

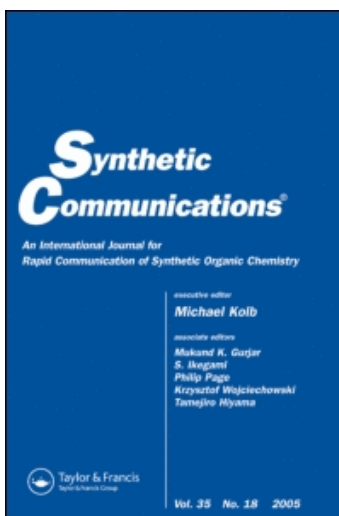
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SYNTHESIS OF 2-ARYLETHYLAMINES BY THE CURTIUS REARRANGEMENT

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2-Arylethylamine derivatives were synthesized using the Curtius reaction and with three different methods of preparing the acyl azide functional group. Carbamates derived from isocyanate were convenient protecting groups for alkylation of amines. Starting from benzaldehyde, amphetamine was prepared in three steps through an oxazolidin-2-one intermediate in 62% overall yield.

Keywords: Curtius rearrangement; isocyanate; oxazolidin-2-one; potassium *tert*-butoxide

Some of the major neurotransmitters in the vertebrate central nervous system are derivatives of 2-arylethylamines (Chart 1). Chemicals that can penetrate the nervous system tissue may have profound effects on the behavior of an organism. Four structural analogs (**1–4**) of dopamine are shown in Chart 2, including amphetamine (**1**), methamphetamine (**2**), 3,4-methylenedioxymethamphetamine (**3**) and mescaline (**4**). This report describes the novel chemical synthesis of compounds **1–4** as part of a project to study the *in vitro* binding assays of these analogs at various dopamine, serotonin, and norepinephrine receptors.

The route developed for the synthesis of **1** and **2** is shown in Scheme 1. Using conditions similar to those employed by Moersch and others,^[1–7] we reacted benzaldehyde with the dilithium dianion of propionic acid at an ice-bath temperature to get β -hydroxycarboxylic acid **5** in a 42:58 erythro/threo diastereomeric ratio based on proton nuclear magnetic resonance (NMR) spectroscopy.^[8] This ratio remained approximately the same over the next steps, and no attempt was made to separate this or the following mixtures (**6,7**) because one chiral center would eventually be eliminated. It was convenient to have several NMR studies on the diastereomers of **6** and **7**.^[9–11] Curtius rearrangement of **5** by diphenylphosphoryl azide (DPPA)^[12] in the presence of triethylamine in refluxing toluene gave the oxazolidin-2-one mixture **6** in excellent yield.^[8,13,14] Effenberger and Jäger^[15] noticed that these 5-aryloxazolidin-2-ones contain an intramolecular cyclized carbobenzyloxy (Cbz) protecting group of the nitrogen atom. As such, these compounds are readily

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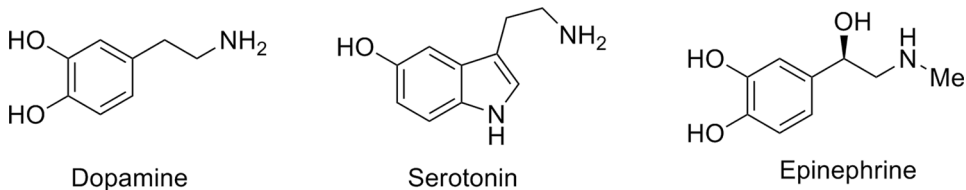
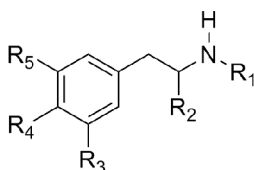


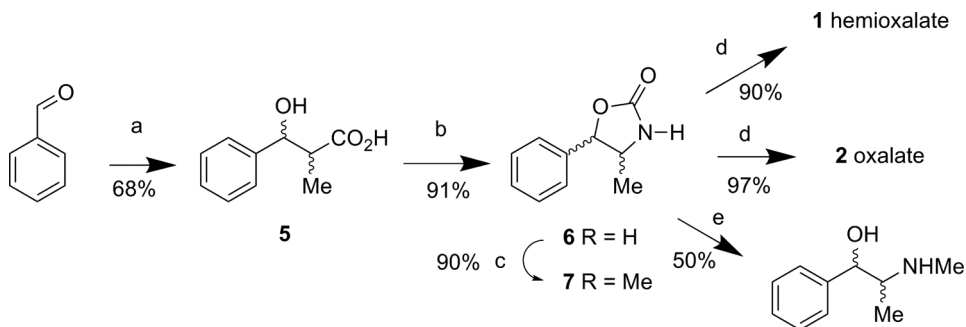
Chart 1. Neurotransmitters.



- 1 $R_1, R_2 = \text{Me}, R_3-R_5 = \text{H}$
 2 $R_1 = \text{Me}, R_2-R_5 = \text{H}$
 3 $R_1, R_2 = \text{Me}, R_3 = \text{H}, R_4-R_5 = \text{O-CH}_2\text{-O}$
 4 $R_1, R_2 = \text{H}, R_3-R_5 = \text{OMe}$

Chart 2. 2-Arylethylamines synthesized.

deprotected by catalytic hydrogenation, which reduces the benzylic position to CH_2 and yields the free 2-arylethylamines. To finish the preparation of racemic **1**, catalytic hydrogenation of **6** gave the free base, which was isolated and precipitated as its hemioxalate salt. Because the N-H acidity ($\text{p}K_a$) of carbamate in dimethylsulfoxide has been measured between 21 and 24,^[16] it is possible to deprotonate it with strong nonhydride-type bases such as potassium *tert*-butoxide.^[17–19] Reaction of **6** with iodomethane in tetrahydrofuran in the presence of this base gave the *N*-methyl mixture **7** in excellent yield. This mixture was a distillable oil, although each pure diastereomer is a solid at room temperature (51 and 91 °C).^[9,20–22] Subsequent



