Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 660–665.
Published online 4 June 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1378

JLCR

Research Article

Synthesis of deuterium-labelled standards of (±)-DOM and (±)-MMDA

AJAM C. SHAIKH, YU-YUN WANG and CHINPIAO CHEN*

Department of Chemistry, National Dong Hwa University, Soufeng, Hualien 974, Taiwan, Republic of China

Received 7 March 2007; Revised 22 March 2007; Accepted 29 March 2007

Abstract: This study describes the synthesis of deuterium-labelled (±)-4-methyl-2,5-dimethoxyamphetamine (DOM) and (±)-1-(7-methoxy-1,3-benzodioxol-5-yl)propan-2-amine (MMDA). The isotopically labelled compounds are potentially used as internal standards in gas chromatography–mass spectrometry (GC–MS) assays. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: DOM; MMDA; deuterium labelled; internal standard

Introduction

Unknown drugs of abuse are generally detected and identified by gas chromatography–mass spectrometry (GC–MS) owing to the high sensitivity of this method and its ability to separate complex mixtures of organic compounds. 4-Methyl-2,5-dimethoxyamphetamine (DOM)[1] is a psychedelic hallucinogenic drug of the phenethylamine class, and is occasionally used as an entheogen. In the United States, DOM is classified as a Schedule 1 substance, and is similarly controlled in other parts of the world.

1-(7-Methoxy-1,3-benzodioxol-5-yl)propan-2-amine (MMDA) is a biologically active derivative of phenethylamine and amphetamine. Its analogs include 3,4-methylenedioxyamphetamine (MDA), lophophine and 3,4-methylenedioxy-*n*-methylamphetamine (MDMA), and it resembles the psychopharmacologically active essential oils elemicin and myristicin, which are found in nutmeg.

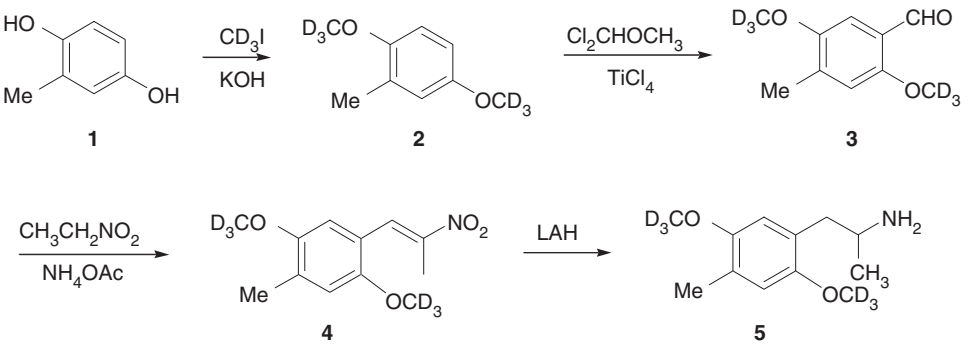
The abuse of psychoactive phenylethylamines and phenylisopropylamines has become a very serious social problem in Taiwan in the last decade.[2,3] Standard samples for analyzing controlled drugs in Taiwan are very difficult to obtain. Many researchers are interested in the preparation of deuterium-labelled control drugs as internal standards for GC–MS analysis.[4–6] This work describes synthetic routes to DOM-d_6 and MMDA-d_3, and presents relevant characteristic analytical data. The compounds investigated in this study have not been examined before.

