Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 22 January 2009, Revised 29 April 2009, Accepted 8 June 2009 Published online 15 July 2009 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1659

High specific activity (+)-amphetamine and (+)-methamphetamine

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High specific activity (+)-amphetamine and (+)-methamphetamine were prepared by reductive dechlorination of (*S*)-(3′,5′-dichlorophenyl)-2-propylazide and (*S*)-2′6′-dichloromethamphetamine, respectively. While the latter was readily obtained by resolution of racemic 2′6′-dichloromethamphetamine using (+)-dibenzoyltartaric acid, the analogous amphetamine resisted all efforts to resolve it. Hence, the required chiral precursor was prepared by stereospecific total synthesis following methodology that had been previously developed in our Laboratories. The tritium labeled compounds had specific activity 30.1 Ci/mmol and 38.3 Ci/mmol, respectively.

Keywords: (*S*)-amphetamine; tritium; (*S*)-methamphetamine; high specific activity

Introduction

Amphetamine (**1**) and methamphetamine (**2**) are extensively implicated in CNS activity and the stereoselectivity of the optical antipodes has been well documented. In general, the (*S*)-(+)-enantiomers of amphetamine [**(*S*)-1**] and methamphetamine [**(*S*)-2**] have been demonstrated to have about five times greater psychostimulant activity than the (*R*)-(−)-forms [**(*R*)-1** and **(*R*)-2**]. In a recent study of the effects of (*S*)- and (*R*)-methamphetamine in humans,[1] the pharmacokinetic parameters for the enantiomers administered separately were found to be similar, but the elimination half-life was longer for (*R*)-methamphetamine, and it did not increase the systolic blood pressure like (*S*)-methamphetamine. Interestingly, (*R*)-methamphetamine was psychoactive, producing intoxication and drug-liking ratings similar to those for (*S*)-methamphetamine at the same dose. However, despite the longer half-life of (*R*)-methamphetamine, its effects were dissipated twice as fast as those of (*S*)-methamphetamine. Investigation of amphetamine binding sites has been hindered by the lack of the separate antipodes, (*S*)- and (*R*)-, of amphetamine [**(*S*)-1** and **(*R*)-1**] and methamphetamine [**(*S*)-2** and **(*R*)-2**] with high specific activity. Thus, it has been reported that, using (+)-[^{3}H]amphetamine (specific activity 15.7 Ci/mmol), binding sites with apparent affinity constants of 96 and 279 nM were detected in hypothalamic membrane preparations from rat brain,[2] but this has been challenged as artefactual, resulting from inadequate filtration technique.[3] Data obtained using both filtration and centrifugation techniques in a follow up investigation were consistent with the presence of a binding site for **(*S*)-1**, but could neither confirm nor exclude the presence of a second binding site.[4] As part of our NIDA supported program to provide useful biochemical tools to researchers, we synthesized higher specific activity (>30 Ci/mmol) (*S*)-amphetamine [**(*S*)-1**] and (*S*)-methamphetamine [**(*S*)-2**].

Results and discussion

In order to provide (*S*)-amphetamine [**(*S*)-1**] and methamphetamine [**(*S*)-2**] labeled at metabolically stable sites, labeling of the aromatic moiety was preferred. Reductive dehalogenation under tritium is a simple, well-known method for introducing tritium onto aromatic moieties. Thus, ring-halogenated (*S*)-amphetamine and (*S*)-methamphetamine were required. In general, aromatic bromides and iodides are used, since they are known to be much more reactive than aromatic chlorides.[5–9] However, our proposed method of synthesis (Scheme 1) was incompatible with these substituents. Since we had successfully utilized a slight modification of a published procedure[10] to reductively tritiate aromatic chlorides, (*S*)-2′,6′-dichloroamphetamine [**(*S*)-3**] and (*S*)-2′,6′-dichloromethamphetamine [**(*S*)-4**] were targeted as tritiation precursors.