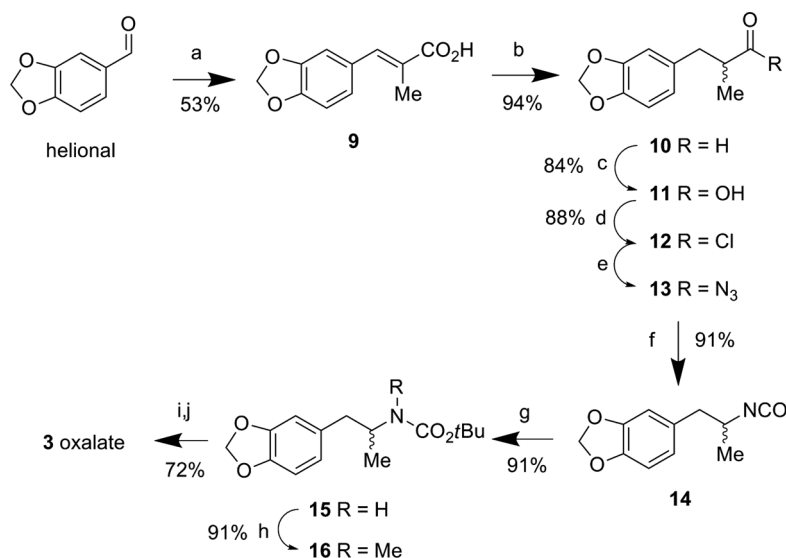
Scheme 1. Synthesis of **1**, **2**, and **8**. Reagents and conditions: (a) $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$, LDA, THF, 0 °C; (b) DPPA, PhMe, reflux; (c) KOtBu, THF; (d) 1. H_2 , 5% Pd/C, EtOH; 2. $(\text{CO}_2\text{H})_2$, EtOH; (e) KOH, H_2O , EtOH, reflux.

catalytic hydrogenation of **7** gave the racemic *N*-methyl derivative **2**, which was isolated and precipitated as its oxalate salt. To demonstrate further utility of the synthetic route, **7** was hydrolyzed with potassium hydroxide in aqueous ethanol to give a mixture of ephedrine and pseudoephedrine.

A different synthetic route was adopted for the synthesis of **3** (Scheme 2). Starting from commercially available heliotropin (**2**), the Perkin reaction using conditions of Mann and Woolf^[23] gave the cinnamic acid derivative **9**.^[24–30] It was not necessary to carry out an elaborate acid/base extraction process because crude **9** precipitated from the aqueous workup. In the next step, catalytic hydrogenation of **9** in tetrahydrofuran gave the racemic propionic acid derivative **11**.^[26] An alternate route to **11** was by oxidation of the commercially available fragrance additive 2-methyl-3-(3,4-methylenedioxyphenyl)propanal^[31–33](**10**) with potassium peroxy-monosulfate (Oxone) in *N,N*-dimethylformamide (DMF).^[34]

When a mixture of **11**, DPPA, and triethylamine in ethanol was refluxed, an excellent yield of the corresponding ethylcarbamate was obtained (data not shown). However, running the same reaction with *tert*-butanol as solvent failed to yield the analogous *tert*-butyloxycarbonyl (Boc)-protected amine (**15**). Instead, a fair yield of a solid was obtained, which appeared by proton NMR spectroscopy to be the corresponding urea. This is reminiscent of the results of Jones and Wallis,^[35] who found that simply heating the desmethylenedioxy analog of **14** in water gave a quantitative yield of the symmetrical urea.^[36] A literature survey found mixed results in the reaction of isocyanates and alcohols that are both sterically hindered.^[37–41]

Continuing in a more linear fashion, the acid **11** was readily converted into the acid chloride **12** by stirring at room temperature with thionyl chloride. Reaction of



Scheme 2. Synthesis of MDMA. Reagents and conditions: (a) CH₃CH₂CO₂Na, (CH₃CH₂CO)₂O, reflux; (b) H₂, 5% Pd/C, THF; (c) oxone, DMF; (d) SOCl₂; (e) NaN₃, H₂O, DCE; (f) 60 °C, DCE; (g) KO_tBu, HO_tBu, THF; (h) MeI, KO_tBu, THF; (i) conc. HCl, THF, 45 °C; (j) (CO₂H)₂, EtOH.

12 with sodium azide in a biphasic mixture of 1,2-dichloroethane and water at ice-bath temperature gave the acyl azide **13**. The latter derivative was not isolated but, after drying its solution in 1,2-dichloroethane, was gently heated to bring about rearrangement to isocyanate **14** in 91% yield over the two steps. With the isocyanate in hand, Boc protection of the amine was chosen because it is easily removed. Following the lesson from the DPPA/*tert*-butanol reaction, the more nucleophilic KO*t*Bu was reacted with **14** in tetrahydrofuran (THF) to obtain carbamate **15** as a crystalline solid.^[42–44]

Typically, carbamates such as **15** can be reduced with hydride reagents such as lithium tetrahydroaluminate to give an *N*-methylated amines.^[45,46] Instead, following the strategy of Trachsel et al.,^[47] **15** was methylated with iodomethane and KO*t*Bu in dimethylformamide to give **16** in excellent yield. It is interesting to note that Tom et al.^[48] used sodium *tert*-butoxide to efficiently remove Boc protection from primary amines.

It was anticipated that **16** would also be a solid at room temperature but was a distillable liquid. This is probably a result of **16** existing as a mixture of rotamers about the N-carbonyl bond.^[49–55] As shown in Fig. 1, the proton NMR spectrum of **16** in deuteriomethylsulfoxide at room temperature (26 °C) had broad peaks across the aliphatic region. The α -CH (~4.25 ppm) appears as two overlapping broad peaks as well as both the *t*-butyl (~1.25 ppm) and α -methyl (~1.05 ppm) groups. When the sample was heated (76 °C) in the probe, the resonances became much sharper as there is free rotation about the amide bond. In addition, the ¹³C NMR spectrum of **16** at room temperature shows two extra peaks for both the α -CH and N-CH₃ (see Experimental) that also each coalesce to single peaks when heated (data not shown).

Finally, there are several methods for the removal of Boc-protected amines such as trifluoroacetic acid, methanesulfonic acid, or dry hydrogen chloride in organic solvent.^[56] Deprotection of **16** to racemic free base **3** was readily achieved in nearly quantitative yield by reaction with concentrated hydrochloric acid in warm THF.^[57–60] For storage and handling convenience, amine **3** was converted into its oxalate salt.