Results and discussion

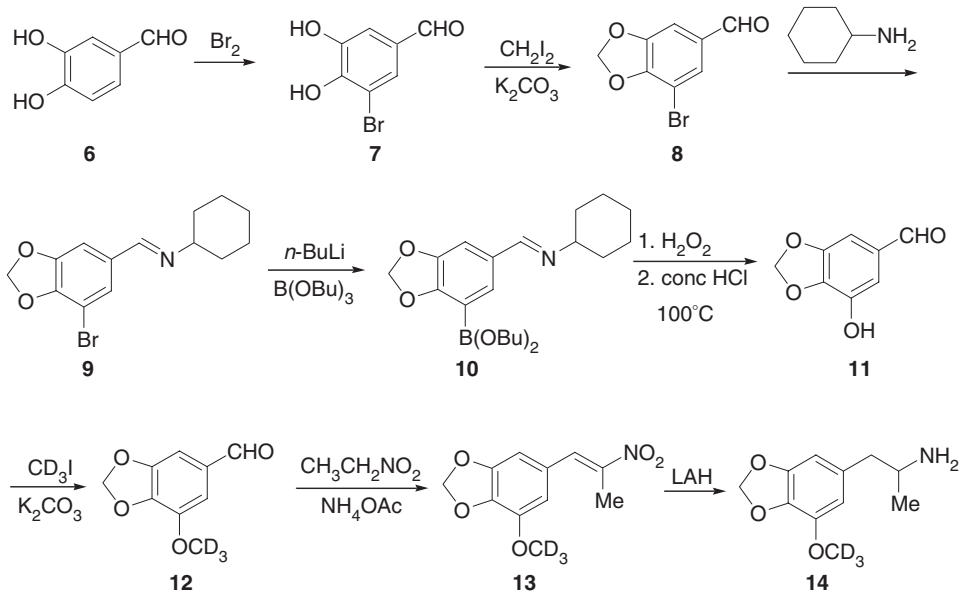
Although DOM[7–14] and MMDA[15] have been readily prepared by several synthetic routes, preparing (±)-[$^2H_6$]-DOM and (±)-[$^2H_3$]-MMDA have not been described. Scheme 1 presents the general scheme for preparing (±)-[$^2H_6$]-DOM (**5**). 1,4-[$^2H_6$]-Dimethoxy-2-methyl-benzene (**2**) was prepared by reacting 2-methyl-benzene-1,4-diol with [$^2H_3$]-methyl iodide.[4–6,16–18] Compound **2** was treated with dichloromethyl methyl ether and $TiCl_4$ to yield 2,5-[$^2H_6$]-dimethoxy-4-methyl-benzaldehyde (**3**),[19–24] which was then condensed with nitroethane to yield 1,4-[$^2H_6$]-dimethoxy-2-methyl-5-(2-nitro-propenyl)-benzene (**4**). The reduction of this compound **4** with $LiAlH_4$ produced (±)-2-(2,5-[$^2H_6$]-dimethoxy-4-methyl-phenyl)-1-methyl-ethylamine (**5**).

Scheme 2 is the general synthesis of (±)-[$^2H_3$]-MMDA (**14**).[15] Bromination of commercially available protocatechualdehyde **6** in acetic acid gave 3-bromo-protocatechualdehyde **7**. Treatment of **7** with diiodomethane under mildly basic conditions gave dioxymethylated aldehyde **8**. The compound **8** was treated with cyclohexylamine in Dean–Stark using toluene as a solvent to form a cyclohexylamine adduct **9**. Treating **9** with *n*-butyllithium caused it to undergo rapid lithium–halogen exchange to form the corresponding lithio

*Correspondence to: Chinpiao Chen, Department of Chemistry, National Dong Hwa University, Soufeng, Hualien 974, Taiwan, Republic of China. E-mail: chinpiao@mail.ndhu.edu.tw
Contract/grant sponsor: National Bureau of Controlled Drugs; contract/grant number: DOH95-NNB-1001



Scheme 1



Scheme 2

derivative, which upon reaction with tributyl borate formed **10** by conversion of the lithio derivative to organoborane. The oxidation of the C–B bond with basic hydrogen peroxide, and finally, the hydrolysis of the protected Schiff's base produced 3-hydroxy-4,5-methylenedioxybenzaldehyde **11** in good yield. Hydroxybenzaldehyde **11** was alkylated by treating it with [$^2H_3$]-methyl iodide in the presence of K_2CO_3 to give myristicinaldehyde **12** in a 80–95% yield. Next, the corresponding myristicinaldehyde **12** was treated with nitroethane to give **13**, which was reduced using lithium aluminum hydride. Attempts to purify obtained amine **14** by column chromatography failed; so firstly, amine was treated with picric acid to give picrate salt, which on recrystallization gave the pure picrate salt of amine. Subsequent treatment of this picrate salt with NaOH and extraction gave pure compound **14**. To convert this amine to the corresponding hydrochloride, this compound **14** was treated with HCl gas to form (±)-3-methoxy-4,5-methylenedioxyamphetamine hydrochloride (MMDA).

