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# Synthesis and Capillary Electrophoretic Analysis of Enantiomerically Enriched Reference Standards of MDMA and its Main Metabolites

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**Abstract**—Enantiomerically-enriched (*S*)-3,4-methylenedioxymethamphetamine (MDMA) and its main metabolites (*S*)-4-hydroxy-3-methoxymethamphetamine (HMMA) and (*S*)-3,4-dihydroxymethamphetamine (HHMA) were prepared for unequivocal identification of the differential enantioselective metabolism of these compounds as well as for its application in the analysis of biological samples. Capillary electrophoresis with cyclodextrin derivatives and a chemical correlation of (*S*)-MDMA, (*S*)-HMMA and (*S*)-HHMA has been performed to assign the absolute stereochemistry of major isomers in analytical standards enriched with such enantiomers. 

## Introduction

3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is an illicit drug frequently misused by the youth, and potentially associated with acute and long-term effects. MDMA is available as its racemate (*R*,*S*)-MDMA but different pharmacological properties for each enantiomer have been reported. Acute effects of MDMA that ultimately may be the cause of death[1] are related to sympathetic hyperactivity in the neural and cardiovascular systems. Neurotoxicity and some psychomimetic properties are related to the (*S*)-isomer.[2] Body disposition of MDMA is also subjected to selective enantiomeric metabolism. Well characterized metabolites of MDMA include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA). 3,4-Dihydroxyamphetamine (HHA) and 3,4-dihydroxymethamphetamine (HHMA) are metabolic intermediates. Analysis of the enantiomeric ratio of major MDMA metabolites in human samples is desirable given the pharmacological relevance of the enantioselectivity of MDMA, HHMA and HMMA. We have recently shown that capillary electrophoresis (CE) using (2-hydroxypropyl)-β-cyclodextrin as enantioselective selector provided an efficient baseline separation of these enantiomers.[3] However, unequivocal identification of elution order of enantiomers is indispensable to characterize the results obtained from the analysis of biological samples. Although two syntheses of (*S*)-MDMA are already described in the literature,[4] preparation of the enantiomers of HMMA and HHMA has not been performed. Accordingly, a study was conducted to undertake the synthesis of standards of MDMA, HMMA and HHMA enriched in its *S* enantiomer. The synthetic chemistry leading to these standards and the chemical correlation used for enantiomer identification in the CE peaks are here reported.

## Results and Discussion

Synthesis of (*S*)-HHMA was originally planned as previously described[5] using the key intermediate (*S*)-(3,4-dibenzyloxyphenyl)-2-propanamine **1** and expecting transformation of **1** into HHMA by *N*-monomethylation followed by hydrogenolytic debenzylation. Racemic **1** was prepared from commercially available 3,4-dibenzyloxybenzaldehyde upon condensation with nitroethane followed by reduction with lithium aluminium hydride

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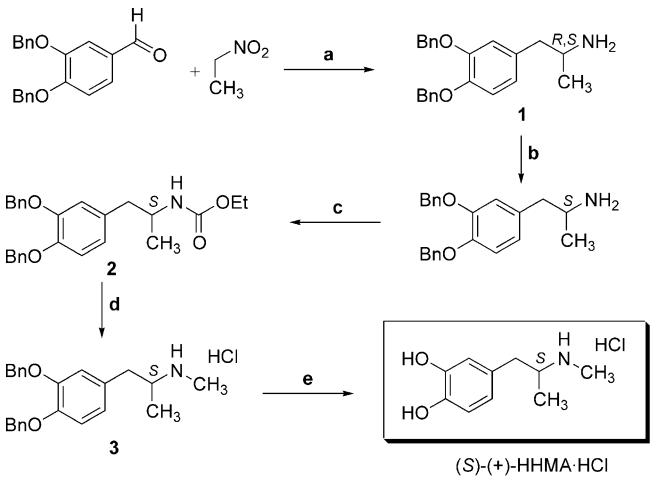



**Scheme 1.** Synthesis of enantiomerically enriched (*S*)-HHMA·HCl. a: 1) $CH_3CO_2NH_4$; 2) $LiAlH_4$; b: resolution; c: $ClCO_2Et$; d: 1) $LiAlH_4$; 2) HCl; e: $H_2$, Pd-C, MeOH.

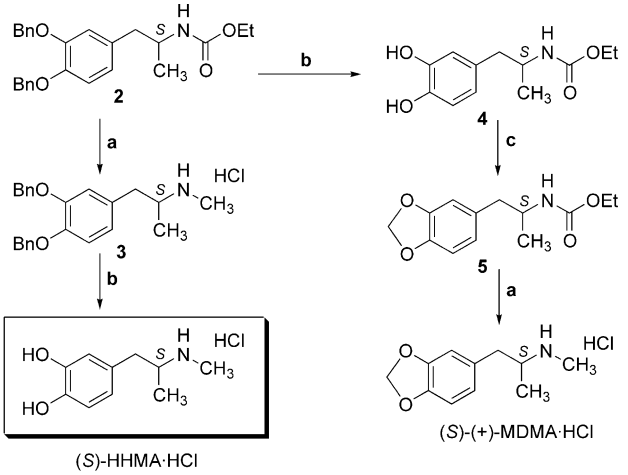
(see Scheme 1). Reaction of amine **1** with an equimolar amount of dibenzoyl-D-(+)-tartaric acid gave rise to a crystalline diastereomeric salt that after a single crystallization step with methanol resulted in a compound with an $[\alpha]_D^{20}$ +65.8 (*c* 0.84, methanol). The optical rotation sign of this compound was opposed to that reported by Pratesi et al. ($[\alpha]_D^{20}$ −62.9 (*c* 0.78, methanol)].[5] This result, however, was confirmed by treating the salt with 1 N NaOH giving rise to a recovered amine **1** with an $[\alpha]_D^{20}$ −6.4 (*c* 1.8, chloroform) that also had an optical rotation sign opposed to that reported in the literature for **1** $[\alpha]_D^{20}$ +12.6 (*c* 3.7, chloroform)].[5]

Resolution of **1** with dibenzoyl-L-(−)-tartaric acid was assessed. Products with specific sign and rotation values consistent with those obtained for resolution of **1** with dibenzoyl-D-(+)-tartaric acid[5] were recovered. Moreover, repeated re-crystallization of the salt formed from **1** with dibenzoyl-L-(−)-tartaric acid resulted in a very slight enrichment after three steps. For this reason, synthesis of HHMA with the enantioenriched amine **1** was continued. Thus, (*S*)-(3,4-dibenzyloxyphenyl)-2-propanamine was converted to the corresponding carbamate **2** by reaction with ethyl chloroformate. Reduction with lithium aluminium hydride and subsequent treatment with an ethereal solution of hydrogen chloride resulted in *N*-methylamine **3** as its hydrochloride salt. Hydrogenation with a catalytic amount of palladium on charcoal yielded (*S*)-HHMA·HCl with an 80% ee. A sample of racemic HHMA·HCl was also prepared from racemic 1-(3,4-dibenzyloxyphenyl)-2-propanamine **1** following the same synthetic scheme.