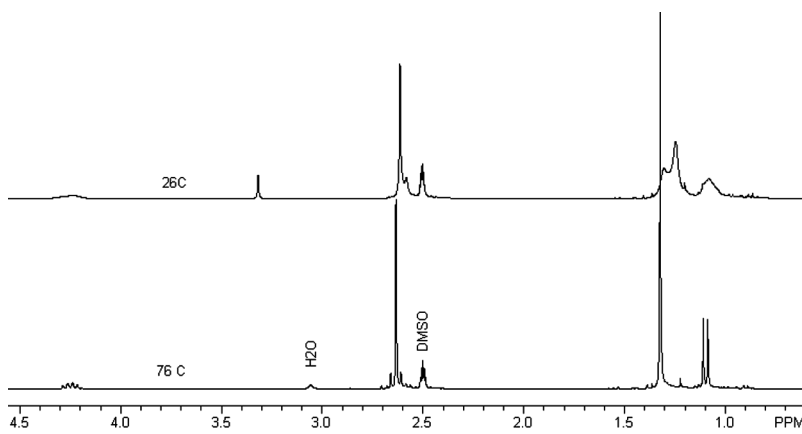
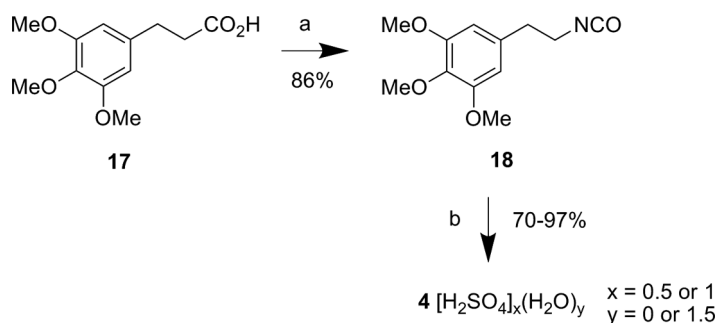


Figure 1. Variable temperature ¹H-NMR study of carbamate **16** in DMSO-*d*₆.



Scheme 3. Synthesis of mescaline salts. Reagents and conditions: (a) 1. ClCO_2Et , TEA, DCE; 2. NaN_3 , H_2O ; 3. reflux; (b) H_2O , 0.5 equiv or excess conc. H_2SO_4 , 80°C .

The starting material for the synthesis of **4**^[61–63] was commercially available **17** (Scheme 3).^[62,64] Several attempts to isolate the acid chloride of **17** from reaction with thionyl chloride failed. Instead, the mixed carboxylic–carbonic anhydride method of Weinstock^[65,66] was used to synthesize the acyl azide of **17** in situ. To eliminate possible formation of the anhydride of **17**, a solution of **17** and triethylamine was added to the solution of ethyl chloroformate.^[67,68] 1,2-Dichloroethane was an excellent choice of solvent as the triethylamine hydrochloride by-product precipitated virtually quantitatively. By proton NMR, there was a characteristic upfield shift of the quartet of the CH_2 group in ethyl chloroformate from 4.4 to 4.2 ppm, indicating formation of the mixed carboxylic–carbonic anhydride. To generate the acyl azide, an aqueous solution of sodium azide was added to the reaction mixture. Thin-layer chromatography (TLC) was convenient to diagnose reaction progress. By proton NMR analysis, the disappearance of the quartet at 4.2 ppm of the mixed carboxylic–carbonic anhydride was indicative of acyl azide formation, and all the other resonances remained unchanged. After washing and drying the 1,2-dichloroethane solution of the acyl azide, refluxing the solution brought about the Curtius rearrangement. The isocyanate **18**^[69–71] was found to be a distillable, low-melting solid.

Because alkylation of the amine of target **4** was unnecessary, **18** was hydrolyzed in aqueous acid. Heating **18** in water with one-half equivalent or excess sulfuric acid caused evolution of carbon dioxide and gave the hemisulfate or sulfate of **4**, respectively.^[61,72] Fortunately, these hydrolyses were not complicated by sulfamic acid formation.^[73]

In conclusion, the Curtius rearrangement was an effective method to install the nitrogen atom of 2-arylethylamine derivatives. Carbamate protection of the amines allowed for the clean alkylation of a primary amine. These routes avoid the use of hazardous metal and metal hydride reagents typically employed in the synthesis of this class of pharmacologic agents.

EXPERIMENTAL

Melting points were collected on an electrothermal capillary melting-point apparatus and are not corrected. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 300-MHz (^1H , 300 MHz; ^{13}C , 75 MHz) instrument. All samples were referenced to tetramethylsilane (TMS) as internal

standard or solvent. Heliotropin (**2**) 99%, sodium propionate 99%, propionic anhydride 97%, iodomethane 99%, thionyl chloride (SOCl₂) 97%, sodium azide 99%, *tert*-butanol (*t*BuOH) 99%, potassium *tert*-butoxide (KO*t*Bu) 95%, anhydrous dimethylformamide (DMF) 99.8%, diphenylphosphoryl azide (DPPA) 97%, tetrabutylammonium bromide (TBAB) 98%, 1,2-dichloroethane (DCE) 99%, anhydrous THF 99% (inhibited with 250 ppm 2,6-di-*tert*-butyl-4-methylphenol), oxalic acid dihydrate 99%, 2.3 M hexyllithium in hexanes, anhydrous diisopropylamine (DIPA), 5% palladium on carbon (Pd/C), Oxone monopersulfate compound, and 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal (**10**, Chemical Abstracts Service Registry Number 1205-17-0) were purchased from Sigma-Aldrich (Milwaukee). All other reagents were obtained commercially and used as received. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