Experimental

General

^{1}H NMR spectra were acquired at 300 MHz (indicated in each case), and ^{13}C NMR were acquired at 75.5 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from

DOI: 10.1002.jlcr

sodium–benzophenone in argon. Benzene and *N*,*N*-dimethylformamide were distilled from calcium hydride. All air-sensitive reactions were performed in dry glassware under nitrogen using a standard glovebox. Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) or basic Al_2O_3 which were purchased from Macherey-Nagel.

All reactions were initially optimized using unlabelled compounds.

Synthesis of 1,4-[$^2H_6$]-dimethoxy-2-methyl-benzene (2). Potassium hydroxide pellets (4.81 g, 85.8 mmol) were round to a powder; tetrabutylammonium bromide (4.14 g, 33.4 mmol) and methylhydroquinone (4.14 g, 33.4 mmol) were added, and the whole ground together in a nitrogen atmosphere at room temperature.[16–19] [$^2H_3$]-Methyl iodide (15.0 g, 6.44 ml, 103.5 mmol; isotopic abundance 99.5%, Cambridge Isotope Laboratories Inc.) was then added and the mixture was heated in an oil bath for four days at 55°C. The crude mixture was then transferred to a separating funnel with water and dichloromethane, and the aqueous phase was extracted using dichloromethane. The extracts were dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue that was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase, producing (**2**) as a yellowish liquid (5.10 g, 32.2 mmol). Yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.76–6.66 (m, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 157.0, 155.6, 131.2, 120.6, 114.2, 114.2, 58.5–57.7 (m), 19.9. IR (KBr, thin film): 3038, 2951, 2923, 2213, 2067, 1499, 1231, 1112, 996, 865, 796, 687 cm^{-1}. MS-EI (*m*/*z*): 158 (M^+, 91), 140 (100), 112 (20), 94 (18), 77 (19), 66 (17), 51 (4). HRMS-EI (*m*/*z*): [M^+] calcd for $C_9H_6D_6O_2$, 158.1208; found 158.1221.

Synthesis of 2,5-[$^2H_6$]-dimethoxy-4-methyl-benzaldehyde (3). To a solution of **2** (5.00 g, 31.6 mmol) in dry dichloromethane (600 ml) that was cooled in an ice bath was added titanium chloride (6.38 ml, 58.2 mmol) and dichloromethyl methyl ether ($C1_2CHOCH_3$) (5.3 ml, 58.8 mmol) in an argon atmosphere.[19–24] The dark red reaction solution was stirred at room temperature for 15 min until all of the starting material was completely consumed, as monitored by thin layer chromatography (TLC). The reaction was quenched by adding water (230 ml), and the dichloromethane layer was washed with water (170 ml) and then dried over anhydrous magnesium sulfate. The solution was filtered, and the filtrate was concentrated by rotary vacuum evaporation. The residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase to give **3** as a white crystalline (5.14 g, 27.6 mmol). Yield: 87%. M.p.: 74–75°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.40 (s, 1H), 7.25 (s, 1H), 6.80 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 189.1, 156.5, 151.8, 136.5, 122.7, 114.6, 107.4, 55.5–54.8 (m), 17.2. IR (KBr, thin film): 3056, 2868, 2776, 2213, 2069, 1658, 1612, 1497, 1416, 1280, 1223, 1111, 1006, 889, 664, 626 cm^{-1}. MS-EI (*m*/*z*): 186 (M^+, 100), 168 (80), 157 (7), 151 (7), 140 (56), 123 (22), 112 (27), 93 (15), 77 (12), 66 (12), 53 (11). HRMS-EI (*m*/*z*): [M^+] calcd for $C_{10}H_6D_6O_3$, 186.1157; found 186.1165.

