solid (58 mg, 0.12 mmol), in 48% yield. Its degree of purity (99%) was determined by analytical HPLC (eluent: solvent A–MeCN 93 : 7 – flow rate: 1 mL min<sup>-1</sup>). UV  $\lambda_{\max}$  (aqueous 0.2 M HCl)/nm 256 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  2630), 292 (1820); <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.10 (d,  $J$  = 6.5 Hz, 3H), 2.01 (m, 2H), 2.36 (t,  $J$  = 7.5 Hz, 2H), 2.54 (s, 3H), 2.61 (m, 1H), 2.76 (m, 1H), 3.06 (m, 1H), 3.24 (m, 2H), 3.69 (s, 2H), 3.82 (m, 1H), 4.26 (m, 1H), 6.64 (s, 1H), 6.73 (s, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  14.7, 25.5, 29.8, 30.9, 34.6, 37.8, 40.9, 52.6, 53.0, 56.2, 117.1, 119.2, 126.0, 128.2, 143.9, 144.4, 172.1, 172.3, 172.8, 174.2. HRMS (ESI)  $m/z$  calcd for [M + H]<sup>+</sup> 487.1857; found, 487.1857.

#### (*S*)-2,5-bis-(*N*-Acetylcystein-*S*-yl)-*N*-methyl- $\alpha$ -methyl-dopamine (**12**)

**General procedure B.** A solution of (*S*)-HHMA, HBr (65.5 mg, 0.25 mmol) in 0.2 M hydrochloric acid (250 mL), was oxidized under nitrogen, at 10 °C, at a platinum grid ( $E$  = +1.0 V *versus* Ag/AgCl). After the consumption of 2 electrons per molecule, the electrolysis was stopped and 3 equiv of *N*-acetylcysteine (125 mg, 0.75 mmol) were added. When the yellow electrolysis solution became colorless, it was oxidized again at +1.0 V *versus* Ag/AgCl. After exhaustive electrolysis ( $n$  = 5.5, that is 2.0 for the first step and 3.5 for the second one), 2 equiv of *N*-acetylcysteine (83 mg, 0.50 mmol) were added to the reaction mixture, which was immediately frozen at –80 °C and then freeze-dried. The residue was subdivided in fractions of about 25 mg. Each fraction was dissolved in 2 mL of water and then purified by semipreparative reversed-phase HPLC, using a mixture of solvent A–solvent B 84 : 16 as the eluent (flow rate: 11 mL min<sup>-1</sup>). Fractions containing (*S*)-2,5-bis-NAC-HHMA (**12**) and (*S*)-5-NAC-HHMA (**8**) were collected individually, immediately frozen at –80 °C and then freeze-dried. Compound **12** was isolated as the major product in 46% yield (white solid, 58 mg, 0.115 mmol), along with compound **8** as the minor one, in 4.5% yield (4 mg, 0.012 mmol). The degree of purity for compound **12** (99%) was determined by analytical HPLC (eluent: solvent A–MeCN 92 : 8 – flow rate: 0.8 mL min<sup>-1</sup>). UV  $\lambda_{\max}$  (aqueous 0.2 M HCl)/nm 274 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  6390), 305sh; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.09 (d,  $J$  = 6.5 Hz, 3H), 1.77 (s, 3H), 1.81 (s, 3H), 2.61 (s, 3H), 2.82 (m, 1H), 3.07 and 3.25 (m, 6H), 4.30 (m, 2H), 6.86 (s, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  14.8, 21.5 ( $\times 2$ ), 30.0, 34.4, 34.7, 37.0, 52.4, 53.3, 56.2, 119.3, 121.1, 126.1, 131.7, 143.8, 146.6, 173.6, 173.7, 173.8 ( $\times 2$ ). HRMS (ESI)  $m/z$  calcd for [M + H]<sup>+</sup> 504.1469; found, 504.1469.

#### (*S*)-2,5-bis-(*N*-Acetylcystein-*S*-yl)-*N*-methyl- $\alpha$ -methyl-dopamine (**13**)

General procedure B, replacing *N*-acetylcysteine with glutathione (392 mg, 1.25 mmol, overall quantity), afforded, after exhaustive electrolysis ( $n$  = 4.5, that is 2 for the first step and 2.5 for the second one) and semipreparative reversed-phase HPLC (eluent: solvent A–solvent B 74 : 26 – flow rate: 4 mL min<sup>-1</sup>), (*S*)-2,5-bis-Glu-HHMA **13** in 40% yield (white solid, 80 mg, 0.10 mmol). The degree of purity for compound **13** (99%) was determined by analytical HPLC (eluent: solvent A–MeCN 95 : 5

