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Stereospecific synthesis of amphetamines

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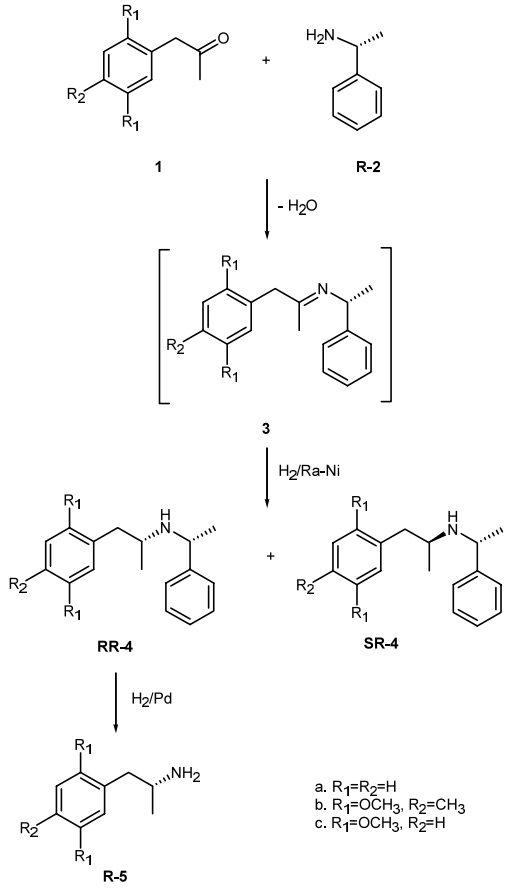
Abstract—Regioselective addition of aryl lithium to commercially available (*S*)-(+)-propylene oxide provides the corresponding (*S*)-aryl-2-propanol. The (*R*)-amphetamine is obtained by conversion of the alcohol to the tosylate followed by azide displacement and hydrogenation. Mitsunobu conversion of the alcohol to the (*R*)-bromide followed by azide displacement and hydrogenation affords the (*S*)-amphetamine.

1. Introduction

Although amphetamines can be resolved using classical methods, specific conditions must be determined for each compound and the yields are often quite poor. An effective method for the preparation of enantiomerically pure amphetamines utilizes commercially available homochiral α-methylbenzylamine as a chiral auxiliary[1] (Scheme 1). Condensation of the appropriate phenyl-2-propanone **1** with homochiral α-methylbenzylamine **2** (e.g. (*R*)-**2** in Scheme 1), followed by hydrogenation of the resulting imine **3** over Raney-nickel affords a pair of diastereomeric *N*-(α-phenethyl)phenylisopropylamines (*RR*)-**4** and (*SR*)-**4**; separation of the diastereomers by crystallization followed by debenzylation of the pure diastereomer (*RR*)-**4** by hydrogenolysis affords the enantiomerically pure amphetamine (*R*)-**5**. Use of (*S*)-α-methylbenzylamine (*S*)-**2** affords (*S*)-**5**. For amphetamines requiring commercially unavailable phenyl-2-propanones (e.g. **1b**), this method can become quite tedious.

This report describes an alternative approach which involves regioselective boron trifluoride diethyl etherate promoted ring opening of propylene oxide **8** with an aryl anion **7**[2] to afford the phenyl-2-propanol **9**, conversion of the alcohol **9** to a tosylate **10**, and S_N2 displacement of the leaving group (Scheme 2). Starting from commercially available bromoarene **6a** and (*S*)-(−)-propylene oxide (*S*)-**8** this approach is expected to provide (*R*)-amphetamine (*R*)-**5a**. The feasibility of this approach is demonstrated by the use of this reaction sequence to prepare (*R*)-(−)-2,5-dimethoxy-4-methyl-



Scheme 1.

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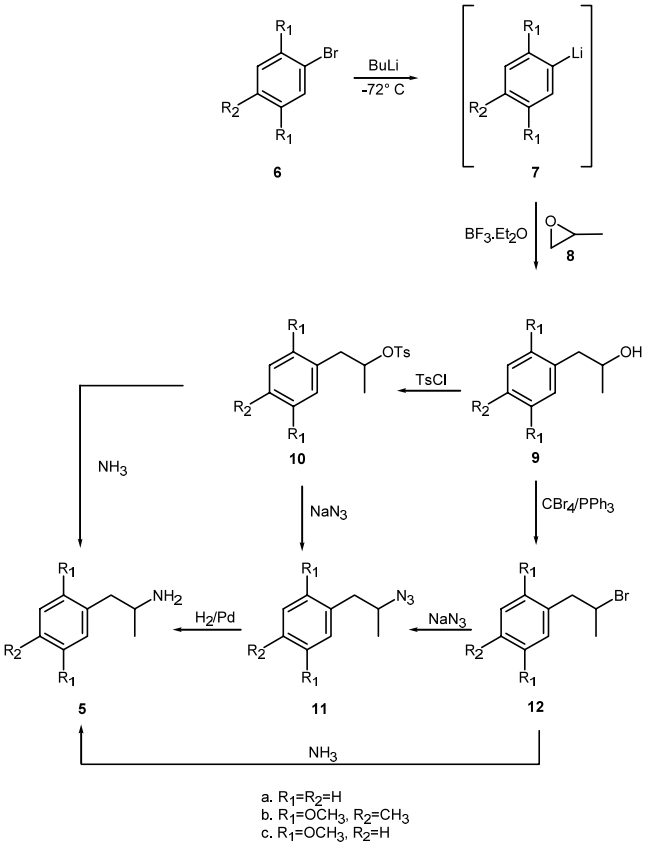


Scheme 2.

amphetamine (*R*)-**5b**, (*R*)-(−)-2,5-dimethoxyamphetamine (*R*)-**5c** and (*R*)-(−)-2,5-dimethoxy-4-iodoamphetamine (*R*)-**5d**.