Synthesis of 1,4-[$^2H_6$]-dimethoxy-2-methyl-5-(2-nitro-propenyl)-benzene (4). A solution of 2,5-[$^2H_6$]-dimethoxy-4-methyl-benzaldehyde (**3**) (5.00 g, 26.9 mmol) in glacial acetic acid (23.1 ml) was treated with nitroethane (3.11 ml, 43.3 mmol) and anhydrous ammonium acetate (2.10 g, 26.9 mmol). This mixture was heated at 100°C for 5 h and the excess reagent and solvent were removed under vacuum. The residue was suspended in water and extracted with dichloromethane. The extracts were dried over anhydrous magnesium sulfate. Following filtration and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:39) as the mobile phase, producing compound **4** (4.10 g, 16.9 mmol). Yield: 63%. M.p.: 90–91°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.29 (s, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 2.42 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 152.4, 151.4, 146.7, 131.1, 130.0, 118.7, 114.0, 111.5, 55.5–54.8 (m), 16.7, 14.3. IR (KBr, thin film): 2924, 2845, 2214, 2072, 1649, 1506, 1310, 1227, 1105, 1004, 969, 866, 656 cm^{-1}. MS-EI (*m*/*z*): 243 (M^+, 100), 209 (4), 196 (28), 178 (32), 161 (24), 150 (3), 140 (4), 132 (4), 115 (4), 103 (4), 93 (3), 77 (5), 65 (4). HRMS-EI (*m*/*z*): [M^+] calcd for $C_{12}H_9D_6NO_4$, 243.1372; found 243.1369.

Synthesis of (±)-2-(2,5-[$^2H_6$]-dimethoxy-4-methyl-phenyl)-1-methyl-ethylamine (5). A solution of 1,4-[$^2H_6$]-dimethoxy-2-methyl-5-(2-nitro-propenyl)-benzene (**4**) (3.90 g, 16.0 mmol) in anhydrous diethyl ether (105 ml) was slowly added to a well-stirred suspension mixture of lithium aluminum hydride (2.44 g, 64.2 mmol) in anhydrous diethyl ether (22 ml). The mixture was then brought up to a reflux, which was maintained for 20 h, and then cooled with an external ice bath; the excess hydride was destroyed by the cautious addition of water. The quenched mixture was filtered through celite, and washed with tetrahydrofuran, and the filtrate was concentrated. The aqueous phase was extracted using dichloromethane. The organic phase was dried over anhydrous sodium

DOI: 10.1002.jlcr

sulfate. After filtration and concentration, the resulting residue was dissolved in dry diethyl ether, and saturated with hydrogen chloride. The formed crystals of (±)-2-(2,5-[$^2H_6$]-dimethoxy-4-methyl-phenyl)-1-methyl-ethylamine (**5**) were removed by filtration, washed with anhydrous diethyl ether. The hydrochloric acid salt of **5** was crystallized from methanol/diethyl ether, yielding **5**.HCl (3.03 g, 12.06 mmol). Yield: 75%. M.p.: 200–201°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.35 (s, br, 2H), 6.67 (s, 2H), 3.71–3.67 (m, 1H), 3.10 (dd, J = 1.33, 5.9 Hz, 1H), 2.86 (dd, J = 13.3, 9.4 Hz, 1H), 2.19 (s, 3H), 1.36 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 151.4, 151.2, 126.3, 121.7, 114.0, 113.7, 5.9–54.4 (m), 48.3, 36.5, 18.3, 16.3. IR (KBr, thin film): 2940, 2736, 2694, 2595, 2507, 2218, 2068, 1994, 1589, 1507, 1408, 1229, 1108, 1014, 968, 674 cm^{-1}. MS-EI (m/z): 215 (M^+–HCl, 4), 172 (100), 154 (28), 139 (8), 125 (4), 107 (5), 92 (7), 79 (7), 77 (6), 65 (3). HRMS-EI (m/z): [M^+] calcd for $C_{12}H_{13}D_6NO_2$, 215.1786; found 215.1794.