Following well-established methodology, commercially available 2,6-dichlorobenzaldehyde (**5**) was converted to 2′,6′-dichlorophenyl-2-nitropropene (**6**)[11] and the latter was reduced to racemic 2′,6′-dichloroamphetamine (**3**) (Scheme 1). The secondary amine, racemic **4**, was prepared by carbamoylation of **3** to give the methyl carbamate **7** followed by reduction (Scheme 1). Attempted resolution of 2′,6′-dichloroamphetamine (**3**) using (+)-tartaric acid, based on reported methodology for amphetamine (**1**),[12] was not successful. Use of camphoric acid or dibenzoyltartaric acid also failed to resolve **3**. On the other hand, treatment of **4** with (+)-dibenzoyltartaric acid resulted in an

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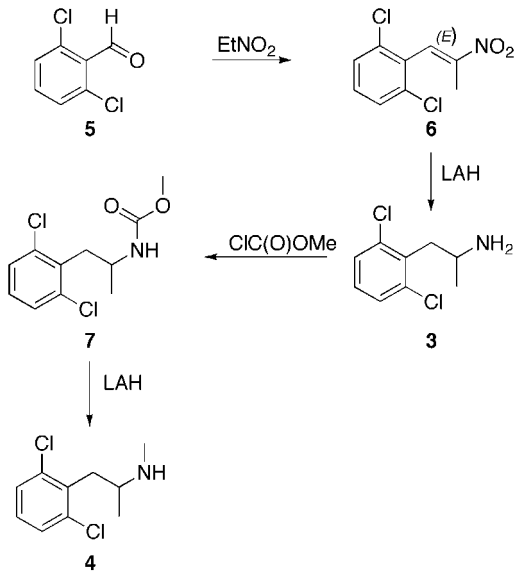
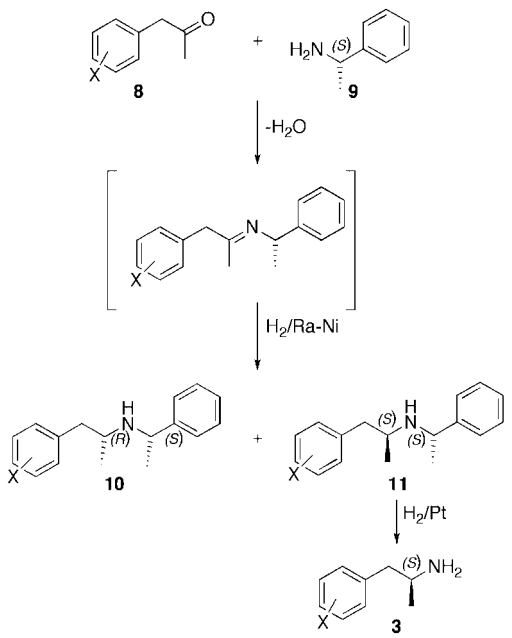


Scheme 1.

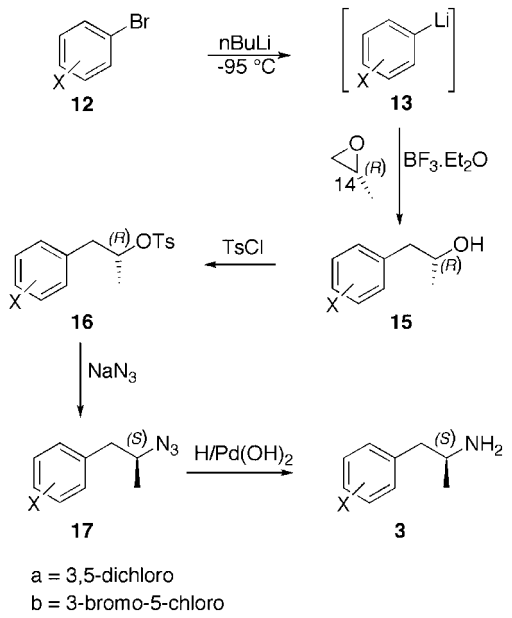


Scheme 2.

optically pure salt after recrystalization. Determination of optical purity was performed by HPLC analysis of the urea formed by reaction with (*R*)-α–methylbenzylisocyanate with the dibenzoyltatrate salt of **4** in the presence of triethylamine.[13] Thus, while the urea from racemic **4** clearly showed the presence of two diastereomers, the urea from the dibenzoyltatrate salt of **4** (**4.DBT**) showed only a small amount (<3%) of the later eluting diastereomer. Additional confirmation of the chirality and of the chiral integrity of **4.DBT** was obtained by reductive dehalogenation of **4.DBT** and analysis of the resulting methamphetamine (**2**). HPLC analysis of the urea formed by reaction of the dehalogenation product with (*R*)-α–methylbenzylisocyanate showed the main component (97.6%) to coelute with the urea formed when (*R*)-α–methylbenzylisocyanate was reacted with authentic (*S*)-methamphetamine [**(*S*)-2**]. Reductive dehalogenation of (*S*)-2′,6′-dichloromethamphetamine (**4**) was accomplished using a slight modification of the published procedure.[10] Thus, we used tetrahydrofuran as the reaction medium to minimize tritium–hydrogen exchange (and increase the specific activity) and used 20% palladium hydroxide on carbon, triethylamine, and a few drops of methanol to effect the tritiation at slightly reduced (650 Torr) pressure. A 6% yield of tritium labeled (*S*)-methamphetamine ([^{3}H(n)]-**2**) with specific activity 38.3 Ci/mmol was recovered after purification.