2-Methyl-3-hydroxy-3-phenylpropionic Acid (**5**) Mixture of Diastereomers

A 500-mL, round-bottomed flask equipped with magnetic stirbar was charged with 150 mL THF and 33 mL DIPA (0.23 mol). A 250-mL addition funnel was attached, and the apparatus was protected with an N₂ bubbler. The mixture was stirred in an ice bath. Once cold, the addition funnel was charged with 100 mL 2.3 M hexyllithium in hexanes (0.23 mol), which were then added in a gentle stream over 20 min. A new addition funnel was equipped and charged with 6.9 mL propionic acid (0.276 mol, 1.2 equiv), which was added dropwise over 15 min. Copious solids precipitated during the addition. The reaction was stirred in a 50 °C bath for 45 min and then cooled in an ice bath once again. A new addition funnel was equipped and charged with 7.8 mL benzaldehyde (0.23 mol), which was added dropwise over 15 min. The cooling bath was removed, and the mixture was stirred at rt for 3 h. A solution of 200 mL 7.5% NaOH was added, and the mixture was stirred for 10 min. The aqueous layer was separated and acidified to pH 3 with 120 mL 6 M HCl and extracted with Et₂O (four times, 100 mL). The combined extracts were washed with 100 mL brine and then dried over anhydrous MgSO₄. Evaporation of the solvent and some residual propionic acid left 9.5 g of a colorless oil (68%). Agitation with 100 mL of 10% Et₂O in hexanes caused the oil to solidify, yielding a white crystalline solid. Mp 64–68 °C. δ_H (DMSO): 12.13 (bs, 2 CO₂H), 7.46–7.15 (m, 10H), 5.43 (bs, 2 OH), 4.87 (d, *J* = 5.8 Hz, 1H, erythro), 4.62 (d, *J* = 9.0 Hz, 1H, threo), 2.67–2.53 (overlapping pentets, 2H), 1.02 (d, *J* = 6.8 Hz, 1H, threo), 0.77 (d, *J* = 7.0 Hz, 1H, erythro); δ_C (DMSO): 176.16, 175.43, 144.21, 143.25, 128.02, 127.87, 127.32, 126.93, 126.83, 126.24, 75.09, 73.22, 47.48, 47.00, 13.66, 11.67. Elemental analysis calculated for C₁₀H₁₂O₃: C, 66.65; H, 6.71. Found: C, 66.47; H, 6.70.

4-Methyl-5-phenyloxazolidin-2-one (**6**) Mixture of Diastereomers

A 500-mL, round-bottomed flask equipped with magnetic stirbar was charged with 50 mL toluene, 4.7 g TEA (46.6 mmol, 1.2 equiv), and 7 g **5** (39 mmol). The mixture was stirred at rt while 12.8 g DPPA (46.6 mmol, 1.2 equiv) was added dropwise over 5 min. The mixture was then stirred at 55 °C, and gentle evolution of N₂ occurred. After stirring overnight at this temperature, the mixture was cooled to

rt, and 50 mL saturated aqueous NaHCO₃ were added along with 50 mL EtOAc. The phases were separated, and the organic layer was further washed with 50 mL 1 M HCl followed by 50 mL H₂O and then 50 mL brine. The organic layer was dried over anhydrous MgSO₄ and rotary evaporated, leaving a crude white solid. The crude was slurried with 50 mL hexanes and filtered on a medium glass frit to give 6.27 g of white solid (91%). ¹H NMR shows the product is a mixture of *cis/trans* diastereomers. δ_{H} (CDCl₃): 7.46–7.20 (m, 10H), 6.22 (bs, NH, *cis*), 6.13 (bs, NH, *trans*), 5.71 (d, *J* = 7.9 Hz, 1H, *trans*), 5.04 (d, *J* = 7.3 Hz, 1H, *cis*), 4.20 (pent, *J* = 7.3 Hz, 1H, *trans*), 3.84 (pent, *J* = 6.1 Hz, 1H, *cis*), 1.39 (d, *J* = 6.1 Hz, 3H, *cis*), 0.81 (d, *J* = 6.7 Hz, 3H, *trans*); δ_{C} (CDCl₃): 159.87, 159.45, 137.94, 135.18, 129.16, 129.05, 128.68, 128.64, 126.16, 126.09, 85.59, 81.21, 56.75, 52.61, 20.13, 17.65. Elemental analysis calculated for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.38; H, 6.24; N, 7.86.

α -Methyl-2-phenylethylamine (1) Hemioxalate

A 100-mL, round-bottomed flask equipped with magnetic stirbar was charged with 1.07 g **5** (6 mmol), 100 mg 5% Pd/C, and 20 mL anhydrous THF. The mixture was hydrogenated (~1 torr, rt) for 3 h. The mixture was filtered through celite and rotary evaporated, leaving 800 mg of a colorless oil of **1** (100%). [δ_{H} (CDCl₃): 7.34–7.14 (m, 5H), 3.16 (hex, *J* = 6.4 Hz, 1H), 2.70 (dd, *J* = 13.3 and 5.5 Hz, 1H), 2.52 (dd, *J* = 13.3 and 8.0 Hz, 1H), 1.46 (bs, NH₂), 1.11 (d, *J* = 6.2 Hz, 3H); δ_{C} (CDCl₃): 139.84, 129.42, 128.55, 126.35, 48.67, 46.79, 23.64]. An EtOH solution of the amine was added dropwise to a stirred mixture of 378 mg oxalic acid dihydrate (3 mmol, 0.5 equiv) dissolved in EtOH. The white precipitate was collected and air dried on the frit; no further purification was necessary. Mp 140 °C (shrank), 190 °C (dec.). δ_{H} (D₂O): 7.45–7.25 (m, 5H), 3.59 (hex, *J* = 6.9 Hz, 1H), 2.91 (dd, *J* = 7.4 and 2.3 Hz, 2H), 1.27 (d, *J* = 6.4 Hz, 3H); δ_{C} (D₂O): 160.66, 128.13, 121.41, 120.97, 119.34, 41.03, 32.04, 9.44. Elemental analysis calculated for C₉H₁₃N · 0.5 C₂H₂O₄: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.51; H, 7.79; N, 7.71.