– flow rate: 0.6 mL min<sup>-1</sup>). UV  $\lambda_{\max}$  (aqueous 0.2 M HCl)/nm 274 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  7200), 305sh; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.08 (d, 3H), 2.01 (m, 4H), 2.33 (m, 2H), 2.39 (m, 2H), 2.59 (s, 3H), 2.82 (m, 1H), 3.10 and 3.30 (m, 6H), 3.71 (s, 2H), 3.73 (s, 2H), 3.79 (m, 2H), 4.24 (m, 2H), 6.85 (s, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  14.7, 25.3, 25.4, 29.9, 30.8 ( $\times 2$ ), 34.5, 34.9, 37.1, 40.9 ( $\times 2$ ), 52.3 ( $\times 2$ ), 52.6, 53.4, 56.2, 118.9, 120.9, 125.8, 131.9, 143.7, 146.8, 171.8 ( $\times 2$ ), 172.1, 172.2, 172.7, 174.0 ( $\times 2$ ), 174.1. HRMS (ESI)  $m/z$  calcd for [M – H]<sup>-</sup> 790.2393; found, 790.2395.

#### (*R*)-2,5-bis-(*N*-Acetylcystein-*S*-yl)-*N*-methyl- $\alpha$ -methyl-dopamine (**14**)

General procedure B replacing *S*-(+)-HHMA, HBr **7** by *R*-(-)-HHMA, HBr afforded, after semipreparative reversed-phase HPLC (eluent: solvent A–solvent B 84 : 16 – flow rate: 11 mL min<sup>-1</sup>), (*R*)-2,5-bis-NAC-HHMA **14** in 53% yield (white solid, 70 mg, 0.14 mmol). The degree of purity for compound **14** (99.5%) was determined by analytical HPLC (eluent: solvent A–MeCN 92 : 8 – flow rate: 0.8 mL min<sup>-1</sup>). UV  $\lambda_{\max}$  (aqueous 0.2 M HCl)/nm 274 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  6390), 305sh; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.08 (d,  $J$  = 6.5 Hz, 3H), 1.75 (s, 3H), 1.82 (s, 3H), 2.60 (s, 3H), 2.83 (m, 1H), 3.07 and 3.30 (m, 6H), 4.26 (m, 2H), 6.84 (s, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  14.9, 21.5 ( $\times 2$ ), 30.0, 34.5, 34.7, 37.0, 52.5, 53.6, 56.2, 119.4, 121.0, 126.3, 131.6, 143.9, 146.6, 173.8 ( $\times 4$ ). HRMS (ESI)  $m/z$  calcd for [M + H]<sup>+</sup> 504.1469; found, 504.1469.

#### (*R*)-2,5-bis-(*N*-Acetylcystein-*S*-yl)-*N*-methyl- $\alpha$ -methyl-dopamine (**15**)

General procedure B, replacing *S*-(+)-HHMA, HBr **7** by *R*-(-)-HHMA and *N*-acetylcysteine with glutathione (392 mg, 1.25 mmol, overall quantity), afforded, after exhaustive electrolysis ( $n$  = 5.5, that is 2 for the first step and 3.5 for the second one) and semipreparative reversed-phase HPLC (eluent: solvent A–solvent B 74 : 26 – flow rate: 4 mL min<sup>-1</sup>), (*R*)-2,5-bis-Glu-HHMA **15** as the major product in 40% yield (pale pink solid, 80 mg, 0.101 mmol), along with compound **11** as the minor one, in 17% yield (0.043 mmol). The degree of purity for compound **15** (99.5%) was determined by analytical HPLC (eluent: solvent A–MeCN 95 : 5 – flow rate: 0.6 mL min<sup>-1</sup>). UV  $\lambda_{\max}$  (aqueous 0.2 M HCl)/nm 274 ( $\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  7200), 305sh; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.08 (d, 3H), 2.01 (m, 4H), 2.33 (m, 2H), 2.40 (m, 2H), 2.58 (s, 3H), 2.85 (m, 1H), 3.10 and 3.28 (m, 6H), 3.70 (s, 2H), 3.73 (s, 2H), 3.80 (m, 2H), 4.24 (m, 2H), 6.84 (s, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  14.8, 25.4, 25.5, 30.0, 30.9 ( $\times 2$ ), 34.6, 34.9, 36.9, 40.9 ( $\times 2$ ), 52.4 ( $\times 2$ ), 52.7, 53.4, 56.3, 119.1, 120.8, 126.0, 131.8, 143.8, 146.7, 171.9 ( $\times 2$ ), 172.1, 172.3 ( $\times 2$ ), 172.7, 174.0, 174.2. HRMS (ESI)  $m/z$  calcd for [M – H]<sup>-</sup> 790.2393; found 790.2386.