The key chiral intermediate, (*S*)-phenyl-2-propanol (*S*)-**9a**, was expected to provide (*S*)-(+)-amphetamine (*S*)-**5a** by utilization of a double inversion procedure (Scheme 2). Thus, Mitsunobu inversion of the configuration of the alcohol (*S*)-**9a** to a bromide (*R*)-**12a**, followed by S_N2 displacement of the bromide was expected to lead to (*S*)-(+)-amphetamine (*S*)-**5a**. The feasibility of this approach was investigated.

2. Results

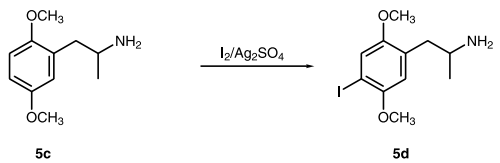
Bromination of commercially available 2,5-dimethoxytoluene with bromine in buffered acetic acid afforded 4-bromo-2,5-dimethoxytoluene **6b**,[3] as a white solid, in 78% yield. Because of the expense of optically active propylene oxide, the subsequent steps in the synthesis were investigated using racemic materials. Conversion of 4-bromo-2,5-dimethoxytoluene **6b** to the lithium reagent **7b** and reaction with racemic propylene oxide **8** provided (2′,5′-dimethoxy-4′-methylphenyl)-2-propanol **9b** in 85% yield. This material was converted to the tosylate **10b** in 90% yield and reaction with ammonia gave (±)-2,5-dimethoxy-4-methylamphetamine **5b**. However, the fact that the reaction proceeded very slowly suggested that it may be proceeding via an S_N1 mechanism and, consequently, stereochemical integrity would be lost in this step. Therefore, the tosylate **10b** was converted to the azide **11b**, and this product was hydrogenated over a palladium catalyst. Racemic 2,5-dimethoxy-4-methylamphetamine **5b** was recovered in 80% yield. Based on this promising result the reaction sequence was repeated with optically active propylene oxide. Reaction of (2,5-dimethoxy-4-methyl)phenyl lithium **7b** with (*S*)-(−)-propylene oxide (*S*)-**8** gave (*S*)-(2′,5′-dimethoxy-4′-methylphenyl)-2-propanol (*S*)-**9b** in 74% yield. The stereochemical integrity of (*S*)-**9b**, based on GC analysis of the (−)-menthyl chloroformate (MCF) derivative, was >99%. The alcohol (*S*)-**9b** was converted to the tosylate (*S*)-**10b** in 77% yield and inversion with sodium azide provided (*R*)-(2′,5′-dimethoxy-4′-methylphenyl)-2-propylazide (*R*)-**11b** in 91% yield. Hydrogenation of (*R*)-**11b** over palladium catalyst afforded (*R*)-(−)-2,5-dimethoxy-4-methylamphetamine (*R*)-**5b** in 77% yield.

Assessment of the enantiomeric excess by GC analysis of the *N*-trifluoroacetyl-L-prolyl chloride (TPC) derivative of the product confirmed >98% enantiomeric excess and the negative specific rotation confirmed the configuration.[4]

Treatment of the alcohol (*S*)-**9b** with carbon tetrabromide and triphenylphosphine, followed by sodium azide and hydrogenation as above, gave (*S*)-(+)-2,5-dimethoxy-4-methylamphetamine (*S*)-**5b** with >97% enantiomeric excess (based on GC analysis).

Preparation of (*R*)-2,5-dimethoxyamphetamine (*R*)-**5c** was carried out analogously. Low temperature lithiation of commercially available 1-bromo-2,5-dimethoxybenzene **6c** with *n*-butyl lithium, followed by boron trifluoride diethyl etherate promoted reaction with (*S*)-propylene oxide (*S*)-**8** gave 100% enantiomerically pure (*S*)-2′5′-dimethoxyphenyl-2-propanol (*S*)-**9c** in 67% yield. Reaction with *p*-toluenesulfonyl chloride in pyridine provided the tosylate (*S*)-**10c** in 57% yield, and reaction with sodium azide converted (*S*)-**10c** to the azide (*R*)-**11c** in 96% yield. Hydrogenation afforded 2,5-dimethoxyamphetamine (*R*)-**5c** in 100% yield. Stereochemical integrity was confirmed by specific rotation, GC analysis of the TPC derivative and comparison with an authentic sample.

Direct iodination of (*R*)-2,5-dimethoxyamphetamine (*R*)-**5c** in the presence of silver sulfate[5] (Scheme 3) gave (*R*)-2,5-dimethoxy-4-iodoamphetamine (*R*)-**5d** in 60% yield after column chromatography. The purified material, as the hydrochloride salt, had mp and specific rotation in excellent agreement with the literature values.[6]

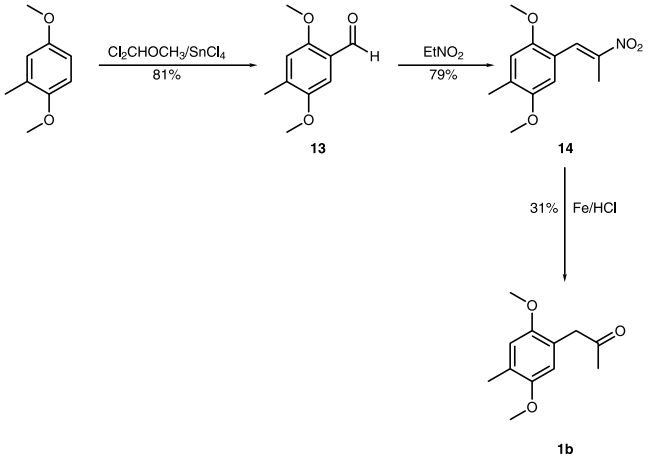


5c **5d**

Scheme 3.