3,4-Dimethyl-5-phenyloxazolidin-2-one (7) Mixture of Diastereomers

A 100-mL, round-bottomed flask equipped with magnetic stirbar was charged with 50 mL THF and 4.71 g **6** (0.027 mol), and the mixture was stirred in an ice bath. In one portion, 4.47 g KO^{*t*}Bu (0.04 mol, 1.5 equiv) were added, and the mixture was stirred for 15 min. In one portion, 7.53 g iodomethane (3.3 mL, 0.05 mol, 2 equiv) were added, and the cooling bath was removed. Shortly thereafter, a precipitate of KI formed. After stirring at rt for 1 h, 100 mL H₂O and 100 mL Et₂O were added. The organic layer was separated, washed with brine, and then dried over anhydrous MgSO₄. Evaporation of the solvent left 4.78 g of a pale yellow oil (94%) that was >97% by ¹H NMR. The oil would not crystallize even after overnight vacuum or cooling to –20 °C. The oil was distilled (0.1 torr) to give the title compound as a nearly colorless oil composed of a *cis/trans* mixture of diastereomers. δ_{H} (CDCl₃): 7.46–7.24 (m, 10H), 5.59 (d, *J* = 8.2 Hz, 1H, *trans*), 4.91 (d, *J* = 8.2 Hz, 1H), 4.03 (pent, *J* = 6.1 Hz, 1H, *trans*), 3.55 (pent, *J* = 6.1 Hz, 1H, *cis*), 2.87 (s, 3H, *trans*), 2.85 (s, 3H, *cis*), 1.37 (d, *J* = 6.1 Hz, 3H, *cis*), 0.79 (d, *J* = 6.5 Hz, 3H, *trans*);

δ_{C} (CDCl_3): 158.11, 157.86, 137.79, 135.35, 129.02, 128.93, 128.54, 125.51, 126.23, 126.01, 82.52, 78.42, 61.34, 57.12, 29.02, 28.83, 17.40, 14.31. Elemental analysis calculated for $\text{C}_{11}\text{H}_{13}\text{NO}_2$: C, 69.09; H, 7.01; N, 7.33. Found: C, 69.14; H, 7.01; N, 7.33.

***N*, α -Dimethyl-2-phenylethylamine (2) Oxalate**

A mixture of 4.3 g **7** (0.02 mol) and 100 mg 5% Pd/C in 20 mL EtOH was hydrogenated at near atmospheric pressure overnight. The catalyst was filtered away through Celite, and the solvent was evaporated, leaving a 2.98 g of a colorless oil of **2** that was more than 97% by ^1H NMR (100%). δ_{H} (CDCl_3): 7.34–7.16 (m, 5H), 2.89–2.72 (m, 2H), 2.67–2.49 (m, 2H), 2.42 (s, 3H), 1.08 (d, $J=6.1$ Hz, 3H); δ_{C} (CDCl_3): 139.47, 129.51, 128.62, 126.43, 56.56, 43.34, 33.83, 19.56. A solution of 2.52 g oxalic acid dihydrate (0.02 mol, 1 equiv) in 25 mL EtOH was stirred, and a solution of the amine in 5 mL EtOH was added. After stirring for 30 min, the salt precipitated and was filtered on a coarse porosity glass frit. After air-drying on the frit, 4.65 g of the title compound was obtained as a white microcrystalline powder that was analytically pure (97%). Mp 149–151 °C. δ_{H} (DMSO): 8.5–7.37 (bs, 3H), 7.37–7.19 (m, 5H), 3.42–3.26 (m, 1H), 3.17 (dd, $J=12.6$ and 3.7 Hz, 1H), 2.68–2.5 (m, 4H), 1.07 (d, $J=6.3$ Hz, 3H); δ_{C} (DMSO): 164.92, 136.89, 129.25, 128.57, 126.74, 55.19, 38.28, 29.67, 14.86. Elemental analysis calculated for $\text{C}_{10}\text{H}_{15}\text{N} \cdot \text{C}_2\text{H}_2\text{O}_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.21; H, 7.10; N, 5.82.

2-(Methylamino)-1-phenylpropan-1-ol (8) Mixture of Diastereomers

A mixture of 1.84 g **7** (9.6 mmol) in 23 mL 20% KOH in H_2O and 23 mL EtOH was refluxed. After 2 h, the mixture was poured into H_2O and extracted three times with 50-mL portions of Et_2O . The organic phases were collected and washed with 25 mL brine and dried over anhydrous MgSO_4 . Evaporation of the solvent left 0.8 g of a white solid (50%). Mp 65–71 °C. δ_{H} (CDCl_3): 7.39–7.21 (m, 10H), 4.76 (d, $J=4.0$ Hz, 1H, erythro), 4.18 (d, $J=8.2$ Hz, 1H, threo), 2.81 (qd, $J=6.6$ and 4.0 Hz, 1H, erythro), 2.61 (dq, $J=8.1$ and 6.6 Hz, 1H, threo), 2.49 (s, 3H, erythro), 2.45 (s, 3H, threo), 0.94 (d, $J=6.4$ Hz, 3H, threo), 0.83 (d, $J=6.4$ Hz, 3H, erythro); δ_{C} (CDCl_3): 142.70, 141.97, 128.42, 128.26, 127.76, 127.19, 126.33, 77.83, 73.38, 61.48, 60.63, 34.14, 33.66, 15.78, 14.34. Elemental analysis calculated for $\text{C}_{10}\text{H}_{15}\text{NO}$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.44; H, 9.31; N, 8.57.

***trans*-3-(3,4-Methylenedioxyphenyl)-2-methylacrylic Acid (9)**

A 1-L, round-bottomed flask equipped with magnetic stirbar and reflux condenser was charged with 62.2 g helional (0.415 mol), 39.8 g sodium propionate (0.415 mol, 1 equiv), and 100.2 mL propionic anhydride (8 equiv). The mixture was refluxed for 3 h. An aliquot of the reaction mixture was dissolved in deuteriomethylsulfoxide, and ^1H NMR showed all the aldehyde had been consumed. While hot, the mixture was poured into 2 L H_2O , causing a tan solid to precipitate. The solid was collected on a coarse-porosity glass frit and air dried for several hours on the frit. The solid was slurried with Et_2O , filtered, washed with hexanes, and air-dried on the frit to give 43.4 g of the product as an off-white powder (53%). The title compound

was obtained in analytically pure form by recrystallization from MeCN. Mp 195–197°C. (lit.^[26] 192–194°C). δ_{H} (DMSO): 7.51 (d, $J=1.5$ Hz, 1H), 7.06 (s, 1H), 6.97 (m, 2H), 6.06 (s, 2H), 2.01 (d, $J=1.5$ Hz, 3H); δ_{C} (DMSO): 169.62, 147.53, 147.51, 137.59, 129.65, 126.97, 124.63, 109.50, 108.45, 101.42, 14.02. Elemental analysis calculated for $\text{C}_{11}\text{H}_{10}\text{O}_4$: C, 64.07; H, 4.89; O, 31.04. Found: C, 64.15; H, 4.78.