Attempts to obtain **(*S*)-1** by demethylation of **(*S*)-2**[14] were not successful. Since it appeared that secondary amphetamines are more readily resolved than their primary counterparts, the N-benzyl analog of **4** was prepared by benzoylation of **3** followed by reduction. This compound failed to afford salts with tartaric acid, dibenzoyltartaric acid, and camphoric acid, suggesting that the benzyl moiety reduced the basicity of the nitrogen to the point that it failed to deprotonate these acids.

In light of these difficulties, the preparation of a suitable precursor by total synthesis was undertaken. Although novel approaches to the preparation of chiral amines by transfer hydrogenation[15,16] of chiral imines have recently been reported, none have been documented for the preparation of chiral amphetamines. The two specific routes to amphetamines are: (a) formation of a diastereomeric mixture by condensation of the



Scheme 3.

appropriate phenylacetone **(8)** with (*S*)-α-methylbenzylamine **(9)**, separation of the (*S,S*)-diastereomer **11** by fractional crystallization, and debenzylation (Scheme 2),[17] (b) elaboration of chiral propylene oxide **(14)** to chiral phenyl-2-propanol **(15)**, followed by conversion of the hydroxyl functionality to an amine **(3)** (Scheme 3).[18] While option (a) is certainly shorter, it can become quite tedious when the required phenylacetone **8** must be synthesized.

We pursued option (b), targeting **17a** as the tritiation precursor to **(*S*)-3**. Reaction of commercially available 3,5-dichlorobromobenzene (**12a**) with butyl lithium at low temperature followed by reaction with (*R*)-propylene oxide (**14**)

gave a mixture of two alcohols. Mass spectral analysis showed that one was the desired alcohol **15a**; the second alcohol contained a single chloro substituent along with a bromo substituent and was presumed to be 3′-bromo-5′-chlorophenyl-2-propanol (**15b**). To obtain tritium labeled **(*S*)-1** either alcohol, or a mixture of the two alcohols, could have been used. However, we preferred to isolate the major fraction so that all intermediates could be well characterized. Column chromatography gave an oil with nuclear magnetic resonance (NMR) and mass spectral data consistent with the desired 3′,5′-dichlorophenyl-2-propanol (**15a**). This alcohol was found to be > 99% ee by gas chromatographic (GC) analysis of the methyl chloroformate (MCF) derivative. The alcohol **15a** was converted to the corresponding tosylate **16a** by reaction with tosyl chloride in pyridine. Displacement with sodium azide gave **17a**. Catalytic reduction of **17a** using conditions that had been found to be effective for the reductive dechlorination of **(*S*)-4** ($Pd(OH)_2/C$ in THF, 650 mm H_2) gave a mixture of products containing **1**. Mass spectral analysis indicated the byproducts to be partially reduced materials. Eventually, it was found that a cleaner reaction product could be obtained using palladium catalyst activated by hydrogen depletion[19] in triethylamine as solvent. Analysis of the product by GC showed it to coelute with a reference standard of amphetamine and further GC analysis of the (*S*)-(-)-N-(trifluoroacetyl)prolyl chloride (TPC) derivative showed the product to be 98% *ee* and to coelute with the TPC derivative prepared from (*S*)-(+)-amphetamine. It follows that displacement of the tosyl group by azide proceeded with inversion of configuration, as expected[18] to afford azide **17a** with *S*-configuration. Reduction of **17a** under tritium gas under the same conditions afforded the product [^{3}H(n)]-**1** in 38% yield. Three preparative TLC purifications were required to achieve > 95% chemical and radiochemical purity. The pure product was recovered in 12% yield and had specific activity 30.1 Ci/mmol.

