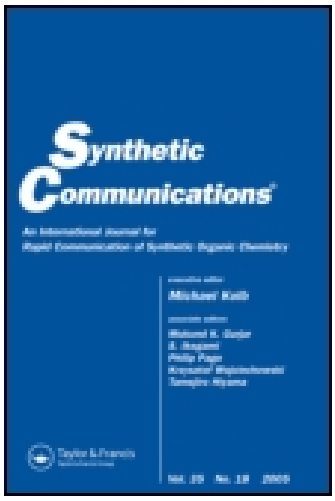

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Aug 2006.

To cite this article: Mark A. Youngman, Nicole M. Willard, Scott L. Dax & James J. McNally (2003) The Synthesis of Novel cis-α-Substituted-β-aminotetralins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:13, 2215-2227, DOI: 10.1081/SCC-120021500

To link to this article: http://dx.doi.org/10.1081/SCC-120021500

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 13, pp. 2215–2227, 2003

The Synthesis of Novel *cis*-α-Substituted-β-aminotetralins

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ABSTRACT

Teteralones were converted, in **1** to **3** steps, to α-substituted tetralones. Subsequent reductive amination with ammonium acetate/sodium cyanoborohydride gave the corresponding α-substituted-β-aminotetralins, on a multigram scale, with minimal chromatography for the entire transformation.

The β-aminotetralin ring system is an important pharmacophoric element in medicinal chemistry. In essence, β-aminotetralins embody a ring-constrained version of the ubiquitous phenethylamine moiety and thus it is not surprising that the β-aminotetralin motif is present in

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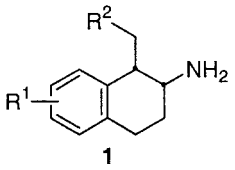
DOI: 10.1081/SCC-120021500 0039-7911 (Print); 1532-2432 (Online)

well-known modulators of biogenic amine receptors. Hydroxylated *N*,*N*-dialkylated β-aminotetralins are illustrative; 7-hydroxy-2-*N*,*N*-dipropylaminotetralin (7-OH-DPAT) is a selective D_3 agonist,[1] 8-hydroxy-2-*N*,*N*-dipropylaminotetralin is a selective 5-HT_{1A} agonist,[2] and other structurally-related congeners exhibit a spectrum of CNS activities.[3] More recently, certain aminotetralins have been reported to antagonize the effects of nicotine on acetylcholine receptors.[4] In conjunction with these areas of research, the preparation of β-aminotetralins substituted with simple alkyl substituents in the α-position have been described.

We recently reported on novel structurally-diverse aminotetralin-derived series of neuropeptide Y Y5 receptor antagonists.[5–7] During the course of this work and as described herein, we investigated and developed several efficient routes for the preparation of α-substituted-β-aminotetralins **1** (Fig. 1). Specifically we have been able to install a host of aryl, heteroaryl, and alkyl α-substituents onto the β-aminotetralin nucleus. Optimization of our chemical processes leads to moderate yields of novel α-substituted-β-aminotetralins that can be readily prepared on a multigram scale with minimal chromatographic purification.

Since we desired access to an array of structurally-diverse β-aminotetralins, we decided to explore several different synthetic strategies. The most versatile route is centered upon conversion of β-tetralone to corresponding pyrrolidinyl enamine and subsequent C-alkylation (Sch. 1). Several β-tetralones were acquired from commercial sources (R^1=H, 6-OMe, 7-OMe) while others needed to be synthesized using the methodology developed by Stjernlof et al.[8] Thus 6-methoxy-β-tetralone (**2**: R^1=–OCH_3) was treated with an excess of pyrrolidine in a variety of solvents (methanol, benzene, tetrahydrofuran), to afford enamine **3**, which was used without purification. This material was dissolved in acetonitrile and then treated with a benzylic, allylic, or alkyl halide to afford the desired C-alkylated iminium salt **4**. Only reactive alkylating agents



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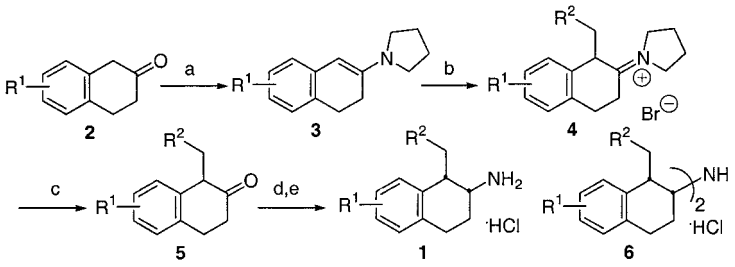
R^1 = H, alkoxy, halo
R^2 = aryl, substituted aryl, heteroaryl, alkyl, alkenyl

Figure 1.