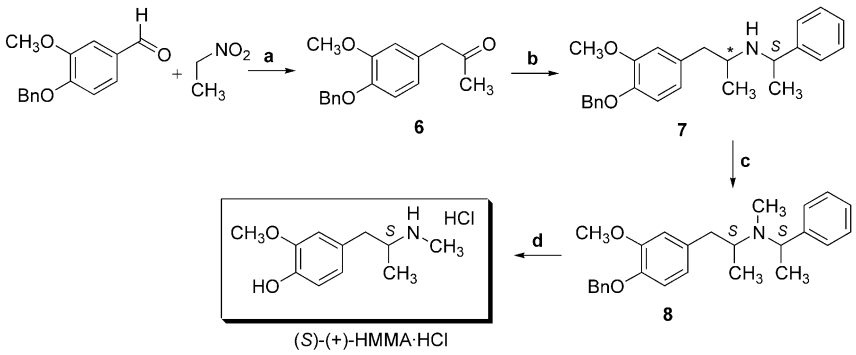
A chemical correlation with (*S*)-MDMA[4] was performed in order to determine the stereochemistry of (*S*)-HHMA·HCl. (*S*)-MDMA was prepared from a common intermediate to the previously synthesized (*S*)-HHMA (Scheme 2). Thus, hydrogenation of (*S*)-*N*-ethoxycarbonyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane **2** with a catalytic amount of Pd/C resulted in (*S*)-*N*-ethoxycarbonyl-1-(3,4-dihydroxyphenyl)-2-aminopropane **4**. The corresponding (*S*)-*N*-ethoxycarbonyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane **5** was obtained after treatment with bromochloromethane and cesium carbonate in anhydrous *N*,*N*-dimethylformamide.

Finally, reduction with lithium aluminium hydride and subsequent hydrochloride formation yielded (*S*)-(+)-MDMA·HCl with an optical rotation of $[\alpha]_D^{20}$ +15.2 (*c* 0.79, $H_2O$). Analysis of this compound by CE gave a 77% ee, confirming that the synthesised (*S*)-*N*-methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane [(*S*)-HHMA] had the expected *S* configuration.

On the other hand, synthesis of (*S*)-HMMA (see Scheme 3) was accomplished following an asymmetric synthesis described for similar compounds.[6] Condensation of the commercially available 4-benzyloxy-3-methoxybenzaldehyde with nitroethane, followed by reduction with iron metal in aqueous HCl resulted in ketone **6**.[7] Reductive amination of **6** with (*S*)-α-methylbenzylamine and sodium cyanoborohydride gave rise to amine **7** as a 67:33 mixture of diastereomers. Methylation of amine **7** with iodomethane and sodium carbonate provided the corresponding *N*-methylamine as a mixture of two diastereomers. They were partially




**Scheme 2.** Chemical correlation of (*S*)-HHMA·HCl with (*S*)-MDMA·HCl. a: 1) $LiAlH_4$, 2) HCl; b: $H_2$, Pd-C, MeOH; c: $BrCH_2Cl$, $CsCO_3$.




**Scheme 3.** Synthesis of enantiomerically enriched (*S*)-HMMA·HCl. a: 1) $CH_3CO_2NH_4$; 2) Fe, HCl-$H_2O$; b: (*S*)-α-methylbenzylamine, Na $BH_4$ CN; c: 1) $CH_3L$, $Na_2CO_3$; 2) chromatography separation; d: 1) HCl; 2) $H_2$, Pd-C, MeOH.

separated by flash column chromatography yielding a fraction enriched in the (*S*,*S*)-isomer **8**. After hydrochloride formation, hydrogenolysis provided the corresponding (*S*)-HMMA hydrochloride with a 72% ee as determined by CE analysis.

The stereochemistry of synthetic (*S*)-HMMA·HCl was confirmed by correlation with HHMA and MDMA. Thus, reaction of (*S*)-*N*-methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane hydrochloride [(*S*)-HHMA·HCl] with an ethereal solution of diazomethane provided the enriched (*S*)-isomer of *N*-methyl-1-(3,4-dimethoxyphenyl)-2-aminopropane hydrochloride [(*S*)-MMMA·HCl] **9** (see Scheme 4) and the same reaction was performed with synthetic (*S*)-HMMA·HCl. Comparison of the results obtained from enantioselective capillary electrophoresis analysis of MMMA·HCl **9** from both sources confirmed that both compounds had the same configuration (see Fig. 1).

To determine the elution order of the enantiomers of the synthesised compounds and the enantiomeric excess for (*S*)-MDMA, (*S*)-HHMA and (*S*)-HMMA, CE analysis was performed following the method developed by our group.[3] Thus, for each analyte, separate analysis was performed for the racemic mixture and the synthesized enantioenriched material. In all cases, (*S*)-enantiomers eluted after the (*R*)-enantiomers (see Fig. 1).