3. Discussion

The described approach to the preparation of optically active amphetamines provides a straightforward enantiospecific synthesis of chiral amines with predetermined configuration. It offers significant advantages over previously utilized methods in cases where the appropriately substituted phenyl-2-propanone is not readily available. For (*R*)-(−)-2,5-dimethoxy-4-methylamphetamine (*R*)-**5b** the previously reported synthesis[1] involved condensation of (2′,5′-dimethoxy-4′-methyl)phenyl-2-propanone **1b** with (*R*)-α-methylbenzylamine (*R*)-**2**, Raney-nickel promoted reduction to (*R*,*R*)- and (*S*,*R*)-*N*-(α-phenethyl)-(2,5-dimethoxy-4-methyl)phenylisopropylamines (*RR*)-**4** and (*SR*)-**4**, purification of (*RR*)-**4** and debenzylation (Scheme 1). The commercially unavailable (2′,5′-dimethoxy-4′-methyl)phenyl-2-propanone **1b** was prepared from (2′,5′-dimethoxy-4′-methyl)phenyl-2-nitropropene **14**,[7] which, in turn, had been prepared by the reaction of 2,5-dimethoxytolualdehyde **13** with nitroethane (Scheme 4).[8] The aldehyde **13** is referred to in the literature,[9,10] but is currently not commercially available; no synthesis for **13** is given. We have prepared **13** in 81% yield by formylation[11] of commercially available 2,5-dimethoxytoluene with α,α-dichloromethylmethylether (Scheme 4). An alternate synthesis of (2′,5′-dimethoxy-4′-methyl)phenyl-2-propanone **1b** that likewise utilizes 2,5-dimethoxytolualdehyde **13** has also been reported.[9] The six-step reaction sequence that has been applied to the synthesis of (*R*)-(−)-2,5-dimethoxy-4-methylamphetamine (*R*)-**5b** (Scheme 4 followed by Scheme 1)[1] results in a 7% overall yield from commercially available 2,5-dimethoxy toluene, based on the literature yields. Our six-step procedure (Scheme 2) provided (*R*)-(−)-2,5-dimethoxy-4-methylamphetamine (*R*)-**5b** in 38% yield from commercially available 2,5-dimethoxy toluene.



Scheme 4.

Furthermore, two of the steps in the preparation of 2′,5′-dimethoxy-4′-methylphenyl-2-propanone **1b** are relatively unpleasant: the formylation of 2,5-dimethoxytoluene and the conversion of the phenylnitropropene **14** to the phenyl-2-propanone **1b**. The first requires α,α-dichloromethylmethylether and tetrachloride and involves isolation and purification of 2,5-dimethoxytolualdehyde **13**, which can be challenging. In the reduction of the phenylnitropropene **14** to the phenyl-2-propanone **1b**, the isolation of pure **1b** from the reaction mixture is difficult as well. Neither of these reactions is amenable to scale-up. Our reaction sequence sidesteps these problems. The reactions are all experimentally simple to carry out and can be performed without purification of intermediates. In fact, the preparation of (*S*)-(+)-2,5-dimethoxy-4-methylamphetamine (*S*)-**5b**, which was carried out to demonstrate the feasibility of using a double-inversion to obtain the (*S*)-enantiomer (*S*)-**5b** from the commercially available (*S*)-epoxide (*S*)-**8**, was completed without purification of the intermediates. Thus, the bromide (*R*)-**12b** was isolated as an oil from treatment of the alcohol (*S*)-**9b** with carbon tetrabromide and triphenyl phosphine, and was converted to the azide (*S*)-**11b** by treatment with sodium azide in dimethylformamide. This reaction was quenched with water and the product (*S*)-**11b** was isolated by extraction and evaporation of the solvent. Hydrogenolysis of (*S*)-**11b** without purification afforded the product, (*S*)-**5b**, in >90% purity.

Finally, the boron trifluoride diethyl etherate promoted regioselective ring opening of propylene oxide **8** with aryl lithium reagents, followed by oxidation of the resulting phenyl-2-propanol **9**, provides a convenient route to phenyl-2-propanones. Since a large variety of substituted aryl halides is readily available, many racemic and optically active amphetamines are synthetically accessible using this general approach.

4. Conclusion

The boron trifluoride diethyl etherate promoted addition of aryl lithium to propylene oxide is the basis for a convenient approach to the stereospecific synthesis of amphetamines. Use of commercially available (*S*)-propylene oxide leads to the (*S*)-aryl-2-propanol and, after displacement of the tosylate with inversion of configuration, to the (*R*)-amphetamine. Mitsunobu conversion of the (*S*)-alcohol to the (*R*)-bromide followed by displacement of the bromide with inversion of configuration affords the (*S*)-amphetamine. Alternatively, use of racemic propylene oxide and oxidation of the racemic aryl-2-propanol, provides a generalized synthetic route to a number of aryl-2-propanones which are useful in a published stereospecific preparation of chiral amphetamines.

5. Experimental

Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as internal standard. Thin layer chromatography was

carried out using Whatman silica gel 60 TLC plates and eluting with $CHCl_3$, unless otherwise noted; visualization was under UV or in an iodine chamber, as appropriate. Gas chromatography was carried out using a Hewlett–Packard 5890 Series II Plus instrument equipped with FID detector, split/splitless injection port, a HP-5 column (crosslinked 5% PhMe siloxane; 30 m×0.32 mm×0.25 μm film thickness) and nitrogen carrier gas.