(a) pyrrolidine/PhH (-H_2O); (b) R^2CH_2Br/CH_3CN; (c) HOAc, H_2O, CH_2Cl_2/MeOH; (d) Na(BH_3)CN, NH_4OAc / MeOH reflux; (e) HCl / Et_2O.

Scheme 1.

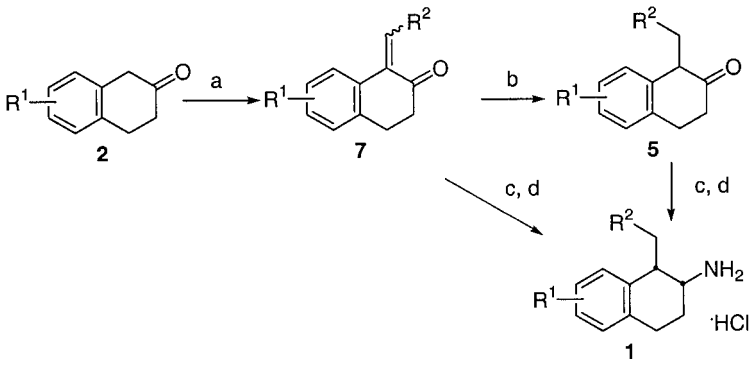
underwent efficient reaction; for example, phenethyl halides and simple alkyl halides formed intractable mixtures of product, starting material and by-products. Mild acidic hydrolysis liberated the α-substituted-β-tetralone **5** in high yields (Sch. 1), which in some cases were used as is, and in other cases were separated from baseline impurities by a quick flash chromatography.

A variety of reductive amination conditions were explored for the conversion of the β-teralone, **5**, to the corresponding β-tetralin, **1**. These conditions included a variety of primary and secondary amines and ammonium acetate as well as a selection of reducing agents including borohydride reagents (sodium, sodium cyano, and sodium triacetoxy) as well as catalytic hydrogenation conditions.

Most of these conditions gave unacceptable yields and mixtures of aminotetralin products, however, reductive amination using sodium cyanoborohydride and ammonium acetate gave the most encouraging results. Aminotetralins, **1**, were formed in modest yields, mixed with the product resulting from *bis*-alkylation of ammonia, **6** (Sch. 1). Optimization of this transformation proved to be successful. Treatment of the β-tetralone with a large excess of ammonium acetate (15-fold) and sodium cyanoborohydride (3-fold) in refluxing methanol, produced good yields of the desired β-aminotetralins. In most cases, treatment of a tetrahydrofuran solution of the α-substituted-β-aminotetralin with ethereal hydrochloric acid allowed for the isolation of the pure *cis*-isomer as a stable, crystalline hydrochloride salt. This procedure works well with a variety of 5-, 6-, 7-, or 8-substituted β-tetralones (Table 1). Both electron-donating and electron-withdrawing substituents on the aryl portion of the tetralin ring are well tolerated, as well as a variety of substituents in the α-position (Tables 1 and 2).

Table 1. Conversion of tetralones, **2**, to α-substituted-β-tetralones, **5**, and subsequent conversion to α-substituted-β-aminotetralins, **1**.

R^1	R^2	Yield (%) **2** to **5**	Yield (%) **5** to **1**
H	Ph	40	64
5-Cl	Ph	66	61
6-Cl	Ph	54	51
7-Cl	Ph	86	58
8-Cl	Ph	28	51
6-OMe	Ph	47	51
6-F	Ph	58	48
6-OMe	$CH{=}CH_2$	85	32



(a) R^2CHO, benzene, piperidine (cat.) benzene ($-H_2O$); (b) H_2, Pd/C, EtOAc; (c) $Na(BH_3)CN$, NH_4OAc / MeOH reflux; (d) HCl / Et_2O.

Scheme 2.

Our program required the synthesis of several heterocyclic derivatives, in which the alkylation of the enamine, **3**, was difficult to achieve due to poor yields, the unavailability and/or the instability of the requisite alkyl halide. Employing a slightly different synthetic route (Sch. 2) circumvented these problems. Condensation of the β-tetralone with the appropriate aldehyde gave, in good yields, a mixture of the corresponding *E* and *Z* unsaturated ketones, **7**. Hydrogenation of the mixture gave the α-substituted-β-tetralone in good yield, which could then be converted to the desired β-aminotetralin using the conditions previously described. However, we have found that subjecting the mixture of *E* and *Z* unsaturated ketones to the reductive amination

Table 2. Conversion of tetralones, **2**, to unsaturated α-substituted-β-tetralones, **7**, and subsequent reductive amination to **1**.