Synthesis of 3-bromo-4,5-dihydroxy-benzaldehyde (7). A solution of commercial 3,4-dihydroxybenzaldehyde **6** (1.80 g, 13.0 mmol) in warm acetic acid (20 ml) was filtered until free of any insoluble solid, yielding a clear solution. Elemental bromine (0.80 ml, 15.6 mmol) was added with vigorous stirring. The reaction became spontaneously hotter, to around 30°C, and solids appeared after about 5 min of stirring, which was continued for 1.5 h. Then, the light gray solids that had formed were removed by filtration and lightly washed using acetic acid. These were dried in vacuum until free from acetic acid. The product was purified by recrystallization using 50% ethanol, producing the product, 3-bromo-4,5-dihydroxybenzaldehyde **7** (1.50 g, 6.9 mmol). Yield: 53%. M.p.: 221–222°C. ^{1}H NMR (300 MHz, CD_3OD, δ): 9.65 (s, 1H), 7.52 (d, J = 3.5 Hz, 1 H), 7.23 (d, J = 3.5 Hz, 1 H). ^{13}C NMR (75 MHz, CD_3OD δ): 190.4, 149.7, 146.3, 129.5, 127.5, 112.5, 109.1. IR (KBr, thin film): 3423, 1652, 1579, 1442, 1309, 1255, 1186, 862, 580 cm^{-1}. MS-EI (m/z): 218 (68), 217 (100), 216 (M^+, 70), 215 (M^+–1, 95), 187 (16), 107 (16), 79 (16), 51 (27). HRMS-EI (m/z): [M^+] calcd for $C_7H_5BrO_3$, 215.9422; found 215. 9418.

Synthesis of 3-bromo-4,5-methylenedioxybenzaldehyde (8). To a solution of 3-bromo-4,5-dihydroxybenzaldehyde **7** (1.10 g, 5.1 mmol) in DMSO (3.6 ml) was added methylene iodide (0.87 ml, 10.8 mmol) followed by anhydrous potassium carbonate (2.00 g), which was heated at 100°C for 3 h. After it had returned to room temperature, it was added to water (100 ml), made strongly basic by the addition of sodium hydroxide, and extracted using dichloromethane. These extracts were dried over anhydrous sodium sulfate, and then the solvent was removed under vacuum. The resulting residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:3) as the mobile phase, producing 3-bromo-4,5-methylenedioxybenzaldehyde **8** (0.73 g, 3.2 mmol) as a white crystalline. Yield: 63%. M.p.: 124–124.5°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.77 (s, 1H), 7.54 (s, 1H), 7.28 (s, 1H), 6.10 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$ δ): 189.0, 151.2, 148.9, 132.8, 130.9, 106.2, 102.5, 100.9. IR (KBr, thin film): 2853, 1686, 1594, 1430, 1270, 1036, 927, 849, 815, 575 cm^{-1}. MS-EI (m/z): 230 (97), 229 (99), 228 (M^+, 100), 227 (M^+–1, 94), 199 (24), 63 (29), 62 (32). HRMS-EI (m/z): [M^+] calcd for $C_8H_5BrO_3$, 227.9422; found 227.9429.