5.1. 4-Bromo-2,5-dimethoxytoluene 6b

To a solution of 2,5-dimethoxytoluene (100 g, 0.657 mol) and NaOAc (56.6 g, 0.690 mol) in HOAc (400 mL) in a 1000 mL three necked, round bottomed flask equipped with N_2 inlet, magnetic stirrer, and addition funnel was added Br_2 (110 g, 0.688 mol), dropwise. The solution changed from clear to yellow and eventually to dark orange. After stirring for 20 min the reaction was quenched with a solution of saturated $NaHSO_3$ and the mixture was extracted with $CHCl_3$ (3×500 mL). The combined organic extract was dried over Na_2SO_4 and concentrated to a yellow solid. Recrystallization from hot EtOAc/hexane gave **6b** as a white crystalline solid; mp 90°C (lit.[3] 91°C), ^{1}H NMR ($CDCl_3$) δ (ppm): 2.22 (s, 3H, ArC**H**$_3$), 3.75 (s, 3H, OC**H**$_3$), 3.84 (s, 3H, OC**H**$_3$), 6.81 (s, 1H, Ar**H**), 7.06 (s, 1H, Ar**H**).

5.2. (2′,5′-Dimethoxy-4′-methylphenyl)-2-propanol 9b

To a solution of 4-bromo-2,5-dimethoxytoluene **6b** (20 g, 0.087 mol) in dry THF (700 mL) in a 1000 mL round bottomed flask equipped with N_2 inlet at −72°C was added a solution of 2.0 M *n*-BuLi in pentane (43 mL, 0.086 mol). After stirring for 10 min, propylene oxide **8** (2.51 g, 0.043 mol) was added. Stirring was continued for 10 min and $BF_3{\cdot}Et_2O$ (9.22 g, 0.065 mol) was added. The reaction was allowed to stir for 15 min. It was then quenched with satd NH_4Cl and extracted with Et_2O (3×250 mL). The combined organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness leaving a residual oil. Treatment with MeOH resulted in a white ppt. The ppt was separated by filtration and discarded, and the MeOH filtrate was evaporated to dryness leaving brown crystals. Purification by column chromatography (SiO_2; hexane:EtOAc 5:1) afforded **9b** (7.67 g, 84%) as white powdery crystals: mp 80–81°C (lit.[9] 80.5–81.5°C), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.23 (d, 3H, CHC**H**$_3$), 2.13 (d, 1H, O**H**), 2.21 (s, 3H, ArC**H**$_3$), 2.75 (ABX, 2H, ArC**H**$_2$CH), 3.78 (s, 6H, OC**H**$_3$), 4.04 (m, 1H, ArCH$_2$C**H**), 6.65 (s, 1H, Ar**H**), 6.70 (s, 1H, Ar**H**), [lit.[9] in DMSO-d_6), 1.01 (d, J=6 Hz, 3H, CHC**H**$_3$), 2.12 (s, 3H, ArC**H**$_3$), 2.65 (m, 1H, ArCH$_2$C**H** overlapping with DMSO), 3.60–4.27 (8H, overlapping ArC**H**$_2$CH and OC**H**$_3$), 4.27 (br, 1H, exchanges with D_2O, O**H**), 6.72 (s, 2H, Ar**H**)].

5.3. (2′,5′-Dimethoxy-4′-methylphenyl)-2-propyl tosylate 10b

A mixture of **9b** (1 g, 0.005 mol), *p*-toluenesulfonyl chloride (1 g, 0.005 mol), and pyridine (20 mL) was prepared while stirring a 1000 mL round-bottomed flask, in an ice bath. The mixture was transferred to the freezer and after 48 h crystals had formed. The reaction mixture was poured over ice, forming a white solid which was filtered, washed with hexanes and water, and dried under vacuum to give **10b** (1.56 g, 90%): mp 99–100°C, ^{1}H NMR ($CDCl_3$) δ (ppm): 1.39 (d, J=6 Hz, 3H, ArCH$_2$CHC**H**$_3$), 2.17 (s, 3H, ArC**H**$_3$), 2.40 (s, 3H, ArC**H**$_3$), 2.70-2.83 (m, 2H, ArC**H**$_2$), 3.62 (s, 3H, OC**H**$_3$), 3.69 (s, 3H, OC**H**$_3$), 4.75–4.86 (m, 1H, ArCH$_2$C**H**), 6.43 (s, 1H, Ar**H**), 6.44 (s, 1H, Ar**H**), 7.13 (d, J=2 Hz, 2H, Ar**H**), 7.50 (d, J=1.5 Hz, 2H, Ar**H**), ^{13}C NMR ($CDCl_3$)δ (ppm): 16.25 (Ar**C**H$_3$), 21.27 (ArCH$_2$CH**C**H$_3$), 21.58 (Ar**C**H$_3$), 37.79 (Ar**C**H$_2$), 55.63 (O**C**H$_3$), 55.86 (O**C**H$_3$), 80.06 (ArCH$_2$**C**H), 113.4 (**Ar**H), 113.8 (**Ar**H), 122.4 (**Ar**C), 125.7 (**Ar**C), 127.5 (**Ar**H), 129.2 (**Ar**H), 134.0 (**Ar**C), 143.8 (**Ar**S), 151.0 (**Ar**O), 151.2 (**Ar**O).