R^1	R^2	Yield (%) **2** to **7**	Yield (%) **7** to **1**	Yield[a] (%) **2** to **1**	cis/trans[b]
6-OMe	1-trityl-4-imidazolyl	66	79	—	81/19
6-OMe	3-thienyl	—	—	47	75/25
6-F	3-pyridyl	—	—	47	83/17
6-OMe	C_3H_5-*c*	92	52	—	all *cis*

[a]In these cases the intermediates, **7**, were not isolated, and the crude mixture was converted to the product, **1**.
[b]Ratio of *cis* vs. *trans* isomers in the isolated product.

conditions effected both reductions in one step, in essentially the same yield.

In this manner we synthesized compounds, which were inaccessible via the methods described in scheme 1, including the compounds listed in Table 2. Note that in the cases where a (heterocycle)methyl group occupies the α-position, conversion to the hydrochloride salts formed amorphous solids. While, in these cases, we were able to isolate mixtures of *cis* and *trans* products, we were unable to isolate the *cis*-product by crystallization.

CONCLUSION

Using the chemistry developed and described above, we were able to prepare gram quantities of novel α-substituted-β-tetralones from β-tetralones in two or three steps, which in most cases, involved no chromatographic purifications. These α-substituted-β-tetralones could be converted to the corresponding α-susbstituted-β-aminotetralins. The cis isomer was the major product, and in most cases could be isolated by a single crystallization of the hydrochloride salt. These intermediates can serve as phenethylamine biosteres and have been used to prepare medicinally important small-molecules such as neuropeptide Y Y5 antagonists.

EXPERIMENTAL

All compounds were identified by a variety of methods including nuclear magnetic resonance spectroscopy, mass spectrometry and in

some cases, infrared spectroscopy and elemental analysis. Nuclear magnetic resonance (300 MHz NMR) data is reported in parts per million downfield from tetramethylsilane. Mass spectra data is reported in mass/charge (m/z) units.

1-Benzyl-3,4-dihydro-1H-naphthalen-2-one (5, R^1=H, R^2=Ph). Under an atmosphere of argon, a solution of β-tetralone (6.33 mL, 47.8 mmol) and pyrrolidine (4.4 mL, 52.6 mmol) in methanol (120 mL) was stirred at room temperature for 1 h. A colorless crystalline solid developed, which darkens when exposed to air. The solvent was evaporated in vacuo, and the residue taken up in 1,2-dichloroethane (DCE) (~50 mL), and the solvent evaporated in vacuo (to remove excess pyrrolidine) to give 1-(3,4-dihydro-naphthalen-2-yl)-pyrrolidine, **3 (R^1=H)**, as a gray solid, 9.66 g (100%). ^{1}H NMR ($CDCl_3$): δ 1.86–1.93 (m, 4H), 2.46 (t, 2H), 2.81 (t, 2H), 3.23–3.27 (m, 4H), 5.12 (s, 1H), 6.78–6.85 (m, 2H), and 6.97–7.05 (m, 2H). MS: m/z 200 (MH^+). The purity was estimated to be 95% by HPLC analysis, and the crude product was used in the subsequent reaction. Enamine **3 (R^1=H)**, (9.5 g, 47.7 mmol) was dissolved in acetonitrile (100 mL), and treated with benzyl bromide (6.25 mL, 52.5 mmol). After stirring the solution for 1 h, the solvent was evaporated in vacuo, and the residue crystallized from diethyl ether, to give 1-(1-benzyl-3,4-dihydro-1H-naphthalen-2-ylidene)-pyrrolidinium bromide, **4 (R^1=H, R^2=Ph)**, as a pale gray hygroscopic solid. ^{1}H NMR (DMSO-d_6): δ 1.79–1.86 (m, 1H), 1.90–2.02 (m, H), 2.97–3.10 (m, 3H), 3.18–3.27 (m, 2H), 3.34–3.47 (m, 3H), 3.86–3.97 (m, 1H), 4.00–4.16 (m, 1H), 4.18–4.25 (m, 1H), 4.50 (t, 1H), 6.94 (d, 1H), 7.11–7.17 (m, 3H), and 7.22–7.43 (m, 5H). MS: m/z 200 (M^+). Purity of the product was estimated to be 97% by HPLC. The solid was dissolved in dichloromethane (70 mL), water (70 mL), methanol (150 mL), and acetic acid (10 mL). The resultant solution was stirred overnight at room temperature. An aqueous layer had developed, and was separated. The aqueous layer was washed with DCM, and the combined organic solutions were washed with saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvent was evaporated and the residue purified by flash chromatography, using ethyl acetate/hexanes (5/95% v/v to 10/90) as the eluant, to give the product as an oil, 4.5 g (40%). ^{1}H NMR ($CDCl_3$): δ 2.45–2.63 (m, 3H), 2.78–2.86 (m, 1H), 3.19–3.22 (m, 2H), 3.73 (t, 1H), 6.86–6.93 (m, 3H), and 7.11–7.23 (m, 6H).