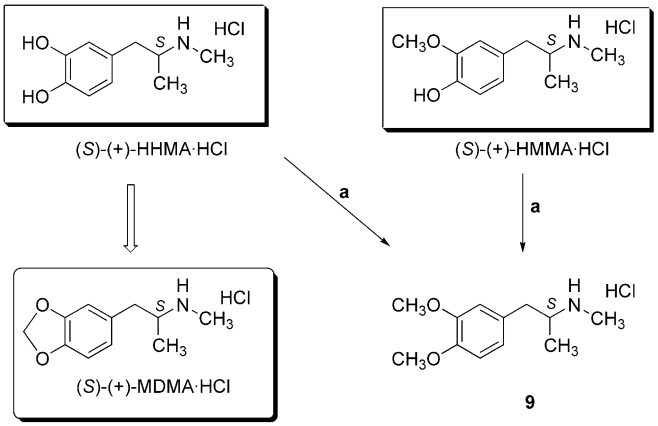
## Conclusion

This is the first report describing the synthesis and chemical correlation of enantioenriched (*S*)-MDMA, (*S*)-HHMA and (*S*)-HMMA. Although these methods would probably allow the preparation of higher enantiomerically pure compounds, it was considered this unnecessary for the current objectives of the present study, and irrelevant from an analytical point of view. The availability of the newly synthesized enantiomeric enriched metabolites of MDMA are crucial for ongoing an future studies on in vivo differential metabolism of MDMA enantiomers and their role in the neurotoxicity and other pharmacological effects of MDMA in humans.

## Experimental

### General methods

Reactions sensitive to moisture were carried out under Ar atmosphere. Commercial grade reagents were used directly without further purification (unless otherwise indicated). Solvents were dried by standard methods and distilled before use. Purification of products by column chromatography was performed on Merck silica gel 60. TLC was carried out on precoated silica gel Merck 60 $F_{254}$ (0.25 mm) sheets. IR spectra were recor-




**Scheme 4.** Chemical correlation of (*S*)-HHMA·HCl and (*S*)-HMMA·HCl with (*S*)-MDMA·HCl. a: $CH_2N_2$-$Et_2O$.

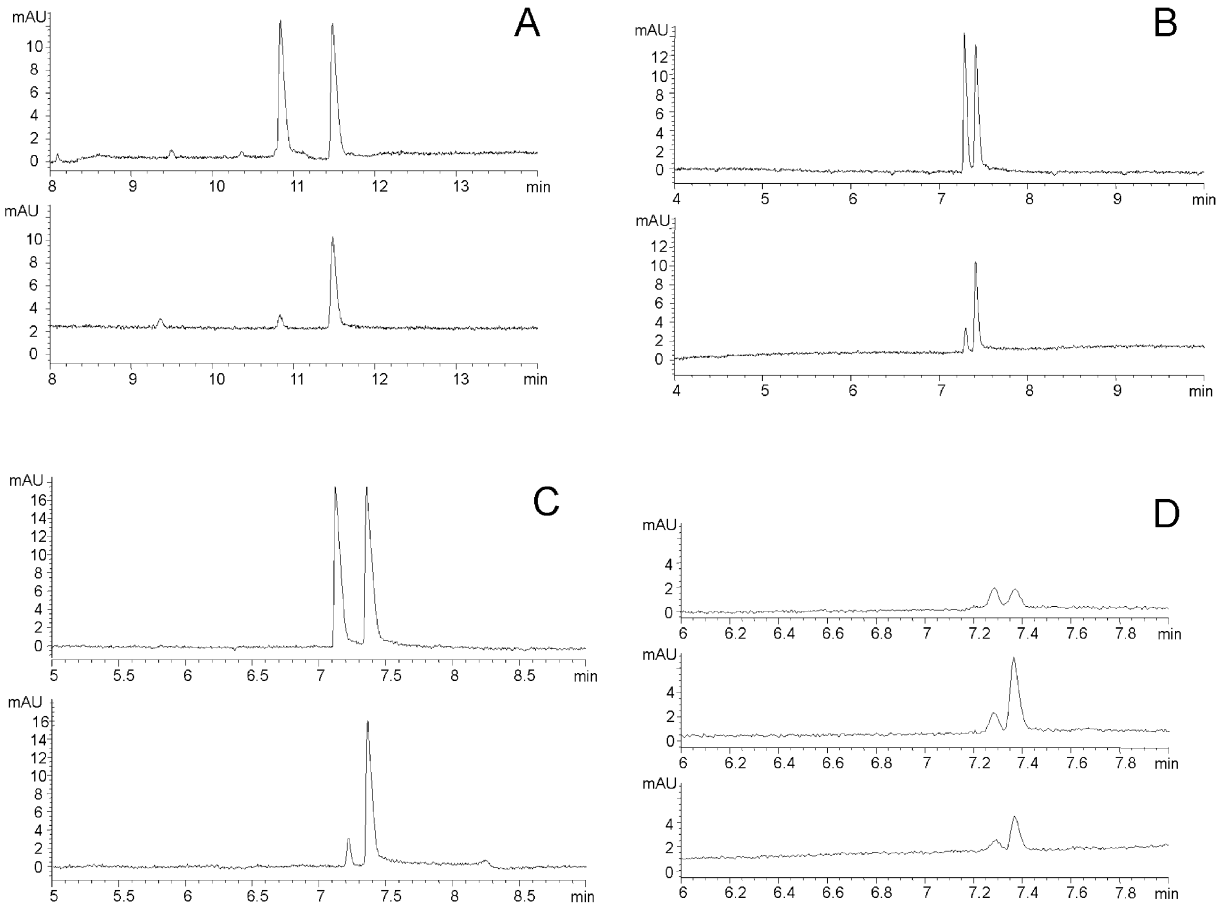



**Figure 1.** Capillary electropherograms for racemic and enantioenriched samples of HHMA, HMMA, MDMA and MMMA. (A) Top: (*R*,*S*)-HHMA; bottom: enriched (*S*)-HHMA; (B) top: (*R*,*S*)-HMMA, bottom: enriched (*S*)-HMMA; (C) top: (*R*,*S*)-MDMA; bottom: enriched (*S*)-MDMA; and (D) top: (*R*,*S*)-MMMA, middle: enriched (*S*)-MMMA from (*S*)-HMMA, bottom: enriched (*S*)-MMMA from (*S*)-HHMA.

ded on a Michelson Bomem MB-120 with Fourier transform instrument and are reported in $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were obtained in $CDCl_3$ Solutions (unless otherwise indicated) on a Varian Gemini XL200 and a Varian Unity 300 spectrometers, operating at 200 and 300 MHz for $^1H$ and 50 and 75 MHz for $^{13}C$, respectiviely. Chemical shifts are reported in delta ($\delta$) units, parts per million (ppm) downfield from $(CH_3)_4Si$, or in ppm relative to the singlet at 7.26 ppm of $CDCl_3$ for $^1H$ and in ppm relative to the centre line of a triplet at 77.0 ppm of $CDCl_3$ for $^{13}C$. $^1H$ NMR: splitting pattern abbreviations include the following: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. $^{13}C$ NMR: multiplicities were determined by DEPT experiments using standard pulse sequences. In case of a mixture of diastereomers, abbreviations 'min' and 'maj' refer to signals of the minor and major diastereomer, respectively; when no specification is mentioned, it either has not been possible to assign the signal to any diastereomer or belongs to both of them.