Synthesis of 3-hydroxyl-4,5-methyenedioxybenzaldehyde (11). A mixture of 3-bromo-4,5-methylenedioxybenzaldehyde **8** (1.30 g, 5.7 mmol), cyclohexylamine (2.2 ml, 19 mmol) and toluene (10 ml) was refluxed in a Dean–Stark apparatus for 3.5 h. After cooling, the excess solvent was removed using a rotary evaporator, and thoroughly dried in vacuum, producing 3-bromo-4,5-methylenedioxybenzylidine-*N*-cyclohexylamine **9** (1.50 g, 4.8 mmol) in a yield of 86%. A solution of compound **9** (3.49 g, 11.3 mmol) in anhydrous diethyl ether (80 ml) was placed in an atmosphere of argon, stirred magnetically, and cooled to −78°C; a white fine crystalline appeared. *n*-Butyllithium (16.54 ml, 13.5 mmol, 0.82 M in hexane) was added, and the fine solids were dissolved; then tributyl borate (6.3 ml, 24 mmol) was added. After the system had returned to room temperature, the reaction was quenched with saturated aqueous ammonium sulfate (32 ml). The organic layer was separated, washed with additional ammonium sulfate solution, and stripped off volatiles in vacuum. The residual oil was dissolved in 50% methanol/water (158 ml), and treated with hydrogen peroxide (3.2 ml, 30%). After it had been swirled for 15 min, the reaction was quenched using a solution of ammonium sulfate (16 g) in water (79 ml). This aqueous phase (pH about 8) was extracted with dichloromethane. The extracts were pooled and the solvent removed under vacuum. The residual oil was treated with dilute HCl and heated at 100°C. After all the residue had dissolved, the solution was cooled to room temperature and extracted with 5% NaOH. Acidification of the pooled aqueous fractions with HCl, followed by extraction with dichloromethane and evaporation of the solvent, yielded a residue which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:3) as the mobile phase, producing white crystals of 3-hydroxyl-4,5-methyenedioxybenzaldehyde **11** (0.91 g,

DOI: 10.1002.jlcr

5.5 mmol). Yield: 49%. M.p.: 134–134.5°C. ^{1}H (300 MHz, CD_3OD, δ): 9.61 (s, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 6.04 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD, δ): 191.0, 149.7, 141.1, 140.2, 131.8, 115.3, 102.3, 100.2. IR (KBr, thin film): 3262, 1633, 1606, 1457, 1336, 1183, 1121, 1091, 920, 834, 753 cm^{-1}. MS-EI (*m/z*): 166 (M^+, 100), 165 (68), 135 (19), 79 (13), 51 (14). HRMS-EI (*m/z*): [M^+] calcd for $C_8H_6O_4$ 166.0266; found 166.0263.

Synthesis of 3-[$^2H_3$]-methoxy-4,5-methylenedioxybenzaldehyde (12). A solution of 3-hydroxy-4,5-methylenedioxybenzaldehyde **11** (1.50 g, 9.0 mmol) in dry acetone (35 ml) was treated with [$^2H_3$]-methyl iodide (1.0 ml, 16.0 mmol) and powdered anhydrous K_2CO_3 (1.70 g, 11.9 mmol) and was maintained at reflux for 5 h. After 1 h of heating, a white suspension appeared. After the reaction had been completed, all volatiles were stripped under vacuum. The residue was dissolved in water; was made strongly basic with NaOH and was extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate. The removal of the solvent under vacuum gave a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase, yielding 3-[$^2H_3$]-methoxy-4,5-methylenedioxybenzaldehyde **12** (1.35 g, 7.4 mmol). Yield: 82%. M.p.: 133.5–134.5°C. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 9.70 (s, 1H), 7.13 (d, $J = 1.2$ Hz, 1H), 7.05 (d, $J = 1.2$ Hz, 1H), 6.10 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$ δ): 190.1, 149.4, 144.0, 140.9, 131.8, 110.3, 103.6, 102.6. IR (KBr, thin film): 2844, 2360, 1697, 1624, 1474, 1232, 1134, 1090, 842, 736 cm^{-1}. MS-EI (*m/z*): 183 (M^+ 100), 182 (86), 135 (14), 79 (17), 51 (18), 50 (10). HRMS-EI (*m/z*): [M^+] calcd for $C_9H_5D_3O_4$, 183.0608; found 183.0614.