***cis*-1-Benzyl-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1=H, R^2=Ph).** A solution of **5 (R^1=H, R^2=Ph)** (4.4 g, 18.6 mmol) and ammonium acetate (21.5 g, 280 mmol) in methanol was treated with sodium cyanoborohydride (5.84 g, 93 mmol) and heated to reflux for 8 h.

The solution was cooled and diluted with water (~200 mL). Sodium hydroxide (50%) was added until the solution became basic, and the product was extracted into DCM (200 mL), dried over sodium sulfate, and the solvent evaporated in vacuo. The residue was taken up in THF, and converted at room temperature to the hydrochloride salt by the addition of ethereal hydrochloride (1 N). The product crystallized from the solution to give the product as a colorless solid, 3.25 g (64%). ^{1}H NMR(DMSO-d_6): δ 2.02–2.16 (m, 2H), 2.38–2.46 (m, 1H), 2.87–3.07 (m, 2H), 3.17–3.21 (m, 1H), 3.31 (m, 1H), 3.55 (br m, 1H), 6.02 (d, 1H), 6.75 (t, 1H), 7.04–7.12 (m, 4H), 7.20–7.28 (m, 3H), and 8.61 (br s, 2H). MS: m/z 238 (MH^+). HRMS; $C_{17}H_{20}N$ Calcd. for 238.159575 (obs. 238.160666).

5-Chloro-β-tetralone, 2 (R^1=5-Cl), and 7-chloro-β-tetralone, 2 (R^1=7-Cl). Thionyl chloride (12.7 mL, 174 mmol) was added to a solution of 3-chlorophenyl acetic acid (9.9 g, 58 mmol) in DCE (150 mL), and the resultant solution was heated to reflux for 4 h. The solvent was evaporated in vacuo to give the corresponding acid chloride, which was used without purification in the subsequent step. 3-Chlorophenylacetyl chloride was dissolved in DCM (50 mL) and added via an addition funnel, over 20 min, to a suspension of aluminum chloride (17 g, 127 mmol) in DCM (200 mL) at −10 to 0°C. Ethylene gas was bubbled into the mixture, for 20 min, causing the temperature to rise to ~5°C, then drop back to −5°C. Ethylene gas was allowed to bubble slowly through the mixture for an additional hour. The mixture was treated with ice (200 g). The organic layer was separated, washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent was evaporated in vacuo, and the individual products were isolated by silica gel chromatography using 10% ethyl acetate in hexanes as the eluant to give 5-chloro-β-tetralone, 1.74 g (17%). ^{1}H NMR ($CDCl_3$): δ 2.57 (t, 2H), 3.24 (t, 2H), 3.59 (s, 2H), 7.04 (d, 1H), 7.16 (t, 1H), and 7.29 (d, 1H). 7-Chloro-β-tetralone, 4.3 g (41%), was isolated as well. ^{1}H NMR ($CDCl_3$): δ 2.57 (t, 2H), 3.04 (t, 2H), 3.57 (s, 2H), 7.12 (s, 1H), and 7.17 (s, 2H). 6-Chloro-β-tetralone, 8-chloro-β-tetralone, and 6-fluoro-β-tetralone were synthesized in the same manner from 4-chlorophenylacetic acid, 2-chlorophenylacetic acid, and 4-fluorophenylacetic acid, respectively.