A 341 Perkin-Elmer polarimeter was used for optical rotatory measures. A gas chromatograph (HP 6890 series GC system, Hewlett-Packard, Palo Alto, CA, USA) equipped with a quadrupole mass spectrometer (HP 5973 mass selective detector) and an autosampler (5683 series injector) was used. A cross-linked 5% phenylmethylsiloxane capillary column (12 m×0.2 mm I.D.×0.3 μm film thickness) (HP, Ultra-2) was employed, with helium as the carrier gas at a flow rate of 1.2 mL/min. The oven was maintained at 100 °C for 1 min and two cycles were programmed, from 100–200 °C at 10 °C/min followed by 200–280 °C at 30 °C/min (total run time 13.67 min). Samples were injected in the split mode. Insert liners packed with silanized glass-wool were used. Injector and interface were set at 280 °C. The mass spectrometer was operated by electron impact ionisation (E.I., 70 eV) and in the scan mode (working range 100–550 amu).

Trifluoroacyl derivatives of each enriched forms were analysed by GC–MS for assessing the purity of all synthesized standards. Methanolic solutions of every racemic and enriched form were allowed to react with an appropriate amount of *N*-methyl-bis(trifluoroacetamide) (MBTFA) at 70 °C for 45 min, and the corresponding *N*-TFA and/or *O*-TFA derivatives were obtained.

A capillary electrophoresis system ($^{3D}$CE, Hewlett-Packard) equipped with a diode-array detector was employed for the enantiomeric separation. Separation was performed in an untreated fused-silica capillary of 48.5 cm total length (40 cm effective length) and a stan-

dard 50 μm optical path length cell. A constant voltage of 30 kV was applied and the cartridge temperature was maintained at 15 °C. The diode-array detector was set to monitor the signal at 204 nm. (2-Hydroxypropyl-β-cyclodextrin (Hewlett-Packard CE grade 97 + %. Part # 8501-0133) in 50 mM $H_3PO_4$ (pH = 2.5) at a concentration of 50 mM as running buffer was used for the enantioselective separation of the enantiomers, with 50 mM $H_3PO_4$ for 1.5 min and running buffer for 1 min as preconditioning conditions before each experiment. Injection of the sample was performed by applying external pressure of 50 mbar for 2 s.

### Synthesis of enantiomerically enriched (*S*)-*N*-methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane [(*S*)-3,4-dihydroxy methamphetamine, (*S*)-HHMA]

**1-(3,4-Dibenzyloxyphenyl)-2-nitropropene.** This compound was synthesized following the method described by Glennon et al.[8] 3,4-Dibenzyloxybenzaldehyde (10 g, 30.77 mmol), nitroethane (150 mL) and ammonium acetate (2.47 g, 30.77 mmol) were dissolved in a 250 mL round bottom flask and the mixture heated at reflux for 17 h. Nitroethane was then removed with a Büchi rotary evaporator and the solid residue was taken up in 250 mL of ethyl acetate and then washed with water (2×40 mL) and brine (40 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed and 1-(3,4-dibenzyloxyphenyl)-2-nitropropene as a yellow powder (11.08 g, 29.55 mmol, 96% yield) was obtained. IR (neat, $\nu_{max}$ $cm^{-1}$): 1600, 1523, 1510, 1454, 1317, 1269, 1236, 1141, 1022, 860, 696. $^1H$ NMR (300 MHz; $CDCl_3$, δ): 2.31 (s, 3H), 5.22 (s, 2H), 5.24 (s, 2H), 6.96–7.01 (m, 3H), 7.32–7.49 (m, 10H), 7.98 (s, 1H). $^{13}C$ NMR (75 MHz; $CDCl_3$, δ): 13.9, 70.8, 71.3, 114.1, 116.6, 124.8, 125.2, 127.0, 127.1, 127.9, 128.0, 128.5, 128.6, 133.6, 136.5, 136.7, 145.9, 148.4, 150.6.

**1-(3,4-Dibenzyloxyphenyl)-2-aminopropane.** According to a method previously described,[8,9] 100 mL of anhydrous tetrahydrofurane (THF) and $LiAlH_4$ (2.5 g, 62.5 mmol) were introduced into a three-neck round bottom flask, previously evacuated (equipped with a thermometer, a dropping funnel with pressure-equalisation arm, and a septum) under an argon atmosphere and with continuous stirring, placed in an ice bath.

A solution of 11.08 g (29.55 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-nitropropene in 75 mL of anhydrous THF was transferred to the dropping funnel via cannula. Its addition over the $LiAlH_4$ suspension was slowly and carefully performed so that the temperature did not exceed 15 °C. Once the addition was complete, the funnel was changed to a condenser and the resulting mixture was refluxed and stirred for 4 h and cooled to room temperature followed by an ice bath. $LiAlH_4$ excess was removed by careful dropwise addition of water and then treated with anhydrous $Na_2SO_4$. After filtration, the solution was concentrated and dried yielding 1-(3,4-dibenzyloxyphenyl)-2-aminopropane **1**, 7.1 g (19.97 mmol, 71% yield) as a pale yellow powder. $^1H$ NMR (300 MHz; $CDCl_3$, δ): 1.07 (d, 3H), 1.20 (bs, 2H), 2.38 (A of an ABX syst., $J$ = 8.2, 13.4 Hz, 1H), 2.61 (B of an ABX syst., $J$ = 5.0, 13.4 Hz, 1H), 3.01–3.12 (X of an ABX syst., m, 1H), 5.15 (s, 2H), 5.17 (s, 2H), 6.68–6.90 (m, 3H), 7.28–7.47 (m, 10H). $^{13}C$ NMR (75 MHz; $CDCl_3$, δ): 23.4, 46.0, 48.4, 71.2, 71.4, 115.1, 116.4, 122.1, 127.2, 127.3, 127.6, 127.7, 128.4, 133.1, 137.2, 137.4, 147.4, 148.6.