5.4. (2′,5′-Dimethoxy-4′-methylphenyl)-2-propyl azide 11b

After stirring overnight in a round bottomed flask, a mixture of **10b** (1 g, 0.003 mol) and NaN_3 (0.75 g, 0.012 mol) in DMF (20 mL) was taken up in water and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness to give **11b** (640 mg, 95%) as a light brown oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.24 (d, J=6.6 Hz, 3H, ArCH$_2$CHC**H**$_3$), 2.21 (s, 3H, ArC**H**$_3$), 2.69–2.83 (m, 2H, ArC**H**$_2$), 3.77 (s, 3H, OC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 6.64 (s, 1H, Ar**H**), 6.67 (s, 1H, Ar**H**), ^{13}C NMR ($CDCl_3$) δ (ppm): 16.63 (Ar**C**H$_3$), 19.70 (ArCH$_2$CH**C**H$_3$), 37.70 (Ar**C**H$_2$), 56.30 (O**C**H$_3$), 56.54 (O**C**H$_3$), 58.28 (ArCH$_2$**C**H), 114.1 (**Ar**H), 114.3 (**Ar**H), 124.3 (**Ar**C), 126.2 (**Ar**C), 151.6 (**Ar**O), 151.9 (**Ar**O).

5.5. 2,5-Dimethoxy-4-methylamphetamine hydrochloride 5b

To a solution of **11b** (640 mg, 2.7 mmol) in MeOH (20 mL) in a Parr flask was added 10% Pd/C catalyst (60 mg) and the mixture was rocked under 40 psi H_2 for 12 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated to dryness. The residual solid was taken up in Et_2O and HCl gas was allowed to bubble through. No solids formed. The Et_2O was evaporated and the residual solid was taken up in a minimal amount of MeOH; Et_2O was added dropwise. The crystals that formed overnight were filtered, washed with Et_2O, and dried to yield **5b** (400 mg, 60%): mp 188–190°C (lit.[12] 184–185°C), ^{1}H NMR (CD_3OD) δ (ppm): 1.28 (d, J=6.6 Hz, 3H, ArCH$_2$CHC**H**$_3$), 2.21 (s, 3H, ArC**H**$_3$), 2.81–2.99 (dd, 2H, ArC**H**$_2$), 3.52–3.63 (m, 1H, ArC**H**$_2$C**H**), 3.805 (s, 3H, OC**H**$_3$), 3.815 (s, 3H, OC**H**$_3$), 6.78 (s, 1H, Ar**H**), 6.83 (s, 1H, Ar**H**), ^{13}C NMR (MeOH) δ (ppm): 15.32 (ArC**H**$_3$), 17.58 (ArCH$_2$CHC**H**$_3$), 35.66 (Ar**C**H$_2$), 48.45 (ArCH$_2$**C**H), 55.32 (O**C**H$_3$), 55.53 (O**C**H$_3$), 113.9 (**Ar**H), 114.0 (**Ar**H), 121.8 (**Ar**C), 126.8 (**Ar**C), 151.7 (**Ar**O), 152.1 (**Ar**O).

5.6. (*S*)-(2′,5′-Dimethoxy-4′-methylphenyl)-2-propanol (*S*)-9b

A solution of **6b** (33 g, 0.143 mol) in freshly distilled THF (1000 mL) in a 2000 mL round bottomed flask was cooled to −72°C. To the chilled, stirring solution was added a solution of 2.0 M *n*-BuLi (71 mL, 0.142 mol) dropwise. After 10 min, *S*-(−)-proplyene oxide (*S*)-**8** (5 mL, 0.072 mol) was added, followed by $BF_3{\cdot}Et_2O$ (13.6 mL, 0.107 mol). After stirring for 15 min the reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3×400 mL). The combined organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was taken up in MeOH, causing a white precipitate to form. The ppt was separated by filtration and discarded, and the MeOH was evaporated to dryness. The residual solid was recrystallized from hot EtOAc/hexanes several times. Evaporation of the combined mother liquors afforded a brown oil which, when eluted through a silica column (hexanes:EtOAc 4:1), afforded additional (*S*)-**9b**, which was combined with the previously recrystallized batches. A further recrystallization from hot EtOAc/hexanes yielded pure (*S*)-**9b** (13.00 g, 74%): mp 90-92°C, $[\alpha]_D^{22}=+10.5$ (*c* 1.01, MeOH), ^{1}H NMR ($CDCl_3$): identical to racemic **9b**; ^{13}C NMR ($CDCl_3$) δ (ppm): 16.6 (Ar**C**H_3), 23.4 (ArCH_2C**H**CH_3), 40.8 (Ar**C**H_2), 56.43 (ArO**C**H_3), 56.46 (ArO**C**H_3), 68.62 (ArCH_2**C**H), 114.37 (**Ar**H), 114.39 (**Ar**H), 125.1 (**Ar**C), 125.9 (**Ar**C), 151.6 (**Ar**OCH_3), 152.0 (**Ar**OCH_3).

5.7. (*S*)-(2′,5′-Dimethoxy-4′-methylphenyl)-2-propyl tosylate (*S*)-10b

A mixture of (*S*)-**9b** (9.88 g, 0.048 mol), *p*-toluenesulfonyl chloride (10.8 g, 0.057 mol), and pyridine (200 mL) was prepared while stirring in a 1000 mL round bottomed flask, in an ice bath. The mixture was transferred to the freezer and after 48 h crystals had formed. These crystals were removed by filtration and washed with hexanes. The volatiles were evaporated from the combined filtrate and washings and the residual liquid was poured over ice. Since no solid was formed, the mixture was extracted with $CHCl_3$. After drying over Na_2SO_4 and evaporation of the solvent, the residue was triturated with hexanes to afford a white solid which was filtered, washed with hexane and water, and dried under vacuum to give (*S*)-**10b** (13.2 g, 77%): mp 77–78°C, ^{1}H and ^{13}C NMR ($CDCl_3$): identical to racemic **10b**.