Experimental

Proton NMR spectra were recorded on either a Bruker AM-250 MHz or a Bruker Avance 300 MHz NMR spectrometer, as indicated. MS were determined on a Perkin-Elmer Sciex API 150EX mass spectrometer outfitted with an APCI source. TLC analyses were carried out on commercial pre-coated silica gel 60F254 glass plates (E. Merck: 5 × 20 cm). GC analyses were performed on a HP 5890 Gas Chromatograph equipped with FID detector, split/splitless injection port, a HP5 column (cross-linked 5% PhMe Siloxane; 30 m × 0.32 mm × 0.25 mM film thickness), Nitrogen as a carrier gas, injection port 300°C, and Detector 300°C; additional conditions are in the text. The HPLC analyses were performed on a dual pump system (Waters 515 solvent delivery system) equipped with a Waters U6K injector, a Rainin UV–Vis detector, and a IN/US Systems β-RAM radio-detector connected after the UV–Vis detector, controlled by IN/US B2 version 3.03/BRSA version 2.1 software. HPLC column and other analysis details are shown in the text. The water used in HPLC analyses was obtained from a Millipore Milli-Q Plus Ultra-Pure Water System. Radioactive samples were counted using a Tri-Carb Liquid Scintillation Analyzer (Packard Bioscience model 2100TR) utilizing IN-FLOW 3 (IN/US Systems) as the liquid scintillation counting cocktail. Melting points were determined using a Fisher–Johns melting point apparatus.

2′,6′-Dichlorophenyl-2-nitropropene (6)

A solution of 2,6-dichlorobenzaldehyde (**5**) (100 g, 0.571 mol) and ammonium acetate (48.4 g, 0.628 mol) in nitroethane (700 mL) was refluxed for 16 h. After cooling to room temperature, the solution was poured over 60 mL ice water, extracted with Et_2O, dried over Na_2SO_4 and evaporated. The resulting oil was dissolved in Et_2O, washed sequentially with H_2O, sat. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to a yellow oil. Crystallization from absolute EtOH gave pale yellow crystals (118 g, 81%), m.p. 48–49°C (Ref.[1]. 48–49°C). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 2.12 (s, 3H, CH_3), 7.31 (t, J = 6.2 Hz, 1H, ArH), 7.34 (d, J = 8.1 Hz, 2H, ArH), 7.83 (s, 1H, ArCH = C).

2′,6′-Dichloroamphetamine Methylcarbamate (7)

To a stirred slurry of $LiAlH_4$ (11.45 g, 0.34 mol) in dry Et_2O (500 mL) was added dropwise a solution of 2′,6′-dichlorophenyl-2-nitropropene (**6**) (11.65 g, 0.05 mol) in Et_2O (250 mL). The mixture was refluxed for 8 h, cooled to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of H_2O (11.45 mL), 15% NaOH (11.45 mL), and H_2O (34.35 mL). The white salts that resulted were removed by filtration, and washed with Et_2O. The filtrate was dried over Na_2SO_4 and evaporated to give 2′,6′-dichoroamphetamine (**3**) as a yellow oil (10.61 g). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.18 (d, J = 6.4 Hz, 3H, CHC**H$_3$**), 1.39 (bs, 2H, NH_2), 3.0 (dd, 2H, ArC**H$_2$**CH), 3.3 (m, 1H, $ArCH_2$C**H**), 7.07 (t, J = 7.4 Hz, 1H, ArH), 7.3 (d, J = 8 Hz, 2H, ArH). Conversion to the methylcarbamate **7** was carried out by the addition of a solution of MCF (7.59 mL, 0.10 mol) in Et_2O (100 mL) to a solution of 2′,6′-dichloroamphetamine (**3**) (12.22 g, 0.06 mol) in Et_2O (50 mL) containing Na_2CO_3 (53.51 g). After stirring overnight the mixture was washed with 1N NaOH (400 mL), 1N HCl (100 mL), and H_2O (200 mL). The Et_2O phase was dried over Na_2SO_4, filtered and evaporated to a white solid (~12 g). Recrystallization from hot hexane (200 mL) gave **7,** 10.01 g (64%), m.p. 83–84°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.99 (d, J = 6.6 Hz, 3H, CHC**H$_3$**), 3.03–3.20 (m, 2H, ArC**H$_2$**CH), 3.40 (s, 3H, OCH_3), 4.10–4.18 (m, 1H, $ArCH_2$C**H**), 7.17 (t, J = 7.5 Hz, 1H, ArH), 7.30 (d, J = 8.1 Hz, 2H, ArH). Anal. Calcd for $C_{11}H_{13}Cl_2NO_2$: C 50.40; H 5.00; N 5.34. Found: C 50.50; H 4.97; N 5.28.