Racemic 3-(3,4-Methylenedioxyphenyl)-2-methylpropionic Acid (11)

Method A from 9. A suspension of 43.4 g **9** (0.21 mol) and 1 g 5% Pd/C in 500 mL THF was hydrogenated on a Parr shaker at 40 psi for 3 h. After this time, uptake of H_2 ceased, and the mixture was filtered through Celite. The colorless filtrate was rotary evaporated to an oil that slowly crystallized to an off-white solid (41.05 g, 94%). Mp 72–74°C (lit.^[26] 77°C). δ_{H} (CDCl_3): 10.27 (bs, CO_2H), 6.67 (d, $J=7.6$ Hz, 1H), 6.62 (d, $J=1.5$ Hz, 1H), 6.57 (dd, $J=7.6$ and 1.9 Hz, 1H), 5.87 (s, 2H), 2.92 (dd, $J=13.2$ and 6.2 Hz, 1H), 2.64 (hexet, $J=7.2$ Hz, 1H), 2.54 (dd, $J=13.2$ and 7.7, 1H), 1.11 (d, $J=7.3$ Hz, 3H); δ_{C} (CDCl_3): 182.77, 147.80, 146.29, 132.96, 122.15, 109.51, 108.36, 101.07, 41.69, 39.21, 16.59. Elemental analysis calculated for $\text{C}_{11}\text{H}_{12}\text{O}_4$: C, 63.45; H, 5.81. Found: C, 63.59; H, 5.66.

Method B from 10. A 500-mL round-bottomed flask equipped with magnetic stirbar was charged with 19.2 g **10** (16.55 mL, 0.1 mol) and 250 mL anhydrous DMF. In one portion, 61.5 g Oxone (0.1 mol, 1 equiv.) was added, and the internal temperature peaked at 55°C and then cooled to rt over 1 h. After this time, TLC showed all the starting aldehyde had been consumed, and the mixture was poured into 1 L H_2O . After stirring for several hours to allow precipitation, 17.42 g of title compound was collected on a medium glass frit (84%). No further purification was necessary. Spectroscopic data for the product were identical to that found from method A.

Racemic 3-(3,4-Methylenedioxyphenyl)-2-methylpropionyl Chloride (12)

A suspension of 5 g **11** (0.24 mol) and 3.5 mL SOCl_2 (2 equiv) was stirred under N_2 overnight. The resulting green solution was evaporated to remove the excess SOCl_2 . A few milliliters of toluene were added, and this was distilled under reduced pressure to chase away residual SOCl_2 , HCl, and SO_2 . The resulting oil was distilled under reduced pressure (0.1 torr) to give 4.8 g of the title compound as a pale yellow liquid (88%). The liquid may solidify on standing over several days. δ_{H} (CDCl_3): 6.68 (d, $J=7.8$ Hz, 1H), 6.59 (d, $J=1.5$ Hz, 1H), 6.57 (dd, $J=7.7$ and 1.8 Hz, 1H), 5.87 (s, 2H), 3.01 (m, 2H), 2.62 (m, 1H), 1.21 (d, $J=6.8$ Hz, 3H); δ_{C} (CDCl_3): 177.19, 148.01, 146.71, 131.39, 122.31, 109.48, 108.56, 101.21, 53.68, 39.17, 16.77. Elemental analysis calculated for $\text{C}_{11}\text{H}_{11}\text{ClO}_3$: C, 58.29; H, 4.89. Found: C, 58.56; H, 4.98.

Racemic 3-(3,4-Methylenedioxyphenyl)-2-propyl Isocyanate (14)

A 250-mL, round-bottomed flask equipped with magnetic stirbar was charged with 12.66 g **12** (55.8 mmol), 100 mg TBAB, and 150 mL DCE. The mixture was cooled in an ice bath while a solution of 4.5 g NaN_3 (69.8 mmol, 1.25 equiv) in

10 mL H₂O was added dropwise over 30 min. The mixture was reacted at 5 °C for 1 h. After this time, ¹H NMR showed all **6** had been consumed to give racemic 3-(3,4-methylenedioxyphenyl)-2-methylpropionyl azide (**13**) [δ_{H} (CDCl₃): 6.73 (d, $J=7.9$ Hz, 1H), 6.65 (d, $J=1.6$ Hz, 1H), 6.61 (dd, $J=7.9$ and 1.6 Hz, 1H), 5.93 (s, 2H), 2.95 (dd, $J=12.5$ and 6.6 Hz, 1H), 2.71–2.53 (m, 2H), 1.16 (d, $J=6.6$ Hz, 3H); δ_{C} (CDCl₃): 183.49, 147.88, 146.40, 132.58, 122.13, 109.45, 108.43, 101.11, 44.09, 39.23, 16.76]. While keeping the organic phase at ice-bath temperature as much as possible, the mixture was separated, and the organic phase was washed with 25 mL H₂O followed by 50 mL brine. The organic layer was dried over 5 g anhydrous MgSO₄ and filtered into a 500-mL Erlenmeyer flask containing a magnetic stirbar. The flask was then placed on a hotplate/stirrer and heated to 60 °C, whereby the smooth evolution of N₂ occurred. After 1 h, ¹H NMR showed all the acyl azide **13** was consumed. The solvent was rotary evaporated, and the remaining liquid was distilled under reduced pressure to give 10.5 g of the title compound as a pale yellow liquid (91%). δ_{H} (CDCl₃): 6.77 (d, $J=7.9$ Hz, 1H), 6.69 (d, $J=1.7$ Hz, 1H), 6.66 (dd, $J=7.5$ and 1.9 Hz, 1H), 5.96 (s, 2H), 3.75 (m, 1H), 2.72 (m, 2H), 1.29 (d, $J=6.5$ Hz, 3H); δ_{C} (CDCl₃): 147.94, 146.71, 131.47, 122.88, 122.59, 109.69, 108.48, 101.16, 53.03, 44.79, 22.93. Elemental analysis calculated for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.60; H, 5.46; N, 6.85.