5.8. (*R*)-(2′,5′-Dimethoxy-4′-methylphenyl)-2-propyl azide (*R*)-11b

After stirring overnight, a mixture of (*S*)-**10b** (12 g, 0.035 mol) and NaN_3 (8.96 g, 0.138 mol) in DMF (200 mL), in a round-bottomed flask, was treated with H_2O and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness to give (*R*)-**11b** (7.4 g, 91%) as a light brown oil. ^{1}H and ^{13}C NMR ($CDCl_3$): identical to racemic **11b**.

5.9. (*R*)-(−)-2,5-Dimethoxy-4-methylamphetamine hydrochloride (*R*)-5b

To a solution of (*R*)-**11b** (7.3 g, 0.032 mol) in MeOH (200 mL), in a Parr flask, was added 10% Pd/C catalyst (600 mg) and the mixture was rocked under 40 psi H_2 for 12 h. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated to dryness. The residual solid was then taken up in $CHCl_3$ and extracted with 1 M HCl. The combined extract was basified with NaOH and extracted with $CHCl_3$. After drying over Na_2SO_4, the solvent was evaporated and the residual solid was taken up in Et_2O. Treatment with HCl gas followed by evaporation of the solvent resulted in a solid hydrochloride salt. The solid was taken up in a minimal amount of MeOH and Et_2O was added dropwise. Crystals formed overnight, which were filtered, washed with Et_2O, and dried under vacuum to yield (*R*)-**5b** (5.3 g, 70%): mp 198–200°C (lit.[1] 204–205°C), $[\alpha]_D^{22}=-16.2$ (*c* 1.00, H_2O) (lit.[1] −17.2, *c* 2 H_2O). ^{1}H NMR and ^{13}C NMR (CD_3OD): identical to racemic **5**.

5.10. *S*-(−)-2,5-Dimethoxy-4-methylamphetamine (*S*)-5b

To a solution of (*S*)-(2′,5′-dimethoxy-4′-methylphenyl)-2-propanol (*S*)-**9b** (0.4 g, 0.002 mol) in dry THF (5 mL) was added triphenylphosphine (1 g, 0.004 mol) and CBr_4 (1.26 g, 0.004 mol). After stirring overnight the solids were removed by filtration and the filtrate was evaporated to dryness. The residual oil was taken up in DMF, sodium azide (0.5 g, 0.008 mol) was added and stirring was continued overnight. The reaction was quenched with H_2O and the mixture was extracted with $CHCl_3$. The organic extract was dried and evaporated to dryness. The residue was dissolved in EtOH, treated with 10% Pd/C and shaken under 40 psi of H_2 overnight. The catalyst was removed by filtration and the solvent was evaporated to near dryness. The residue was taken up in H_2O and the pH was adjusted to 7. After washing with Et_2O the pH was adjusted to 11 and the solution was extracted with $CHCl_3$. The organic extract was dried over Na_2SO_4 and evaporated to dryness. GC analysis showed the product to be (*S*)-**5b** of 97% optical purity.

5.11. (*S*)-2,5-Dimethoxyphenyl-2-propanol (*S*)-9c

To a solution of 1-bromo-2,5-dimethoxybenzene **6c** (43.41 g, 0.200 mol) in dry THF (700 mL) in a 1000 mL three necked round bottom flask equipped with an N_2 inlet and cooled to −72°C was added a solution of 2.0 M *n*-BuLi in pentane (100 mL, 0.200 mol). After stirring for 10 min, (*S*)-propylene oxide (*S*)-**8** (6.00 g, 0.103 mol) was added. Stirring was continued for 10 min and $BF_3{\cdot}Et_2O$ (21.29 g, 0.15 mol) was added. After stirring for 15 min the solution was quenched with saturated NH_4Cl and extracted with Et_2O (3×250 mL). The combined organic extract was dried over Na_2SO_4, filtered, and evaporated to dryness leaving an oil with a precipitated solid. The solid was filtered off, washed with MeOH and discarded. The oil was again evaporated, dried in vacuo and purified by column chro-

matography (SiO_2; hexane:EtOAc 5:1). The fractions that contained the product were evaporated and recrystallized from EtOAc/hexane yielding (*S*)-**9c**. (13.60 g, 67% yield) as clear colorless needle crystals. The chiral purity of the product was determined to be 100% by GC analysis of a diastereomeric mixture obtained by derivatizing with menthyl chloroformate (MCF). The compound had mp 56–57°C and $[\alpha]_D^{23} = +14.8$ (c 1.01, MeOH). ^{1}H NMR (CD_3OD) δ (ppm): 1.09–1.12 (q, 3H, CHC**H**$_3$), 2.61–2.67 (q, 1H, ArC**H**$_2$CH), 2.73–2.79 (q, 1H, ArC**H**$_2$CH), 3.72 (d, 3H, OC**H**$_3$), 3.75 (d, 3H, OC**H**$_3$), 3.95–3.99 (m, 1H, ArCH$_2$C**H**), 6.70–6.75 (m, 2H, Ar**H's**), 6.82–6.85 (m, 1H, Ar**H**). Anal calcd for $C_{11}H_{16}O_3$; C, 67.32; H, 8.22. Found: C, 67.49; H, 8.22.