(*S*)-2′,6′-Dichloromethamphetamine (*S*-4) hydrochloride

A solution of **7** (9.91 g, 0.04 mol) in Et_2O (300 mL) was added dropwise over a period of 90 min to a stirring solution of $LiAlH_4$ (19.13 g, 0.05 mol) in Et_2O (600 mL). The reaction mixture was stirred for 4 h, and then quenched with H_2O (19.13 mL), 15% NaOH (19.13 mL), and H_2O (57.39 mL). Periodically, Et_2O had to be added to keep the mixture stirring. The solids were removed by filtration. The filtrate was dried over Na_2SO_4 and evaporated to give **4** as a pale yellow oil (8.03 g, 92%). ^{1}H NMR (300 MHz, MeOD) δ (ppm): 1.28 (d, J = 6.3 Hz, 3H, CC**H$_3$**), 2.80 (s, 3H, NC**H$_3$**), 3.28–3.42 (m, 2H, ArC**H$_2$**CH), 3.61–3.65 (m, 1H, $ArCH_2$C**H**), 7.29 (t, J = 7.2 Hz, 1H, Ar**H**), 7.50 (d, J = 7.8 Hz, 2H, Ar**H**). To resolve the racemic product a solution of 2′,6′-dichloromethamphetamine (**4**) (2.00 g, 0.009 mol) in absolute EtOH (40 mL) was treated with (+)-dibenzoyl tartaric acid (4.60 g, 0.013 mol). After 4 h, the precipitated solid was collected (2.3 g) and recrystallized from hot absolute EtOH (50 mL) to give the (+)-dibenzoyl tartrate of **4** (**4.DBT**) as a white solid, (1.45 g). Optical purity was determined

by HPLC analysis of the urea formed as follows: (*R*)-(+)-α-methylbenzylisocyanate (4 mL) followed by Et_3N (6–7 drops) was added to a suspension of **4.DBT** (50–100 mg) in dry THF (0.5 mL). The sample was analyzed using a Radial Pak silica gel cartridge, eluting with isooctane:iPrOH:HOAc 95:4.5:0.5 at 1 mL/min and detecting at 254 nm. For racemic **4** this analysis resulted in two signals of equal areas, with Rt 11.15 and 13.87 min. For the isolated **4.DBT**, the later eluting peak was >97%. Further authentication of optical purity was obtained by treatment of a solution of **4.DBT** (900 mg, 1.56 mmol) in MeOH (20 mL) with 20% $Pd(OH)_2/C$ (0.42 g), sparging with N_2(g) and stirring under H_2(g) overnight at reduced pressure. The catalyst was removed by filtration and the filtrate was evaporated to a residue that was dissolved in CH_2Cl_2 (50 mL). The solution was washed with 1N NaOH (50 mL) and H_2O (100 mL). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to an oil. The oil was dissolved in MeOH and evaporated to ensure that all the CH_2Cl_2 had been removed. The oil was dried on a vacuum pump for 0.5 h. Analysis by GC (95°C isothermal, carrier flow 1.8 mL/min; Rt 6.87 min) confirmed that the product was methamphetamine (**2**). HPLC analysis of the urea formed with (*R*)-(+)-α-methylbenzyl-isocyanate as above and using the above HPLC conditions showed a standard of racemic methamphetamine to have two peaks with equal areas and Rt 17.47 and 19.84 min; analogous analysis of the reductive dehalogenation product showed the later eluting material (>97%) to coelute with standard (+)-methamphetamine (Rt 20.96 min). To prepare the hydrochloride salt a suspension of **4.DBT** (2.9 g. 0.005 mol) in 4 N NaOH (20 mL) was extracted with ether (3 × 20 mL). The combined extract was dried over anhydrous Na_2SO_4 and concentrated. The residual oil (0.98 g) was taken up in ether (30 mL) and HCl gas was bubbled in. After overnight at ambient temperature the precipitated solid was collected and dried under vacuum (1.00 g, 78%). M.p. 200–202°C; ^{1}H NMR (300 MHz, MeOD) δ (ppm): 1.08 (d, J = 9 Hz, 3H, CCH_3), 2.80 (s, 3H, N CH_3), 3.36–3.42 (m, 2H, CH_2), 3.61–3.65 (m, 1H, CH), 7.31 (t, J = 4.5 Hz, 1H, ArH), 7.47 (d, J = 4.5 Hz, 2H, ArH); Anal. calcd. for $C_{10}H_{14}Cl_3N$: C,47.18; H 5.54; N 5.50. Found: C 47.42; H5.58; N 5.43.