### Acknowledgements

This research was supported by the joint grants of the “Mission Interministérielle de Lutte contre la Drogue et la Toxicomanie” (MILDT) and the “Institut National de la Santé et de la Recherche Médicale” (INSERM). (Appel à projets commun

2007 MILDT-INSERM “Recherche sur les drogues et la toxicomanie”). C.M.M. is a PhD student funded by the French MRT.

## Notes and references

- 1 A. R. Green, A. O. Mechan, J. M. Elliot, E. O’Shea and M. I. Colado, *Pharmacol. Rev.*, 2003, **55**, 463.
- 2 For recent reviews see: (a) J. Lyles and J. L. Cadet, *Brain Res. Rev.*, 2003, **42**, 155; (b) M. H. Baumann, X. Wang and R. B. Rothman, *Psychopharmacology*, 2007, **189**, 407; (c) J. L. Cadet, I. N. Krasnova, S. Javanthi and J. Lyles, *Neurotoxic. Res.*, 2007, **11**, 183; (d) J. P. Capela, H. Carmo, F. Remiao, M. Lourdes Bastos, A. Meisel and F. Carvalho, *Mol. Neurobiol.*, 2009, **39**, 210; (e) E. Puerta, I. Hervias and N. Aguirre, *Neuropsychobiology*, 2009, **60**, 119; (f) S. Sakar and L. Schmued, *Curr. Pharm. Biotechnol.*, 2010, **11**, 460.
- 3 (a) C. J. Schmidt and V. L. Taylor, *Eur. J. Pharmacol.*, 1988, **156**, 121; (b) J. M. Paris and K. A. Cunningham, *Brain Res. Bull.*, 1992, **28**, 115; (c) B. Esteban, E. O’Shea, J. Camarero, V. Sanchez, A. R. Green and M. I. Colado, *Psychopharmacology*, 2001, **154**, 251; (d) I. Escobedo, E. O’Shea, L. Orío, V. Sanchez, M. Segura, R. de la Torre, M. Farre, A. R. Green and M. I. Colado, *Br. J. Pharmacol.*, 2005, **144**, 231.
- 4 (a) R. T. Miller, S. S. Lau and T. J. Monks, *Chem. Res. Toxicol.*, 1995, **8**, 634; (b) R. T. Miller, S. S. Lau and T. J. Monks, *Chem. Res. Toxicol.*, 1996, **9**, 457; (c) R. T. Miller, S. S. Lau and T. J. Monks, *Eur. J. Pharmacol.*, 1997, **323**, 173; (d) F. Bai, S. S. Lau and T. J. Monks, *Chem. Res. Toxicol.*, 1999, **12**, 1150; (e) F. Bai, D. C. Jones, S. S. Lau and T. J. Monks, *Chem. Res. Toxicol.*, 2001, **14**, 863; (f) D. C. Jones, S. S. Lau and T. J. Monks, *J. Pharmacol. Exp. Ther.*, 2004, **311**, 298; (g) T. J. Monks, D. C. Jones, F. Bai and S. S. Lau, *Ther. Drug Monit.*, 2004, **26**, 132; (h) J. P. Capela, C. Macedo, P. S. Branco, L. M. Ferreira, A. M. Lobo, E. Fernandes, F. Remiao, M. L. Bastos, U. Dirnagl, A. Meisel and F. Carvalho, *Neuroscience (Oxford)*, 2007, **146**, 1743; (i) X. Perfetti, B. O’Mathuna, N. Pizarro, E. Cuyas, O. Khymenets, B. Almeida, M. Pellegrini, S. Pichini, S. S. Lau, T. J. Monks, M. Farré, A. J. Pascual, J. Joglar and R. de la Torre, *Drug Metab. Dispos.*, 2009, **37**, 1448.
- 5 (a) D. C. Jones, C. Duvauchelle, A. Ikegami, C. M. Olsen, S. S. Lau, R. de la Torre and T. J. Monks, *J. Pharmacol. Exp. Ther.*, 2005, **313**, 422; (b) G. V. Erives, S. S. Lau and T. J. Monks, *J. Pharmacol. Exp. Ther.*, 2008, **324**, 284.