**(*S*)-1-(3,4-Dibenzyloxyphenyl)-2-aminopropane.**[5] 10 g of racemic 1-(3,4-dibenzyloxyphenyl)-2-aminopropane was placed in a 500 mL round bottom flask containing 250 mL of boiling methanol, and 10 g of dibenzoyl-L-(−)-tartaric acid was added. Once the solution reached the room temperature, it was stored in the refrigerator for about one week until the crystals precipitated. Crystals were filtered, washed with cool methanol and dried achieving a total amount of 9.48 g. The crystals were dissolved in 50 mL of dichloromethane and treated with 15 mL of 1 N NaOH aqueous solution. The organic layer was decanted and the aqueous layer extracted with dichloromethane (3×5 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ to obtain the free amine. After two repetitions of these steps 3.90 g of salt with an $[\alpha]_D^{20}$ −59.5 (*c* 0.82, methanol) were obtained [literature:[5] $[\alpha]_D^{20}$ −59.3 (*c* 0.84, methanol) for the salt of the dibenzoyl-D-(+)-tartaric acid]. After treatment with base, it yielded 1.44 g of (*S*)-1-(3,4-dibenzyloxyphenyl)-2-aminopropane with an $[\alpha]_D^{20}$ +10.89 (*c* 3.35, chloroform) [literature:[5] $[\alpha]_D^{20}$ +15.1 (*c* 3.4, chloroform)].

**(*S*)-*N*-Ethoxycarbonyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane (2).** Carbamate **2** was synthesized as described by Yousif et al.[9] Again, 10 mL of anhydrous THF, 1.24 g (3.57 mmol) of (*S*)-1-(3,4-dibenzyloxyphenyl)-2-aminopropane, 1.1 mL (7.14 mmol, 2 equiv) of triethylamine and 6.74 mg (0.06 mmol, 0.01 equiv) of 4-(dimethylamino)pyridine (DMAP) were placed in an ice cooled 100 mL round bottom flask under an argon atmosphere and continuous stirring. A solution of ethyl chloroformate (0.66 mL, 6.95 mmol, 2 equiv) in 10 mL of anhydrous THF was slowly added, and the mixture left at room temperature for 6 h. The residue was dissolved in diethyl ether (60 mL) and washed with 20 mL of water. Ether was decanted and the aqueous phase extracted with diethyl ether (2×25 mL). The combined organic extracts were washed with water (10 mL), HCl 1 N (20 mL) and saturated NaCl (10 mL), dried over anhydrous $Na_2SO_4$, and evaporated to obtain 1.22 g (2.90 mmol, 81%) of (*S*)-*N*-ethoxycarbonyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane **2** as a white solid. $^1H$ NMR (300 MHz; $CDCl_3$): δ 1.03 (d, 3H), 1.24 (t, 3H), 2.57 (A of an ABX syst., $J$ = 7.2, 13.5 Hz, 1H), 2.75 (B of an ABX syst., $J$ = 5.4, 13.5 Hz, 1H), 3.80–3.96 (X of an ABX syst., m, 1H), 4.10 (q, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 6.67–6.88 (m, 3H), 7.28–7.47 (m, 10H). $^{13}C$ NMR (75 MHz; $CDCl_3$): δ 14.6, 20.0, 42.2, 47.7, 60.5, 71.2, 71.3, 115.0, 116.5, 122.4, 127.2, 127.3, 127.6, 127.7, 128.4, 131.3, 137.2, 137.4, 147.6, 148.6, 155.8.

**(*S*)-*N*-Methyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane hydrochloride (3).** This reaction has been previously described.[9] In this case, 11 g of $LiAlH_4$ (2.86 mmol, 3 equiv) and 6 mL of anhydrous THF were added in a

three-neck round bottom flask, previously evacuated and filled with argon (equipped with a thermometer, a dropping funnel with pressure-equalization arm, and a septum) and placed on an ice bath. A solution of carbamate **2** (0.4 g, 0.95 mmol) in 18 mL of anhydrous THF was slowly added through the dropping funnel controlling to keep the temperature below 15 °C. When the addition was done, the funnel was exchanged by a condenser and the resulting mixture was refluxed and stirred for 18 h, obtaining a grey suspension. The $LiAlH_4$ excess was destroyed by addition of water (drop by drop) and then of anhydrous $Na_2SO_4$. The resulting solid was filtered, washed with diethyl ether (2×25 mL) giving rise to a colorless solution. This solution was concentrated and dried under vacuum yielding an oil that was purified by column chromatography (silica gel) using dichloromethane/methanol (1500 mL, 9:1, v/v). A total of 264.1 mg (0.73 mmol, 78% yield) of colorless oil was obtained. $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.03 (d, 3H), 2.35 (s, 3H), 2.55 (A of an AB syst., $J$ = 2.4 Hz, 1H), 2.58 (B of an AB syst., $J$ = 2.1 Hz, 1H), 2.64–2.75 (m, 1H), 5.15 (s, 2H), 5.18 (s, 2H), 6.70–6.90 (m. 3H), 7.28–7.49 (m, 10H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 19.5, 33.9, 42.9, 56.2, 71.1, 71.3, 115.0, 116.3, 122.0, 127.1, 127.2, 127.5, 127.6, 128.3, 132.7, 137.2, 137.3, 147.4, 148.5. Finally, HCl 3 N in anhydrous diethyl ether was added (dropwise) to the oil dissolved in 5 mL of anhydrous diethyl ether. A pale yellow solid precipitate was filtered and dried yielding (*S*)-*N*-methyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane hydrochloride (278.5 mg, 0.70 mmol, 74% yield from **2**) that was used without further characterization.