5.12. (*S*)-2,5-Dimethoxyphenyl-2-propyl tosylate (*S*)-10c

To a solution of (*S*)-2,5-dimethoxyphenyl-2-propanol (*S*)-**9c** (10.19 g, 0.052 mol) in pyridine (70 mL) in a 1000 mL round bottomed flask was added *p*-toluenesulfonyl chloride (11.88 g, 0.062 mol) while stirring in an ice bath. The flask was then transferred to the freezer and left for three days. The flask was full of crystals, which were collected by filtration. The pyridine solution was washed with a cold biphase of aqueous 3% NaOH and $CHCl_3$. The $CHCl_3$ layer was drawn off and washed with cold aqueous 2% HCl. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to an oil. The oil was then recrystallized from EtOAc and hexane yielding (*S*)-**10c** (10.38 g, 57% yield) as white crystals. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.35–1.37 (d, 3H, CHC**H**$_3$), 2.41 (s, 3H, ArC**H**$_3$), 2.77–2.80 (d, 1H, Ar**CH**$_2$CH), 3.63 (s, 3H, OC**H**$_3$), 3.71 (s, 3H, OC**H**$_3$), 4.78–4.88 (m, 1H, ArCH$_2$C**H**), 6.55–6.60 (q, 2H, Ar**H's**), 6.65–6.69 (q, 1H, Ar**H**), 7.15–7.18 (d, 2H, Ar**H's**), 7.55–7.58 (d, 2H, Ar**H's**). Anal calcd for $C_{18}H_{22}O_5S$: C, 61.69; H, 6.33. Found: C, 61.72; H, 6.30.

5.13. (*R*)-2,5-Dimethoxyphenyl-2-propyl azide (*R*)-11c

To a solution of (*S*)-2,5-dimethoxyphenyl-2-propyl tosylate (*S*)-**10c** (10.17 g, 0.029 mol) in DMF (80 mL) was added sodium azide (7.55 g, 0.116 mol) and the solution was stirred for 5 days. TLC indicated complete conversion. The mixture was taken up in water and extracted with Et_2O (3×300 mL). The Et_2O layers were combined and washed with H_2O to remove excess DMF. The aqueous layer was back-extracted with Et_2O (200 mL). The combined organic extract was dried over Na_2SO_4, filtered, and evaporated to give (*R*)-**11c** (6.19 g, 96% yield) as a clear light yellow colored oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.23–1.25 (d, 3H, CHC**H**$_3$), 2.69–2.75 (q, 1H, ArC**H**$_2$CH), 2.79–2.86 (q, 1H, ArC**H**$_2$CH), 3.77 (s, 3H, OC**H**$_3$), 3.79 (s, 3H, OC**H**$_3$), 6.76–6.77 (d, 2H, Ar**H**), 6.78–6.79 (d, 1H, Ar**H's**); the proton corresponding to ArCH$_2$C**H** is overlapped by the two methoxy groups. Anal calcd for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83; N, 18.99. Found C, 59.88; H, 6.95; N, 18.69.

5.14. (*R*)-2,5-Dimethoxyamphetamine (*R*)-5c

To a solution of (*R*)-2,5-dimethoxyphenyl-2-propyl-azide (*R*)-**11c** (6.19 g, 0.028 mol) in MeOH (200 mL) was added 10% Pd/C (0.65 g) and the slurry was hydrogenated at 40–45 psi overnight. The catalyst was removed by filtration through celite and the MeOH was evaporated to leave (*R*)-**5c** (5.42 g, 100% yield) as a clear light yellow colored oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10–1.13 (d, 3H, CHC**H**$_3$), 2.48–2.55 (q, 1H, ArC**H**$_2$CH), 2.68–2.75 (q, 1H, ArC**H**$_2$CH), 3.16–3.23 (m, 1H, ArCH$_2$C**H**), 3.75 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 6.70–6.74 (m, 2H, Ar**H's**), 6.77–6.80 (q, 1H, Ar**H**). GC analysis indicated 98% enantiomerically pure (*R*)-**5c**.

5.15. (*R*)-4-Iodo-2,5-dimethoxyamphetamine (*R*)-5d

To a solution of (*R*)-2,5-dimethoxyamphetamine (*R*)-**5c** (5.42 g, 0.028 mol) in EtOH (100 mL) was added I_2 (14.10 g, 0.066 mol) and Ag_2SO_4 (17.32 g, 0.066 mol) and the reaction mixture was allowed to stir overnight. The precipitated yellow solid was collected by filtration and the EtOH evaporated. The solid residue was dissolved in $CHCl_3$ and washed with aqueous 5% NaOH (250 mL). The aqueous layer was extracted with $CHCl_3$ (2×300 mL) and the organic layers were combined and washed with H_2O. The organic layer was then dried over Na_2SO_4, filtered, and evaporated down to a purplish brown solid (8.45 g). Column chromatography (SiO_2, 8% EtOH/$CHCl_3$) gave (*R*)-**5d** (4.31 g, 48% yield) as an off white solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.10–1.13 (d, 3H, CHC**H**$_3$), 2.48–2.55 (q, 1H, ArC**H**$_2$CH), 2.68–2.74 (q, 1H, ArC**H**$_2$CH), 3.17–3.24 (m, 1H, ArCH$_2$C**H**), 3.76 (s, 3H, OC**H**$_3$), 3.83 (s, 3H, OC**H**$_3$), 6.74 (s, 1H, Ar**H**), 7.22 (s, 1H, Ar**H**). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.61 (**Ar**OCH$_3$), 152.40 (**Ar**OCH$_3$), 129.63 (**Ar**CH$_2$CH), 121.69 (**Ar**C), 114.30 (**Ar**C), 82.58 (**Ar**I), 57.13 (ArO**C**H$_3$), 56.12 (ArO**C**H$_3$), 47.00 (CH$_2$**C**HCH$_3$), 41.28 (**C**H$_2$CHCH$_3$), 23.72 (**C**H$_2$CHCH$_3$).