Synthesis of 1-(3-[$^2H_3$]-methoxy-4,5-mehylenedioxyphenyl)-2-nitropropene (13). A solution of 3-[$^2H_3$]-methoxy-4,5-methylenedioxybenzaldehyde **12** (0.70 g, 3.8 mmol) in glacial acetic acid (2.1 ml) was treated with nitroethane (0.35 ml, 4.9 mmol) and anhydrous ammonium acetate (0.27 g, 3.5 mmol). This was heated at 100°C for 1.5 h. After the reaction had completed, it was treated with water with good stirring until just short of turbidity. It was then extracted with dichloromethane. Extracts were dried over anhydrous sodium sulfate and concentration yielded a residue which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (3:97) as the mobile phase, producing light yellow solids of 1-(3-[$^2H_3$]-methoxy-4,5-mehylenedioxyphenyl)-2-nitropropene **13** (0.46 g, 1.9 mmol). Yield: 50%. M.p.: 106–108°C. ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.00 (s, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 6.05 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$ δ): 149.3, 146.5, 143.7, 137.1, 133.7, 126.6, 111.3, 103.7, 102.1, 44.0, 14.2. IR (KBr, thin film): 2916, 2349, 1626, 1521, 1343, 1297, 1157, 854, 617 cm^{-1}. MS-EI (*m/z*): 240 (M^+ 100), 194 (13), 193 (79), 136 (41), 118 (23), 90 (20), 89 (29), 63 (15). HRMS-EI (*m/z*): [M^+] calcd for $C_{11}H_8D_3NO_5$, 240.0822; found 240.0820.

Synthesis of (±)-2-(7-[$^2H_3$]-methoxy-benzo[1,3]dioxol-5-yl)-1-methyl-ethylamine (14). A suspension of lithium aluminum hydride (0.83 g, 22.0 mmol) in anhydrous diethyl ether (50 ml) was magnetically stirred, and heated in an inert atmosphere to a gentle reflux. The condensing diethyl ether leached 1-(3-[$^2H_3$]-methoxy-4,5-methylenedioxyphenyl)-2-nitropropene **13** (1.11 g, 4.6 mmol) from a Soxhlet thimble in a shunted reflux condenser. Subsequently, compound **13** was added to the reaction medium as a warm saturated diethyl ether solution. When the addition had been completed, the refluxing was maintained for an additional 2 h. The reaction was then cooled and the excess hydride was destroyed by adding 1.5 N H_2SO_4 (45 ml, the first 20 ml a drop at a time and with very good stirring). The phases were separated and then sufficient saturated aqueous Na_2CO_3 was added to the aqueous phase to bring the pH up to about 6. The system was heated to 80°C and filtered through a coarse sintered glass funnel to remove some of the insoluble fines. The clear filtrate was heated almost to boil, and treated with a solution of 1.10 g of 90% picric acid in 12 ml boiling EtOH. Crystals of the picrate formed immediately at the edges, and as the reaction flask was cooled in an ice bath, the entire reaction set to a yellow mass of crystals, which were removed by filtration, washed sparingly with 80% EtOH, and dried in air to give the picrate salt of MMDA. This sample was recrystallized using EtOH. The salt was treated with 7 ml 5% NaOH, before the red solution was decanted from some insolubles. Added water and NaOH effectively dissolved everything and the resulting basic aqueous phase was extracted with dichloromethane. The pooled extracts were stripped off in vacuum, and the residue dissolved in 30 ml anhydrous Et_2O and saturated with anhydrous HCl gas. White crystals precipitated strongly, and were removed by filtration, washed with Et_2O, and air dried to give (±)-3-[$^2H_3$]-methoxy-4,5-methylenedioxyamphetamine hydrochloride (MMDA) **14** (0.72 g, 2.9 mmol). Yield: 63%. M.p.: 190.0–191.5°C. ^{1}H NMR (300 MHz, CD_3OD, δ): 6.46 (d, $J = 1.5$ Hz, 1H), 6.43 (d, $J = 1.5$ Hz, 1H), 5.9 (s, 2H), 3.4 (m, 1H), 2.78 (m, 2H), 1.6 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD, δ): 149.4, 143.8, 134.5, 130.2, 109.2, 102.7, 101.2, 48.9, 43.4, 40.2, 17.0. IR (KBr thin film): 3457, 2975, 1634, 1514, 1107, 1135. MS-EI (*m/z*): 212 (M^+–Cl, 1.5), 169 (100), 168 (41),

DOI: 10.1002.jlcr

120 (9), 92 (11), 79 (6), 64 (13). HRMS-EI (*m/z*): [M^+–Cl] calcd for $C_{11}H_{12}D_3NO_3$, 212.1237; found 212.1237.