**(*S*)-*N*-Methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane hydrochloride, (*S*)-HHMA·HCl.**[8,9] In a 10 mL round bottom flask were placed 115 mg of (*S*)-*N*-methyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane hydrochloride dissolved in 2 mL of anhydrous methanol and a catalytic amount of palladium (10 wt% on carbon powder) and the flask was capped with a septum. By means of a three-way stopcock connected to a hydrogen containing ballon, a water aspirator, and the flask, three cycles of vacuum/hydrogen filling were done. The flask was then left under hydrogen atmosphere and stirred for 4 h. After that time, the solution was filtered through Celite®, washing the solid with previously degassed anhydrous methanol. Finally, the solution was concentrated and dried to yield 58 mg (0.26 mmol, 92% yield) of grey oil that was conserved under nitrogen atmosphere and protected from the light until its use. $^1$H NMR (DMSO-$d_6$, 200 MHz): δ 1.01 (d, 3H), 2.34 (A of an AB syst., $J$ = 12.4 Hz, 1H), 2.94 (B of an AB syst., $J$ = 13.0 Hz, 1H), 3.00–3.20 (m, 1H), 3.09 (s, 3H), 6.38–6.64 (m, 3H), 8.97 (bs, 2H). $^{13}$C NMR (DMSO-$d_6$, 50 MHz): δ 14.9, 29.5, 37.7, 55.5, 115.8, 116.6, 119.9, 127.3, 144.1, 145.2. GC–MS (*N*-TFA, *O*-TFA derivative); $m/z$ 110, 154, 343.

**Synthesis of racemic *N*-methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane (3,4-dihydroxymethamphetamine, HHMA).** Following the above-mentioned method for the enantiomerically enriched (*S*)-*N*-methyl-1-(3,4-dihydroxyphenyl)-2-aminopropane hydrochloride [(*S*)-HHMA·HCl], 475 mg (2.18 mmol, 54% overall yield) of racemic *N*-methyl - 1 - (3,4 - dihydroxyphenyl) - 2 - aminopropane hydrochloride (HHMA·HCl) were obtained starting from 880 mg (2.76 mmol) of 3,4-dibenzyloxybenzaldehyde.

**Synthesis of enantiomerically enriched (*S*)-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride [(*S*)-3,4-methylenedioxymethamphetamine, (*S*)-MDMA]**

**(*S*)-*N*-Ethoxycarbonyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane** (5).[10] In a round bottom flask were dissolved 373 mg (0.89 mmol) of (*S*)-*N*-ethoxycarbonyl-1-(3,4-dibenzyloxyphenyl)-2-aminopropane **2** in 8 mL of methanol. A catalytic amount of Palladium 10 wt. % on carbon powder was added and hydrogenation was performed as usual. After the workup were obtained 202 mg (0.84 mmol, 95% yield) of (*S*)-*N*-ethoxycarbonyl-1-(3,4-dihydroxyphenyl)-2-aminopropane **4** that was used without further purification. This crude product was dissolved in a 50 mL round bottom flask in 3 mL of anhydrous dimethylformamide. To this solution was added 100 μL (1.34 mmol, 1.6 equiv) of $BrCH_2Cl$ and 0.44 g (1.34 mmol, 1.6 equiv) of $CsCO_3$ and the mixture was stirred for 2 h. After that time, the solution was filtered through a Celite® pad and taken to dryness under vacuum. The residue was then dissolved in 200 mL of ethyl acetate and washed with water (2×25 mL) and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed giving a solid that was dried under vacuum. This product was purified by column chromatography (silica gel) using hexane/ethyl acetate (starting with hexane and increasing ethyl acetate concentration in 5% every 100 mL, 1200 mL of total volume). Finally, 213.2 mg (0.85 mmol, 95% yield) of (*S*)-*N*-ethoxycarbonyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane **5** were obtained. $^1$H NMR ($CDCl_3$; 200 MHz): δ 1.07 (d, 3H), 1.19 (t, 3H), 2.55 (A of an ABX syst., $J$ = 11.2, 13.4 Hz, 1H), 2.73 (B of an ABX syst., $J$ = 5.8, 13.4 Hz, 1H), 3.71–3.96 (X of an ABX syst., 1H), 4.05 (q, 2H), 4.67 (bs, 1H), 5.88 (s, 2H), 6.53–6.76 (m. 3H).

**(*S*)-3,4-Methylenedioxyphenyl-2-aminopropane hydrochloride.** To a previously evacuated 100 mL Schlenck flask, and under argon atmosphere, containing 97 mg of $LiAlH_4$ (2.55 mmol, 3 equiv) in 5 mL of anhydrous THF, were dropwise added 213 mg of (*S*)-*N*-ethoxycarbonyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane **5** in 10 mL of anhydrous THF. The mixture was refluxed with stirring for 2 h and then was cooled to room temperature and worked-up as performed for compound **3** achieving 160.4 mg (0.83 mmol, 98% yield) of the white solid (*S*)-MDMA. $^1$H NMR ($CDCl_3$; 200 MHz): δ 1.02 (d, 3H), 1.84 (bs, 1H), 2.36 (s, 3H), 2.46–2.75 (m, 3H), 5.89 (s, 2H), 6.55–6.77 (m, 3H). This compound was then dissolved in anhydrous diethyl ether and HCl 3 N (in anhydrous diethyl ether) was dropwise added, yielding 180 mg (0.79 mmol, 94% yield) of (*S*)-3,4-methylenedioxyphenyl-2-aminopropane hydrochloride, (*S*)-MDMA·HCl, as a white solid whose optical rotation was $[\alpha]_D^{20}$ +15.16 (*c* 0.79, $H_2O$). GC–MS (N-TFA derivative); $m/z$ 110, 135, 154, 162, 289.