Racemic *tert*-Butyl *N*-{3-(3,4-methylenedioxyphenyl)-2-propyl}carbamate (15**)**

A 500-mL, round-bottomed flask equipped with magnetic stirbar was charged with 100 mL anhydrous THF, 5.4 g *t*BuOH (73 mmol, 2 equiv), and 4 g KO^{*t*}Bu (36.5 mmol, 1 equiv). The mixture was stirred in an ice bath, and then a solution of 7.49 g **14** (36.5 mmol) dissolved in 25 mL anhydrous THF was added by addition funnel over 10 min. All the solids dissolved, and the mixture became clear and light yellow in color. The cooling bath was removed, and the mixture was stirred at rt for 1 h. Water (100 mL) containing 2.09 mL glacial HOAc (36.5 mmol, 1 equiv) was added. The phases were separated, and the aqueous phase was extracted twice with 50-mL portions of Et₂O. The organic phases were collected and washed with 50 mL H₂O followed by 50 mL brine. After drying over 3 g anhydrous MgSO₄, the solvent was rotary evaporated, leaving 9.27 g of a pale yellow oil that slowly crystallized (91%). The crude product was recrystallized from hexanes to obtain the title compound as colorless needles. Mp 51–53 °C. δ_{H} (CDCl₃): 6.72 (d, $J=7.8$ Hz, 1H), 6.67 (d, $J=1.2$ Hz, 1H), 6.61 (dd, $J=7.7$ and 1.1 Hz, 1H), 5.90 (s, 2H), 4.49 (bs, NH), 3.82 (pent, $J=6.3$ Hz, 1H), 2.74 (dd, $J=13.5$ and 5.9 Hz, 1H), 2.57 (dd, $J=13.9$ and 7.2 Hz, 1H), 1.43 (s, 9H), 1.08 (d, $J=6.8$, 3H); δ_{C} (CDCl₃): 155.38, 147.65, 146.45, 132.20, 122.44, 109.89, 108.19, 100.87, 79.21, 47.76, 42.84, 28.52, 20.21. Elemental analysis calculated for C₁₅H₂₁NO₄: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.36; H, 7.53; N, 4.97.

Racemic *tert*-Butyl *N*-{3-(3,4-Methylenedioxyphenyl)-2-propyl}-*N*-methylcarbamate (16**)**

A 250-mL, round-bottomed flask equipped with magnetic stirbar was charged with 6.38 g **15** (23 mmol) and 50 mL anhydrous DMF. The mixture was cooled in an

ice bath, and 2.55 g KO^tBu (23 mmol, 1 equiv) was added in one portion. After the solid had dissolved (10 min), 2.84 mL iodomethane (6.47 g, 46 mmol, 2 equiv) were added in one portion. The cooling bath was replaced with a 55 °C bath, and the mixture was stirred for 1 h. A second addition of the same amounts of base and iodide were added, and after stirring for a total of 2 h at 55 °C, 100 mL H₂O were added. The mixture was extracted with three times with 50-mL portions of hexanes, and the organic phases were combined. After washing with 50 mL H₂O followed by 50 mL brine, the organic phases was dried over anhydrous MgSO₄. The solvent was rotary evaporated, leaving 6.48 g of a pale yellow oil. The oil was distilled under reduced pressure (0.1 torr) to give 6.1 g of the title compound as a colorless oil (91%). δ_{H} (DMSO; 349 K): 6.77–6.55 (m, 3H), 5.91 (s, 2H), 4.59–4.19 (m, 1H), 2.80–2.48 (m, 5H), 1.39 (s, 9H), 1.14 (d, $J=6.4$ Hz, 3H); δ_{C} (CDCl₃; 300 K): 155.73, 147.68, 146.09, 133.09, 122.06, 109.59, 108.27, 100.92, 79.27, 52.89, 51.72, 40.46, 28.56, 27.73, 18.31, 17.72. Elemental analysis calculated for C₁₆H₂₃NO₄: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.30; H, 7.92; N, 4.57.

Racemic *N*, α -Dimethyl-2-(3,4-methylenedioxyphenyl)ethylamine (3)

A 1.8-g portion of **16** (6.1 mmol) was dissolved in 50 mL THF and heated to 45 °C, and then 3.42 mL conc. HCl (41 mmol, 6.7 equiv.) was added dropwise over 5 min. The mixture was stirred at this temperature for 3 h, after which time TLC showed the reaction was complete. After cooling to rt, the mixture was diluted with 50 mL H₂O and extracted with 50 mL Et₂O. The organic layer was discarded, and the aqueous layer was basified by slow addition of solid K₂CO₃. The mixture was extracted twice with 50-mL portions of Et₂O. The organic phases were collected and washed with 25 mL brine. The organic layer was separated and dried over 3 g anhydrous MgSO₄. After filtration, the solvent was rotary evaporated, leaving a 1.11 g of a colorless oil (95%). The crude oil was further purified by distillation under reduced pressure (0.1 torr). δ_{H} (CDCl₃): 6.74 (d, $J=8.0$ Hz, 1H), 6.69 (d, $J=1.6$ Hz, 1H), 6.63 (dd, $J=7.9$ and 1.7 Hz, 1H), 5.92 (s, 2H), 2.73 (hexet, $J=6.5$ Hz, 1H), 2.66–2.49 (m, 2H), 2.39 (s, 3H), 1.05 (d, $J=6.2$ Hz, 3H); δ_{C} (CDCl₃): 147.76, 146.05, 133.39, 122.27, 109.63, 108.27, 100.92, 56.57, 43.32, 34.17, 19.80. Solids formed after storage of this compound in a stoppered flask overnight, as the amine absorbs atmospheric CO₂. Elemental analyses (C, H, N) were carried out, but results did not correspond to the free amine on this account.