(*S*)-(+)-[2′,6′-^{3}H(n)]Methamphetamine [^{3}H(n)]-(2)

A solution of (*S*)-2′,6′-dichloromethamphetamine (***S*-4**) HCl (10.58 mg; 0.042 mmol) in THF (0.5 mL) containing 10 drops MeOH and Et_3N (100 mL) was pretreated with 20% $Pd(OH)_2/C$ (9.83 mg) and filtered through a celite plug into a 2 mL tritiation flask containing 20% $Pd(OH)_2/C$ (10.64 mg). The catalyst was washed with THF (0.5 mL) and the wash was added to the reaction vessel. The mixture was stirred under tritium gas overnight at reduced pressure. Tritium uptake was 4.54 Ci. The catalyst was removed by filtration and washed with MeOH. The combined filtrate and washings were concentrated under vacuum. The residue was stirred in MeOH and phosphate buffer pH 11.2 to remove labile tritium. The solution was extracted with CH_2Cl_2 (4 × 30 mL), and the extract was dried over anhydrous Na_2SO_4. TLC radioscan of this material (SiO_2, EtOAc-CH_2Cl_2-MeOH-NH_4OH 15:10:4:0.5, Rf 0.19) showed the mixture to contain 60% of **2**, and 40% of two impurities. The impure product was streaked onto two 20 × 20 cm SiO_2 plates, 25 mm, F-254 nm and eluted with EtOAc-CH_2Cl_2-MeOH-NH_4OH 15:10:4:0.5, Rf 0.19. The band corresponding to **2** was removed and extracted with EtOH. The extract was filtered through a nylon syringe filter into a volumetric flask containing EtOH (95 mCi, 98% pure by TLC-radioscan, as above). The specific activity was determined by GC (as above). (+)-Amphetamine HCl (Rt 5.23 min) was used as the internal standard. The specific activity was found to be 38.3 Ci/mmol; 257.4 mCi/mg.

(*R*)-(3′,5′-Dichlorophenyl)-2-propanol (15a)

A solution of 1-bromo-3,5-dichlorobenzene (**12**) (7.5 g; 0.033 mol) in dry THF (150 mL) in a three necked flask equipped with a thermometer, dropping funnel and a septum, was stirred and cooled under nitrogen in an N_2 (l)/hexane slush bath. At −94°C, n-BuLi (16.6 mL; 0.033 mol 2 M in pentane) was slowly added using a dropping funnel. After stirring 10 min, propylene oxide (**14**) (0.96 g, 0.017 mol) was slowly added. After stirring 15 min, BF_3Et_2O (3.53 g; 0.025 mol) was added via syringe. The solution was stirred for 15 min and then quenched with saturated NH_4Cl. The solution was extracted with ether (3 × 50 mL). The combined organic extract was dried over Na_2SO_4, filtered, and the solvent was evaporated. The residual yellow oil was chromatographed and the product-containing fractions (1:3 SiO_2 EtOAc-hexane, R_f 0.24) were combined and evaporated to give **15a** as a light yellow oil (0.85 g, 25%). GC analysis of the MCF derivative (HP-5 column- 215°C, isothermal) showed the optical purity of **15a** (Rt 9.960 min.) to be >99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.25-(d, J = 6 Hz, 3H, CH**CH_3**), 2.65–2.76 (m, 2H, Ar**CH_2**CH), 3.99–4.07 (m, 1H, $ArCH_2$**CH**), 7.31 (d, J = 9 Hz, 2H, ArH), 7.39–7.46 (t, J = 9 Hz, 1H, ArH), M/Z calcd for $C_9H_{10}Cl_2O$, 204.2; found 204.15.