**Synthesis of enantiomerically enriched (*S*)-*N*-methyl-1-(4-hydroxy-3-methoxyphenyl)-2-aminopropane [(*S*)-4-hydroxy-3-methoxymethamphetamine, (*S*)-HMMA]**

**1-(4-benzyloxy-3-methoxyphenyl)-2-nitropropene.** This compound was prepared as already described for 1-(3,4-dibenzyloxyphenyl)-2-nitropropene. By reaction of 12.3 g (50 mmol) of 4-benzyloxy-3-methoxybenzaldehyde were obtained 14.22 g (47.5 mmol, 95%) of 1-(4-benzyloxy-3-methoxyphenyl)-2-nitropropene. IR (neat, $\nu_{max}$ $cm^{-1}$): 1632, 1594, 1515, 1500, 1463, 1422, 1387, 1314, 1268, 1241, 1170, 1145, 1037, 998, 990, 915, 850, 815, 749, 697. $^1H$ NMR (300 MHz; $CDCl_3$): δ 2.47 (s, 3H), 3.92 (s, 3H), 5.21 (s, 2H), 6.93–7.00 (m. 3H), 7.32–7.50 (m, 10H), 8.05 (s, 1H). $^{13}C$ NMR (75 MHz; $CDCl_3$): δ 14.1, 56.0, 70.8, 113.4, 113.5, 123.8, 125.2, 127.1, 128.0, 128.6, 133.7, 136.3, 145.9, 149.5, 149.8. GC–MS *m*/*z* 91, 176, 242, 267, 299.

**1-(4-benzyloxy-3-methoxyphenyl)-2-propanone 6.**[7] A mixture of 11 g (37 mmol) of 1-(4-benzyloxy-3-methoxyphenyl)-2-nitropropene, 15 g (257 mmol, 7 equiv) of iron, 60 mg (0.37 mmol, 0.01 equiv) of $FeCl_3$ and 25 mL of water were placed in a 250 mL round bottom flask. The mixture was refluxed and stirred, and 6 mL of concentrated HCl were carefully added through the condenser. After 6 h, it was allowed to cool to room temperature and 100 mL of benzene were added. The resulting suspension was filtered off through a Celite® pad and the solids were washed with benzene (2×50 mL). Then, the benzene layer was separated and washed with diluted HCl (25 mL) and water (2×25 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed and the residue was dried under vacuum and purified by column chromatography (silica gel) using hexane/ethyl acetate (1:1, v/v) to give 9.5 g (35.14 mmol, 95% yield) of 1-(4-benzyloxy-3-methoxyphenyl)-2-propanone as an orange oil. IR (neat, $\nu_{max}$ $cm^{-1}$): 1708, 1591, 1514, 1463, 1454, 1419, 1261, 1228, 1157, 1139, 1033, 1026, 738, 698. $^1H$ NMR (300 MHz; $CDCl_3$): δ 2.15 (s, 3H), 3.63 (s, 2H), 3.89 (s, 3H), 5.15 (s, 2H), 6.74–6.87 (m. 3H), 7.28–7.56 (m, 10H). $^{13}C$ NMR (75 MHz; $CDCl_3$) δ 29.1, 50.6, 55.9, 71.0, 112,8, 114.1, 121.5, 127.2, 127.8, 128.3, 128.5, 137.1, 147.2, 149.7, 206.8. GC–MS *m*/*z*: 43, 91, 137, 227, 270.

***N*-(*S*)-(1-phenylethane)-(*R*,*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane (7).**[11] In a 500 mL round bottom flask was dissolved 5.2 g (19.2 mmol) of 1-(4-benzyloxy-3-methoxyphenyl)-2-propanone in 50 mL of methanol and 10.1 mL (76.9 mmol, 4 equiv) of 1-(*S*)-phenyletanamine. To this solution were also added 1.3 g (21.1 mmol, 1.1 equiv) of $NaBH_4CN$ in 2 mL of diethyl ether/HCl. The resulting orange mixture was stirred at room temperature for 28 h, and after that time, concentrated HCl was added dropwise until pH < 2 was achieved and the solution was then concentrated to dryness. The resulting mixture was dissolved with water (150 mL) and ethyl acetate (250 mL) and the organic layer was decanted. The aqueous layer was extracted with ethyl acetate (2×250 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated to give 6.74 g of a dark orange oil which was redissolved in 200 mL of $CH_2Cl_2$ and treated with 3N NaOH aqueous solution until pH > 12, decanted and extracted with $CH_2Cl_2$ (2×50 mL). The combined organic layer was washed with water (2×25 mL) and brine (25 mL). Drying with $MgSO_4$ and concentration produced 4.25 g (11.32 mmol, 59% yield) of *N*-(*S*)-(1-phenylethane)-(*R*,*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane as a yellow oil. Attempts to separate the two diastereomers were not successful at this point. $^1H$ NMR ($CDCl_3$; 300 MHz): δ 0.95 (d, 3H, maj), 1.08 (d, 3H, min), 1.28 (d, 3H, min), 1.33 (d, 3H, maj), 2.29 (bs, 1H), 2.40–2.86 (m, 3H), 3.80 (s, 3H, min), 3.83 (s, 3H, maj), 3.84–3.97 (m, 1H), 5.13 (s, 2H, maj), 5.18 (s, 2H, min), 6.57–6.97 (m, 3H), 7.16–7.52 (m, 10H). $^{13}C$ NMR ($CDCl_3$, 300 MHz): δ 19.8, 21.0, 24.3, 24.7, 41.9, 43.5, 50.7, 52.0, 54.7, 55.3, 55.7, 55.8, 71.0, 104.8, 112.5, 112.9, 113.9, 114.0, 121.1, 121.2, 126.2, 126.5, 126.6, 126.8, 127.1, 127.2, 127.3, 127.6, 127.7, 128.2, 128.4, 132.2, 132.7, 137.2, 145.1, 145.7, 146.3, 146.4, 149.3, 149.5. GC–MS *m*/*z* 91, 105, 148, 228, 270, 360, 376.