***cis*-1-Benzyl-5-chloro-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1=5-Cl, R^2=Ph).** Prepared from **2 (R^1=5-Cl)** in the same manner as **1 (R^1=H)**. ^{1}H NMR (DMSO-d_6): δ 2.11 (m, 2H), 2.44 (t, 1H), 2.73–2.86 (m, 1H), 3.01–3.07 (m, 1H), 3.21 (d, 1H), 3.24 (m, 1H), 3.52–3.63 (m, 1H), 5.96 (d, 1H), 6.81 (t, 1H), 7.10 (d, 1H), 7.17–7.30

(m, 4H), and 8.70 (br s, 2H). MS: m/z 272 (MH^+). HRMS; $C_{17}H_{19}ClN$ Calcd. for 272.120602 (obs. 272.120501).

***cis*-1-Benzyl-6-chloro-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1=6-Cl, R^2=Ph).** Prepared from **2 (R^1=6-Cl)** in the same manner as **1 (R^1=H)**. ^{1}H NMR (DMSO-d_6): δ 2.02 (m, 2H), 2.41 (t, 1H), 2.83–3.10 (m, 2H), 3.18 (d of d, 1H), 3.30 (m, 1H), 3.52–3.56 (m, 1H), 5.98 (d, 1H), 6.52 (d of d, 1H), 7.09 (d, 1H), 7.21–7.29 (m, 3H), and 8.62 (br s, 3H). MS: m/z 272 (MH^+). HRMS; $C_{17}H_{19}ClN$ Calcd. for 272.120602 (obs. 272.121077).

***cis*-1-Benzyl-7-chloro-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1=7-Cl, R^2=Ph).** Prepared from **2 (R^1=7-Cl)** in the same manner as **1 (R^1=H)**. ^{1}H NMR (DMSO-d_6): δ 2.02–2.11 (m, 2H), 2.41 (t, 1H), 2.80–2.92 (m, 1H), 2.97–3.05 (m, 1H), 3.20 (d of d, 1H), 3.34 (m, 1H), 3.53–3.63 (m, 1H), 5.90 (s, 1H), 7.09 (d, 2H), 7.14 (s, 2 H), 7.23–7.40 (m, 3H), and 8.63 (br s, 1H). MS: m/z 272 (MH^+). HRMS; $C_{17}H_{19}ClN$ Calcd. for 272.120602 (obs. 272.121018).

***cis*-1-Benzyl-8-chloro-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1 = 8-Cl, R^2 = Ph).** Prepared from **2 (R^1 = 8-Cl)** in the same manner as **1 (R^1 = H)**. ^{1}H NMR (DMSO-d_6): δ 2.05–2.13 (m, 2H), 2.53 (m, 1H), 2.86–2.97 (m, 1H), 3.03–3.18 (m, 1H), 3.25 (d of d, 1H), 3.48–3.58 (m, 1H), 3.81–3.87 (m, 1H), 6.93–6.97 (m, 2H), 7.02–7.07 (m, 1H), 7.12–7.17 (m, 5H), and 8.66 (br s, 3H). MS: m/z 272 (MH^+). HRMS; $C_{17}H_{19}ClN$ Calcd. for 272.120602 (obs. 272.120898).

***cis*-1-Benzyl-6-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1 = 6-OMe, R^2 = Ph).** Prepared from **2 (R^1 = 6-OMe)** in the same manner as **1 (R^1 = H)**. ^{1}H NMR ($CDCl_3$): δ 2.05–2.30 (m, 2H), 2.50–2.60 (m, 1H), 2.83–3.03 (m, 3H), 3.30–3.40 (m, 2H), 3.71 (s, 3H), 6.00 (d, 1H), 6.35 (d of d, 1H), 6.60 (d, 1H), 7.02–7.16 (m, 5H), 8.53 (bs, 1H), and 8.96 (bs, 2H). MS: m/z (MH^+) 268. HRMS; $C_{18}H_{22}NO$ Calcd. for 268.170140 (obs. 268.171181).

***cis*-1-Benzyl-6-fluoro-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1 = 6-F, R^2 = Ph).** Prepared from **2 (R^1 = 6-F)** in the same manner as **1 (R^1 = H)**. ^{1}H NMR (DMSO-d_6): δ 1.96–2.13 (m, 2H), 2.40 (t, 1H), 2.82–3.12 (m, 2H), 3.17 (dd, 1H), 3.28–3.37 (m, 1H), 3.47–3.60 (br m, 1H), 5.98 (m, 1H), 6.62 (m, 1H), 6.98 (m, 1H), 7.08 (d, 2H), 7.18–7.30 (m, 3H), and 8.64 (br s, 3H). MS: m/z 256 (MH^+). HRMS; $C_{17}H_{19}FN$ Calcd. for 256.150153 (obs. 256.150147).