(*S*)-(3′,5′-Dichlorophenyl)-2-propyl Azide (17)

A solution of (*R*)-3′,5′-dichlorophenyl-2-propanol (**15b**) (790 mg, 3.85 mmol) in pyridine (20 mL) was stirred in an ice bath and p-toluenesulfonyl chloride (880 mg, 4.62 mmol) was added. After stirring to mix, the solution was placed in the freezer. After three days the crystals that formed were removed by filtration and the solution was added to a cold biphase of 3% NaOH (100 mL) and $CHCl_3$ (75 mL). The layers were separated and the aqueous phase was re-extracted with cold $CHCl_3$ (75 mL). The combined organic extract was washed with cold aqueous 2% HCl (100 mL), dried over anhydrous Na_2SO_4, and concentrated to give (*R*)-(3′,5′-dichlorophenyl)-2-propyl tosylate (**16**) (1.27 g mg, 92%: m.p. 77–81°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24–1.26 (d, J = 6 Hz, 3H, CH**CH_3**), 2.43 (s, 3H, $ArCH_3$), 2.70–2.77 (m, 2H, Ar**CH_2**CH), 4.61–4.68 (m, 1H, $ArCH_2$**CH**), 6.86 (s, 2H, ArH) 7.12 (s,1H, ArH), 7.18 (d, J = 6 Hz, 2H, ArH), 7.54 (d, J = 6 Hz, 2H, ArH). To form the azide, NaN_3 (880 mg; 13.5 mmol) was added to a solution of **16** (1.22 g; 0.003 mol) in DMF (5 mL) and the solution was stirred under N_2 at room temperature for three days. The reaction was quenched with H_2O, and extracted into Et_2O (3 × 30 mL). The combined extract was washed with water, then dried over Na_2SO_4, filtered and concentrated. The residual oil was dried *in vacuo* overnight and then purified by column chromatography (SiO_2, 4:1 hexane/EtOAc). The product-containing fractions were combined and evaporated to yield **17** as a yellow oil that was dried on the pump (570 mg, 72%). ^{1}H NMR (300 MHz $CDCl_3$) δ (ppm): 1.29 (d, J = 6 Hz, 3H, CH**CH_3**), 2.66–2.78 (m, 2H, Ar**CH_2**CH), 3.66–3.72 (m, 1H, $ArCH_2$**CH**), 7.10 (s, 2H, ArH), 7.26 (s, 1H, Ar**H**), M/Z calcd for $C_9H_9Cl_2N_3$ (m-2N+1) 204.2; found: 204.3.

Reduction of the azide 17 to amphetamine (1a)

A solution of **17** (14.7 mg, 0.06 mol) in Et_3N (0.5 mL) was pretreated with hydrogen-depleted[19] 10%Pd/C (15 mg). The

catalyst was removed by filtering the mixture through a syringe filter into a 2 mL round bottomed flask containing a stir bar and fresh hydrogen-depleted 10%Pd/C (14.9 mg). The collected catalyst was washed with additional Et_3N (0.5 mL) that was added into the tritiation flask. The material in the flask was stirred under H_2 for 48 h. The reaction mixture was filtered through a celite plug into a vial and the solvent was removed under a stream of N_2. The residue was dissolved in H_2O (3 mL), acidified with 0.2 N HCl, and the solution was washed with Et_2O. The aqueous phase was basified with NH_4OH and extracted with Et_2O. The ether extract was dried over Na_2SO_4 and filtered through a syringe filter into a tared vial. The ether was removed under a N_2 stream and the residue was dried overnight under vacuum (7.45 mg, 100%). The oil was dissolved in CH_2Cl_2 (1 mL) and 10 μL was analyzed by GC: 70°C isothermal, carrier flow 1.8 mL/min; Rt 11.98 min (coeluted with standard amphetamine). To determine the chiral integrity the TPC derivative was prepared by adding a solution of the product (3.73 mg) in $CHCl_3$ (0.5 mL) to 1 mL of a 0.1 M solution in CH_2Cl_2, (97% by GLC, Sigma-Aldrich) followed by the addition of one drop Et_3N. After 10 min 6N HC (2 mL) was added and the phases were separated. The organic phase was dried with a small amount Na_2SO_4. The solution was pipetted into a vial and the solvent was removed under a stream of nitrogen. Similarly the TPC derivative of standard (+)- and (-)-amphetamine were prepared. After the samples were dried under vacuum they were dissolved in CH_2Cl_2. (0.1 mL) and analyzed by GC (program: 100 to 280°C at 5°C/min and holding 5 min with the carrier flow at 1.8 mL/min). The retention time of the TPC derivative of the (+)-amphetamine standard was 21.45 min and the retention time of the TPC derivative of (-)-amphetamine standard was 20.81 min. The TPC derivative of the product had retention time 21.36 min with a very small peak (4% by area) with retention time 20.79 min. Since the derivatizing agent was 97% ee, this indicated that the product was 98% ee.