***N*-methyl-*N*-[(*S*)-(1-phenylethane)]-(*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane (8).** 2.26 g (6.03 mmol) of *N*-(*S*)-(1-phenylethane)-(*R*,*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane were dissolved in 50 mL of $CH_2Cl_2$ in a round bottom flask. To this solution 1.9 g (18 mmol, 3 equiv) of $Na_2CO_3$ and 760 μL (12.05 mmol, 2 equiv) of $CH_3I$ were also added. After 16 h of stirring at room temperature, another 760 μL of $CH_3I$ were added and mixture was then stirred for 48 h. The resulting solution was washed with water (2×25 mL) and brine (25 mL), dried with $MgSO_4$ and concentrated to give 2.22 g (0.60 mmol, 94% yield) of a yellow solid consisting in a 6:4 diastereomeric mixture of *N*-(*S*)-(1-phenylethane)-(S,*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane and *N*-(*S*)-(1-phenylethane)-(*R*,*S*)-1-(4-benzyloxy-3-methoxyphenyl)-2-aminopropane. Silica gel column chromatography purification of this diastereomeric mixture, eluting with hexane/ethyl acetate (1:1, v/v) resulted in the obtention of different diastereomeric ratio mixtures depending on the column fractions collected, observing that the minor component of the crude mixture was the first one in eluting from the column. Four different fractions were obtained: fraction 1 (256 mg) contained a 30:70 (*S*,*S*)/(*R*,*S*) diastereoisomers ratio (determined by 300 MHz $^1H$ NMR) $[\alpha]_D^{20}$ −93.13 (*c* 0.99, chloroform), fraction 2 [991 mg, 50:50 (*S*,*S*)/(*R*,*S*) ratio], fraction 3 (404 mg, 80:20 (*S*,*S*)/(*R*,*S*) ratio), and fraction 4 (390 mg, 92:8 (*S*,*S*)/(*R*,*S*) ratio $[\alpha]_D^{20}$ +77.36 (*c* 0.98, chloroform]. IR (neat, $\nu_{max}$ $cm^{-1}$): 3060, 3029, 2967, 2933, 2869, 2848, 2748, 1588, 1513, 1492, 1463, 1451, 1417, 1368, 1262, 1224, 1156, 1139, 1025, 734, 699. $^1H$ NMR ($CDCl_3$, 300 MHz): δ Major isomer: 0.92 (d, 3H), 1.35 (d, 3H), 2.28 (A of an ABX syst., 1H containing a s, 3H), 2.91 (B of an ABX syst., *J* = 4.5, 12.9 Hz, 1H), 2.97–3.11 (X of an ABX syst., 1H), 3.71 (q, 1H), 3.79 (s, 3H), 5.12 (s, 2H), 6.48–6.80 (m, 3H), 7.15–7.50 (m, 10H). Minor isomer, 0.87 (d, 3H), 1.33 (d, 3H), 2.28 (s, 3H), 2.38 (A of an ABX syst., *J* = 8.4, 13.2 Hz, 1H), 2.76 (B of an ABX syst., *J* = 5.7, 13.2 Hz, 1H), 2.85–2.97 (X of an ABX syst., 1H), 3.62 (q, 1H), 3.80 (s, 3H), 5.15 (s, 2H), 6.48–6.80 (m, 3H), 7.15–7.50 (m, 10H). $^{13}C$ NMR ($CDCl_3$, 300 MHz): δ Major isomer:

15.7, 22.0, 32.3, 37.0, 55.7, 55.8, 62.2, 71.0, 112.5, 113.8, 120.9, 126.6, 127.1, 127.2, 127.6, 128.3, 128.4, 134.3, 137.3, 146.0, 146.3, 149.2. Minor isomer: 12.5, 22.1, 31.7, 40.6, 55.7, 56.0, 62.0, 71.1, 112.8, 113.7, 121.0, 126.4, 126.7, 127.2, 127.6, 128.1, 128.2, 128.4, 134.2, 137.4, 146.1, 146.1, 149.1. GC–MS *m*/*z* 91, 107, 136, 227, 262.

***N*-methyl-*N*-(*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylpropanamine hydrochloride, (*S*)-HMMA·HCl.** In a pressure resistant glass reactor, were dissolved 150 mg (0.38 mmol) of *N*-methyl-*N*-(*S*)-(1-phenylethane)-(*S*)-1-(4 - benzyloxy - 3 - methoxyphenyl) - 2 - aminopropane **8** [(*S*,*S*)/(*R*,*S*) 80:20 ratio] in diethyl ether and treated with a solution of HCl/diethyl ether. The white solid that precipitated was taken to dryness and redissolved in 8 mL of previously degassed methanol, and to this solution was added a catalytic amount of Pd/C. Hydrogenation was performed at 3 bar pressure with continuous stirring at room temperature for 24 h. After filtration through Celite® of the residue and concentration were obtained 82 mg (0.35 mmol, 92%) of *N*-methyl-*N*-(*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylpropanamine hydrochloride as a white solid. $^1$H NMR ($CD_3OD$; 300 MHz): δ 1.41 (d, 3H), 2.87 (A of an ABX syst., 1H containing a s, 3H), 3.21 (B of an ABX syst., $J = 4.1$, 13.4 Hz, 1H), 3.53–3.70 (X of an ABX syst., 1H), 4.03 (s, 3H), 5.10 (bs, 4 H), 6.81–7.09 (m, 3H). $^{13}$C NMR ($CD_3OD$, 75 MHz): δ 15.8, 31.0, 39.9, 56.4, 57.9, 113.8, 116.4, 122.9, 128.1, 146.9, 149.2. GC–MS (N-TFA, O-TFA derivative); *m*/*z* 110, 154, 260, 387.

### Synthesis of *N*-1-(3,4-dimethoxyphenyl)-2-aminopropane hydrochloride (3,4-dimethoxymethamphetamine hydrochloride, MMMA·HCl) and enantiomerically enriched (*S*)-*N*-1-(3,4-dimethoxyphenyl)-2-aminopropane hydro chloride [(*S*)-3,4-dimethoxymethamphetamine hydro chloride, (*S*)-MMMA·HCl]

**General procedure.** To an Erlenmeyer flask containing the corresponding substrate dissolved in methanol was slowly added an excess of an ethereal solution of $CH_2N_2$ and the resulting solution was left to stand overnight. Then, the excess of reagent was evaporated by passing a stream of argon, the solvent removed on a rotaevaporator and the resulting residue dried under vacuum yielding a solid in almost quantitative yield. $^1$H NMR ($CD_3OD$; 300 MHz): δ 1.96 (d, 3H), 2.53 (s, 3H), 2.60–2.73 (m, 1H), 2.85–3.01 (m, 2H), 3.85 (bs, 2H), 3.90 (s, 6H), 6.87–7.08 (m, 3H). $^{13}$C NMR ($CD_3OD$, 75 MHz): δ 19.0, 33.6, 43.4, 56.4, 56.5, 57.7, 113.1, 114.1, 122.6, 133.2, 149.1, 150.5. In all cases, GC–MS (N-TFA derivative); *m*/*z* 110, 151, 178, 305.

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