Racemic *N*, α -Dimethyl-2-(3,4-methylenedioxyphenyl)ethylamine (3) Oxalate Salt

A 250-mL, round-bottomed flask equipped with magnetic stirbar was charged with 5.7 g oxalic acid dihydrate (46 mmol, 1.1 equiv) and 100 mL EtOH. After all the solids had dissolved, a solution of 8.07 g **3** (42 mmol) in 25 mL EtOH was added in one portion. After 30 min, a white crystalline solid had precipitated, was collected on a medium glass frit, and air-dried several hours (9.74 g, 76%). No further purification was necessary. Mp 105–107 °C. δ_{H} (DMSO): 8.83 (bs, 3H), 6.89–6.85 (m, 2H), 6.71 (dd, $J=8.0$ and 1.5 Hz, 1H), 6.00 (s, 2H), 3.31 (m, 1H), 3.06 (dd, $J=13.2$ and 4.3 Hz,

1H), 2.58 (s overlapping m, 4H), 1.09 (d, $J=6.5$ Hz, 3H); δ_C (DMSO): 164.93, 147.39, 146.02, 130.45, 122.38, 109.48, 108.27, 100.86, 55.27, 37.95, 29.67, 14.88. Elemental analysis calculated for $C_{11}H_{15}NO_2 \cdot C_2H_2O_4$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.09; H, 6.01; N, 4.93.

2-(3,4,5-Trimethoxyphenyl)ethyl Isocyanate (18)

A 250-mL, round-bottomed flask equipped with magnetic stirbar and 100 mL addition funnel was charged with 50 mL DCE and 5.21 g ethyl chloroformate (1 equiv) and cooled in an ice bath. In a separate flask, a solution of 11.5 g **17** (0.01 mol), 4.84 g TEA (1 equiv), and 50 mL DCE was made. The addition funnel was charged with the latter solution, which was run in over 20 min. After stirring another 20 min, 1H NMR showed the reaction was complete. A solution of 4.68 NaN_3 (1.5 equiv) in 50 mL H_2O was added to the addition funnel, which was run in over 20 min. After stirring another 15 min, TLC and 1H NMR showed the reaction was complete. In the following steps, the organic phase was kept at $<10^\circ C$ with an ice bath. The organic phase was separated and washed in sequence with 50 mL cold H_2O , 50 mL cold saturated aqueous $NaHCO_3$, and finally 50 mL cold brine. The organic phase was dried over 3 g anhydrous $MgSO_4$ and filtered into a 500-mL, round-bottomed flask containing a magnetic stirbar. A reflux condenser was attached, and the mixture was heated at $80^\circ C$ overnight. The next morning, 1H NMR showed the reaction was complete, and rotary evaporation of the mixture gave 9.76 g of a slightly yellow oil (86%). Reduced pressure distillation (0.1 torr) gave the title compound as a colorless oil. The product crystallized to a white solid at $-20^\circ C$ and did not melt when returned to room temperature. Mp $26-28^\circ C$. δ_H ($CDCl_3$): 6.44 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.51 (t, $J=6.6$ Hz, 2H), 2.84 (t, $J=6.6$ Hz, 2H); δ_C ($CDCl_3$): 153.43, 137.21, 133.53, 122.68, 105.98, 60.81, 56.15, 44.29, 38.08. Elemental analysis calculated for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.9. Found: C, 60.64; H, 6.23; N, 6.06.

2-(3,4,5-Trimethoxyphenyl)ethylamine (4) Hydrogen Sulfate

A 100-mL, round-bottomed flask equipped with magnetic stirbar was charged with 3.89 g **18** (16.4 mmol) and a solution of 2.73 mL conc. H_2SO_4 (49.2 mmol, 3 equiv) in 15 mL H_2O . The mixture was heated to $80^\circ C$ for 1 h, whereupon evolution of CO_2 was observed, and the mixture became a homogeneous solution. After cooling to $10^\circ C$, a portion of the product precipitated as a white crystalline solid and was filtered on a medium-porosity glass frit (1.1 g). The reaction mixture was rotary evaporated to give a second crop of product, which was washed with EtOH and filtered on a medium-porosity glass frit (2.46 g, total yield 70%). Recrystallization from EtOH gave the title compound as colorless needles. Mp $140-155^\circ C$. δ_H (DMSO): 7.82 (bs, OH), 6.6 (s, 2H), 6.57 (bs, NH_3), 3.78 (s, 6H), 3.63 (s, 3H), 3.06 (m, 2H), 2.83 (m, 2H); δ_H (D_2O): 6.71 (s, 2H), 3.88 (s, 6H), 3.79 (s, 3H), 3.29 (t, $J=7.3$ Hz, 2H), 2.97 (t, $J=7.3$ Hz); δ_C (DMSO): 153.01, 136.38, 133.03, 106.21, 60.01, 55.95, 40.25, 33.29. Elemental analysis calculated for $C_{11}H_{17}NO_3 \cdot H_2SO_4$: C, 42.71; H, 6.19; N, 4.53. Found: C, 42.78; H, 6.14; N, 4.56.

2-(3,4,5-Trimethoxyphenyl)ethylamine (4) Hemisulfate Hydrate

A 100-mL, round-bottomed flask equipped with magnetic stirbar was charged with 2.24 g **18** (9.5 mmol) and a solution of 460 mg conc. H₂SO₄ (4.75 mmol, 0.5 equiv) in 10 mL H₂O. The mixture was heated to 80 °C for 1 h, whereupon evolution of CO₂ was observed, and the mixture became a homogeneous solution. After cooling to rt, the product precipitated as colorless needles and was filtered on a medium-porosity glass frit (2.39 g, 87%). The solid was recrystallized from isopropanol to give the title compound as colorless needles. Mp 162–180 °C (lit.^[72] 172–183 °C). δ_H (DMSO): 6.55 (s, 2H), 3.67 (s, 6H), 2.76 (s, 3H), 3.03 (m, 2H), 2.93 (m, 2H); δ_H (D₂O): 6.71 (s, 2H), 3.89 (s, 6H), 3.79 (s, 3H), 3.29 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H); δ_C (DMSO): 152.78, 136.09, 134.02, 105.90, 59.78, 55.64, 40.52, 33.74. Elemental analysis calculated for C₁₁H₁₇NO₃ · 0.5 H₂SO₄ · 1.5 H₂O: C, 48.21; H, 7.12; N, 5.11. Found: C, 48.00; H, 7.36; N, 5.08.

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