(*S*)-(+)-[3′,5′-^{3}H(n)]Amphetamine ((S)-1[^{3}H(n)]-1c))

A solution of *(S)*-3′,5′-dichlorophenyl-2-propylazide (**17**), (14.7 mg; 0.0638 mmol) in dry Et_3N (0.5 mL) was pretreated with hydrogen-depleted[19] 10%Pd/C (15 mg) for 15 min. The mixture was filtered through a nylon frit into a 2 mL tritiation flask containing hydrogen-depleted 10%Pd/C (15.42 mg). The catalyst was washed with Et_3N (0.5 mL) and the washing was added to the reaction vessel. The solution was stirred under tritium gas for 5 h and then filtered through celite into a small round-bottomed flask. The amount of tritium used was 4.72 Ci. The reaction solvent was removed by vacuum distillation and the residue was dissolved in H_2O (3 mL). The solution was treated with 0.2N HCl (1 mL) and extracted into Et_2O. The aqueous phase was basified to pH 9 with NH_4OH and extracted with Et_2O. Spotting onto a TLC plate and radioscanning (without elution) indicated that both extracts contained radioactivity. Most of the Et_2O was removed from each extract and the residues were each reconstituted in EtOH. An aliquot was removed from each and counted. The organic extract from the acid wash contained 111 mCi. The organic extract from the base wash contained 738 mCi. TLC-radioscan of each (SiO_2, EtOAc-Hxn-EtOH-NH_4OH 60:25:14:1) showed tritiated amphetamine (**1**) to be present in the organic extract from the base wash. The solvent was concentrated and the residue was streaked onto 2–20 × 20 cm SiO_2 plates 0.25 mm, F-254 nm and eluted with the same solvent as above. The band corresponding to amphetamine (**1**) (Rf 0.3) was removed and eluted with EtOH. The extract was filtered through a nylon frit into a 250 mL volumetric flask and diluted to the mark with EtOH. An aliquot was removed and counted showing a recovery of 232 mCi. TLC radioscan of the purified material on SiO_2 and eluting in EtOAc-CH_2Cl_2-MeOH-NH_4OH [15:10:4:2] (Rf 0.35) and in EtOAc-Hxn-EtOH-NH_4OH [60:25:14:1] (Rf 0.13) showed the purity to be 96.6%. However, a purity check using HPLC β-Ram (Waters C_{18} Nova-Pak column, MeOH-H_2O (3.5 g/L ammonium carbonate, 75:25, Rt 4.34 min) showed the purity to be only 91.9%. Forty-six millicuries were removed for the stock solution and concentrated. The residue was streaked into a 20 × 20 cm SiO_2 plate and eluted with EtOAc-CH_2Cl_2-MeOH-NH_4OH 15:10:4:1, Rf 0.13. The area surrounding the Rf of unlabeled **1** was removed and the material was extracted into EtOH. The extract was filtered into a 25 mL volumetric flask and filled to the mark with EtOH. Counting of an aliquot indicated a recovery of 14.5 mCi. The purity of this material was > 95% (HPLC β-Ram as above). The specific activity was determined to be 30.1 Ci/mmol; 223.3 mCi/mg using GC (95°C; isothermal; carrier flow at 1.8 mL/min, Rt 5.23 min) with (+)-methamphetamine HCl (Rt 6.87 min) as the internal standard.

Conclusions

(*S*)-(3′,-5′-dichlorophenyl)-2-propyl azide and (*S*)-2′,6′-dichloromethamphetamine have been prepared as precursors suitable toward the preparation of relatively large amounts (> 70 mCi) of tritium labeled (+)-amphetamine and (+)-methamphetamine. Reduction of these precursors has afforded the products in 38 and 6% yield, respectively, and with high specific activity (> 30 Ci/mmol).

Acknowledgement

The authors gratefully acknowledge Contracts No. NO1-DA-3-7736 and NO1-DA-8-7763 from NIDA for supporting this work.

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