5.16. (*R*)-4-Iodo-2,5-dimethoxyamphetamine (*R*)-5d hydrochloride

Treatment of a $CHCl_3$ solution of (*R*)-**5d** (6.29 g, 0.020 mol) with HCl/MeOH, followed by evaporation of the solvent gave a solid that was recrystallized using MeOH/Et_2O. The white crystals were collected and washed with Et_2O giving *R*-**5d** hydrochloride (5.50 g, 0.015 mol, 79% yield): TLC single spot using UV visualization R_f 0.72 (chloroform: methanol:ammonium hydroxide (80:18:2)), mp 222–223°C (lit.[6] 218–219°C), $[\alpha]_D^{23} = -12.7$ (*c* 1.01, H_2O). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.34–1.36 (d, 3H, CHC**H**$_3$), 2.82–2.89 (q, 1H, ArC**H**$_2$CH), 3.05–3.11 (q, 1H, ArC**H**$_2$CH), 3.66–3.73 (m, 1H, ArCH$_2$C**H**), 3.80 (s, 3H, OC**H**$_3$), 3.84 (s, 3H, OC**H**$_3$), 6.72 (s, 1H, Ar**H**), 7.24 (s, 1H, Ar**H**).

5.17. Determination of enantiomeric excess

5.17.1. (2′,5′-Dimethoxy-4′-methylphenyl)-2-propanol 9b. In a solution of 0.1 M of (–)-MCF in toluene, (1.5 mL) was dissolved **9b** (15 mg) and pyridine (1 drop) was added. The solution was shaken, then washed with H_2O, dried over Na_2SO_4, and used for GC analysis at 215°C. Analysis of the racemate gave two peaks of equal area at 17.7 and 18.2 min.

Application of this procedure of the chiral alcohol (*S*)**-9b** yielded a single peak at 17.4 min.

5.17.2. (2′,5′,-Dimethoxyphenyl)-2-propanol 9c. The procedure used for **9b** was followed. Analysis of the racemic alcohol gave two peaks of equal area at 15.02 and 15.48 min. Analysis of (*S*)**-9c** gave a single peak at 14.88 min.

5.17.3. 2,5-Dimethoxy-4-methylamphetamine 5b. In a vial, racemic 2,5-dimethoxy-4-methylamphetamine (25 mg) was dissolved in $CHCl_3$ (1 mL) and 2 mL of 0.1 M TPC in $CHCl_3$ (3.4% D isomer present) was added along with TEA (1 drop). This mixture was kept at ambient temperature for 10 min, then washed with HCl (6.0 M); the $CHCl_3$ layer was used for GC analysis: 100–280°C @ 6°C/min, 5 min final hold. The racemate exhibited two peaks, one at 26.3 and 26.8 min. Since the second peak integrated larger, a correction factor of 0.906 was applied to the second peak to equalize the areas. Analysis of (*R*)**-5b** showed a major peak at 26.4 min and a minor peak of 26.7 min. After applying the correction factor (*R*)**-5b** was found to be 98% enantiomerically pure.

In a subsequent experiment the racemate had peaks at 24.6 and 25.1 min; these peaks required a correction factor of 0.918 for the later eluting peak. Analysis of (*S*)**-5b** showed a major peak at 25.2 and a minor peak at 24.5 min. The enantiomeric purity was 97%.

5.17.4. 2,5-Dimethoxyamphetamine 5c. The procedure used for **5b** was followed. Analysis of the racemic amphetamine gave two peaks, one at 19.0 min and 19.5 min. Since the second peak integrated larger, a correction factor of 0.908 was applied to the second peak. Analysis of (*R*)**-5c** showed a major peak at 18.9 min and a minor peak at 19.3 min. After applying the correction factor (*R*)**-5c** was 97% enantiomerically pure.

5.17.5. 2,5,-Dimethoxy-4-iodoamphetamine 5d. Attempts to determine the enantiomeric excess of 2,5-dimethoxy-4-iodo-amphetamine hydrochloride using TPC and MTPA[1] followed by GC analysis were unsuccessful. In each case GC analysis of the racemic derivatization product failed to yield two separate peaks.

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References

1. Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B.; Bennington, F.; Morin, R. D. *J. Med. Chem.* **1973**, *16*, 480–483.
2. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.
3. McHale, D.; Mamalis, P.; Green, J.; Marcinkiewicz, S. *J. Chem. Soc.* **1958**, 1600–1603.
4. Snyder, S. H.; Unger, S.; Blatchley, R.; Barfknecht, C. F. *Arch. Gen. Psychiatry* **1974**, *31*, 103–106.
5. Sy, W.-W. *Tetrahedron Lett.* **1993**, *34*, 6223–6224.
6. Glennon, R. A.; Young, R.; Bennington, F.; Morin, R. D. *J. Med. Chem.* **1982**, *25*, 1163–1168.
7. Ho, B. T.; Tansey, L. W. *J. Med. Chem.* **1971**, *14*, 156–157.
8. Ho, B. T.; McIsaac, W. M.; An, R.; Tansey, L. W.; Walker, K. E.; Englert, L. F., Jr.; Noel, M. B. *J. Med. Chem.* **1970**, *13*, 26–30.
9. Coutts, R. T.; Malicky, J. L. *Can. J. Chem.* **1974**, *52*, 395–399.
10. Ho, B. T.; Tansey, L. W.; McIsaac, W. M. *J. Med. Chem.* **1970**, *13*, 1022.
11. Lewin, A. H.; Parker, S. R.; Fleming, N. B.; Carroll, F. I. *Org. Prep. Proc. Internat.* **1978**, *10*, 201–204.
12. Phillips, G. F.; Mesley, R. J. *J. Pharm. Pharmacol.* **1969**, *21*, 9–17.