- 6 M. Mueller, J. Yuan, A. Felim, A. Neudörffer, F. T. Peters, H. H. Maurer, U. D. McCann, M. Langeron and G. A. Ricaurte, *Drug Metab. Dispos.*, 2009, **37**, 2079.
- 7 (a) M. Hiramatsu, T. Nabeshima, T. Kameyama, Y. Maeda and A. K. Cho, *Pharmacol., Biochem. Behav.*, 1989, **33**, 343; (b) M. P. Johnson, A. J. Hoffman and D. E. Nichols, *Eur. J. Pharmacol.*, 1986, **132**, 269; (c) W. E. Fantegrossi, T. Godlewski, R. L. Karabenick, J. M. Stephens, T. Ullrich, K. C. Rice and J. H. Woods, *Psychopharmacology*, 2003, **166**, 202; (d) N. Pizarro, M. Farré, M. Pujadas, A. M. Peiro, P. N. Roset, J. Joglar and R. de la Torre, *Drug Metab. Dispos.*, 2004, **32**, 1001; (e) W. E. Fantegrossi, *Exp. Clin. Psychopharmacol.*, 2008, **16**, 1; (f) W. E. Fantegrossi, N. Murai, B. O. Mathuna, N. Pizarro and R. de la Torre, *J. Pharmacol. Exp. Ther.*, 2009, **329**, 1006; (g) K. S. Murnane, N. Murai, L. L. Howell and W. E. Fantegrossi, *J. Pharmacol. Exp. Ther.*, 2009, **331**, 717; (h) K. S. Murnane, W. E. Fantegrossi, J. R. Godfrey, M. L. Banks and L. L. Howell, *J. Pharmacol. Exp. Ther.*, 2010, **334**, 642; (i) P. Huot, T. H. Johnston, K. D. Lewis, J. B. Koprach, M. G. Reyes, S. H. Fox, M. J. Piggott and J. M. Brotchie, *J. Neurosci.*, 2011, **31**, 7190.
- 8 (a) M. R. Meyer, F. T. Peters and H. H. Maurer, *Drug Metab. Dispos.*, 2008, **36**, 2345; (b) A. E. Schwaninger, M. R. Meyer, A. J. Barnes, E. A. Kolbrich-Spargo, D. A. Gorelick, R. S. Goodwin, M. A. Huestis and H. H. Maurer, *Biochem. Pharmacol.*, 2012, **83**, 131.
- 9 M. R. Meyer and H. H. Maurer, *Chem. Res. Toxicol.*, 2009, **22**, 1205.
- 10 A. E. Schwaninger, M. R. Meyer and H. H. Maurer, *Drug Metab. Dispos.*, 2011, **39**, 1998.
- 11 A. E. Schwaninger, M. R. Meyer, J. Zapp and H. H. Maurer, *Drug Metab. Dispos.*, 2009, **37**, 2212.
- 12 M. Segura, J. Ortuno, M. Farré, J. A. McLure, M. Pujadas, N. Pizarro, A. Llebaria, J. Joglar, P. N. Roset, J. Segura and R. de la Torre, *Chem. Res. Toxicol.*, 2001, **14**, 1203.
- 13 N. Pizarro, R. de la Torre, J. Joglar, N. Okumura, X. Perfetti, S. S. Lau and T. J. Monks, *Chem. Res. Toxicol.*, 2008, **21**, 2272.
- 14 A. Felim, G. Herrera, A. Neudörffer, M. Blanco, J. E. O’Connor and M. Langeron, *Chem. Res. Toxicol.*, 2010, **23**, 211.
- 15 N. Pizarro, R. de la Torre, M. Farré, J. Segura, A. Llebaria and J. Joglar, *Bioorg. Med. Chem.*, 2002, **10**, 1085.
- 16 (a) A. Felim, A. Urios, A. Neudörffer, G. Herrera, M. Blanco and M. Langeron, *Chem. Res. Toxicol.*, 2007, **20**, 685; (b) A. Felim, A. Neudörffer, F. P. Monnet and M. Langeron, *Int. J. Electrochem. Sci.*, 2008, **3**, 266.
- 17 (a) A. P. Marcus, A. S. Lee, R. L. Davis, D. J. Tantillo and R. Sarpong, *Angew. Chem., Int. Ed.*, 2008, **47**, 6379; (b) Y. Ishida, Y. Kai, S. Y. Kato, A. Misawa, S. Amamo, Y. Matsuoka and K. Saigo, *Angew. Chem., Int. Ed.*, 2008, **47**, 8241; (c) L. Z. Zhang, Y.-J. Jiang, X.-Z. Jiao, P. Xie and D. B. Zhao, *Hecheng Huaxue*, 2008, **16**, 712.