Acknowledgements

The authors thank Ms Hsu, L. M. at the Instruments Center, National Chung Hsing University, for her help in obtaining HRMS. We would also like to thank the National Bureau of Controlled Drugs, Department of Health, Taiwan, Republic of China, for financially supporting this work under Contract DOH95-NNB-1001.

REFERENCES

1. http://en.wikipedia.org/wiki/2%2C5-Dimethoxy-4-methylamphetamine.
2. Yang CC, Wu JF, Ong HC, Hung SC, Kuo YP, Sa CH, Chen SS, Deng JF. *J Toxicol Clin Toxicol* 1996; **34**: 651–663.
3. Yen CF, Chang YP. *Psychiatry Clin Neurosci* 2005; **59**: 77–82.
4. Xu YZ, Chen C. *J Chin Chem Soc* 2007; **54**: 493–502.
5. Xu YZ, Chen C. *J Label Compd Radiopharm* 2006; **49**: 897–902.
6. Xu YZ, Chen C. *J Label Compd Radiopharm* 2006; **49**: 1187–1200.
7. Fentiman F. *J Label Compd Radiopharm* 1976; **12**: 69–74.
8. Aldous FAB, Barrass BC, Brewster K, Buxton DA, Green DM, Pinder RM, Rich P, Skeels M, Tutt KJ. *J Med Chem* 1974; **17**: 1100–1111.
9. Glennon RA, Raghupathi R, Bartyzel P, Teitler M, Leonhardt S. *J Med Chem* 1992; **35**: 734–740.
10. Coutts RT, Malicky JL. *Can J Chem* 1974; **52**: 395–399.
11. Matin SB, Callery PS, Zweig JS, O'Brien A, Rapoport R, Castagnoli N. *J Med Chem* 1974; **17**: 877–882.
12. Zweig JS, Castagnoli N. *J Med Chem* 1977; **20**: 414–421.
13. Nichols DE, Barfknecht CF, Rusterholz DB, Benington F, Morin RD. *J Med Chem* 1973; **16**: 480–483.
14. Wagner JM, McElhinny Jr CJ, Lewin AH. *Tetrahedron: Asymmetry* 2003; **14**: 2119–2126.
15. Shulgin AT. *Experientia* 1964; **20**: 366.
16. Loupy A, Sansoulet J, Díez-Barra E, Carrillo JR. *Synth Commun* 1991; **21**: 1465–1471.
17. Xu ZY, Xu DQ, Liu BY. *Org Prep Proced Int* 2004; **36**: 156–161.
18. Eynde JJV, Mailleux I. *Synth Commun* 2001; **31**: 1–7.
19. Standridge RT, Howell HG, Tilson HA, Chamberlain JH, Holava HM, Gylys JA, Partyka RA, Shulginet AT. *J Med Chem* 1980; **23**: 154–162.
20. Sullivan B, Djura P, McIntyre DE, Faulkner DJ. *Tetrahedron* 1981; **37**: 979–982.
21. Broadhurst MJ, Hassall CH. *J Chem Soc Perkin Trans 1* 1982; **9**: 2227–2238.
22. Nishitani S, Kurata N, Sakata Y, Misumi S, Karen A, Okada T, Matagaet N. *J Am Chem Soc* 1983; **105**: 7771–7772.
23. Oberlender RA, Kothari PJ, Nichols DE, Zabik JE. *J Med Chem* 1984; **27**: 788–792.
24. Maruyama K, Nagai N, Naruta Y. *J Org Chem* 1986; **51**: 5083–5092.