- 18 J. Liu, N. Ikemoto, D. Petrillo and J. D. Armstrong III, *Tetrahedron Lett.*, 2002, **43**, 8223.
- 19 (a) M. C. Myers, J. Wang, J. A. Iera, J.-K. Bang, T. Hara, S. Saito, G. P. Zambetti and D. H. Appella, *J. Am. Chem. Soc.*, 2005, **127**, 6152; (b) S. Hanessian, G. J. Reddy and N. Chahal, *Org. Lett.*, 2006, **8**, 5477.
- 20 J. C. Lee and J. K. Cha, *Tetrahedron*, 2000, **56**, 10175.
- 21 C. Valdivia, N. Marquez, J. Eriksson, A. Vilaseca, E. Munoz and O. Sterner, *Bioorg. Med. Chem.*, 2008, **16**, 4120.
- 22 (a) J. J. Eisch, Z.-R. Liu and M. P. Boleslawski, *J. Org. Chem.*, 1992, **57**, 2143; (b) C. R. G. Grenier, W. Pisula, T. J. Joncheray, K. Müllen and J. R. Reynolds, *Angew. Chem., Int. Ed.*, 2007, **46**, 714.
- 23 J. E. Norlander, M. J. Payne, F. G. Njoroge, M. A. Balk, G. D. Laikos and V. M. Vishwanath, *J. Org. Chem.*, 1984, **49**, 4107.
- 24 C. K. Lau, C. Dufresne, P. C. Bélanger, S. Piétre and J. Scheiget, *J. Org. Chem.*, 1986, **51**, 3038.
- 25 R. O. Hutchins, C. A. Milewski and B. E. Maryanoff, *J. Am. Chem. Soc.*, 1973, **95**, 3662.
- 26 (a) V. P. Miller, D.-Y. Yang, T. M. Weigel, O. Han and H. W. Liu, *J. Org. Chem.*, 1989, **54**, 4175; (b) S. Kim, C. H. Oh, J. S. Ko, K. H. Ahn and Y. J. Kim, *J. Org. Chem.*, 1985, **50**, 1927; (c) D. F. Taber, Y. Wang and T. F. Pahustski, *J. Org. Chem.*, 2000, **65**, 3861.
- 27 P. E. Lindner and D. M. Lemal, *J. Am. Chem. Soc.*, 1997, **119**, 3259.
- 28 C. Macedo, P. S. Branco, L. M. Ferreira, A. M. Lobo, J. P. Capela, E. Fernández, M. de Lourdes Bastos and F. Carvalho, *J. Health Sci.*, 2007, **53**, 31.
- 29 See for example: (a) D. Nematollahi and H. Goodarzi, *J. Org. Chem.*, 2002, **67**, 5036; (b) D. Nematollahi and E. Tammari, *J. Org. Chem.*, 2005, **70**, 7769; (c) D. Xu, A. Chiaroni and M. Langeron, *Org. Lett.*, 2005, **7**, 5273; (d) C.-C. Zeng, D.-W. Ping, Y.-S. Xu, L.-M. Hu and R.-G. Zhong, *Eur. J. Org. Chem.*, 2009, **33**, 5832; (e) C.-C. Zeng, D.-W. Ping, L.-M. Hu, X.-Q. Song and R.-G. Zhong, *Org. Biomol. Chem.*, 2010, **8**, 2465; (f) X.-G. Gao, C.-W. Yang, Z.-Z. Zhang, C.-C. Zeng, X.-Q. Song, L.-M. Hu, R.-G. Zhong and Y.-B. She, *Tetrahedron*, 2010, **66**, 9880.
- 30 (a) F. Zhang and G. Dryhurst, *J. Electroanal. Chem.*, 1995, **398**, 117; (b) X.-M. Shen, B. Xia, M.-Z. Wrona and G. Dryhurst, *Chem. Res. Toxicol.*, 1996, **9**, 1117; (c) R. Xu, X. Huang, K. J. Kramer and M. D. Hawley, *Bioorg. Chem.*, 1996, **24**, 110; (d) F. Zhang and G. Dryhurst, *J. Med. Chem.*, 1994, **37**, 1084.
- 31 X.-M. Shen and G. Dryhurst, *J. Med. Chem.*, 1996, **39**, 2018.
- 32 X. Huang, R. Xu, M. D. Hawley, T. L. Hopkins and K. J. Kramer, *Arch. Biochem. Biophys.*, 1998, **352**, 19.
- 33 A. Neudörffer, M. Mueller, C. M. Martinez, A. Mechan, U. McCann, G. A. Ricaurte and M. Langeron, *Chem. Res. Toxicol.*, 2011, **24**, 968.