***cis*-1-Allyl-6-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride(1, R^1=6-OMe, R^2=CH=CH_2).** Prepared from **2 (R^1=6-OMe)** in the same manner as **1 (R^1=H)**, substituting allyl bromide for benzyl bromide. ^{1}H NMR (DMSO-d_6): δ 1.91–2.10 (m, 3H), 2.54 (m, 1H),

2.77–2.96 (m, 2H), 3.00–3.06 (m, 1H), 3.42–3.50 (m, 1H), 3.71 (s, 3H), 4.98 (d, 1H), 5.00 (s, 1H), 5.72–5.83 (m, 1H), 6.64 (s, 1H), 6.67 (d, 1H), 6.94 (d, 1H), and 8.4 (br s, 3H). MS: m/z 218 (MH^+). HRMS; $C_{14}H_{20}NO$ Calcd. for 218.154489 (obs. 218.154932).

***cis*-6-Methoxy-1-(1-trityl-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-ylamine (1, R^1=6-OMe, R^2=1-trityl-4-imidozolyl).** 6-Methoxy-β-tetralone (5.78 g, 32.8 mmol) was dissolved in 125 mL benzene with stirring. To this solution was added 1-tritylimidazole-4-carboxaldehyde (10.03 g, 29.6 mmol) and catalytic piperidine (0.081 mL, 0.82 mmol). This suspension was heated under Dean-Starke conditions under a nitrogen atmosphere for 22 h. The organics were removed in vacuo and the residue was purified by chromatography on silica gel eluted with hexanes to hexanes:ethyl acetate (1:1), to give the product **7 (R^1=6-OMe, R^2=1-trityl-4-imidazolyl)**, a 1:1 mixture of *Z* and *E* isomers, as a yellow foam.

All of the product from the previous reaction was dissolved in 300 mL ethyl acetate and hydrogenated with 10% palladium on charcoal (0.739 g) for 24 h at which time an additional amount of the catalyst (0.753 g) was added and the hydrogenation was continued for another 5 days. The material was then filtered through a pad of celite. The solvent was evaporated in vacuo and the residue was triturated in 100 mL methanol. The product was collected by filtration, washed with methanol, and dried under vacuum to give a light yellow powder 10.60 g (66%), **5 (R^1=6-OMe, R^2=1-trityl-4-imidazolyl)**.

A mixture of tetralone **5 (R^1=6-OMe, R^2=1-trityl-4-imidazolyl)** from the previous reaction (7.53 g, 15.1 mmol) was suspended as a slurry in 250 mL methanol with stirring. Ammonium acetate (17.68 g, 229.4 mmol) and sodium cyanoborohydride (4.77 g, 75.9 mmol) was added and the mixture was heated to reflux for 2 h. The solvent was evaporated in vacuo to yield a residue that was subsequently suspended in 500 mL water and made basic with 100 mL 1 N NaOH. This aqueous mixture was extracted three times with 250 mL methylene chloride. The combined organics were washed twice with 100 mL brine and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography using a gradient of DCM to DCM/methanol/NH_4OH (85/15/1) to give the product, **1 (R^1=6-OMe, R^2=1-trityl-4-imidazolyl)**, as an off white powder, 5.93 g, (79%). NMR ($CDCl_3$): 7.43–7.28 (m, 10H), 7.10 (m, 6H), 6.84 (d, 1H), 6.60 (m, 2H), 6.35 (s, 1H), 3.77 (s, 3H), 3.42–3.17 (m, 2H), 3.02 (m, 1H), 2.89–2.75 (m, 3H), 1.93 (br m, 1H), 1.74 (br m, 1H). MS: m/z 500.2 (MH^+). HPLC (220 nm): 81% cis, 19% trans. HRMS; $C_{34}H_{34}N_3O$ Calcd. for 500.270188 (obs. 500.272296).

***cis*-6-Methoxy-1-thiophen-3-ylmethyl-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (1, R^1=6-OMe, R^2=3-thienyl).** 6-Methoxy-β-tetralone (12.55 g, 71.2 mmol) was dissolved in 200 mL benzene with stirring. To this solution was added thiophene-3-carboxaldehyde (5.6 mL, 63.9 mmol) and catalytic piperidine (0.176 mL, 1.78 mmol). This solution was heated under Dean-Starke conditions under a nitrogen atmosphere for 20 h. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel using a gradient of hexanes to hexanes:ethyl acetate (9:1) to yield the product **5 (R^1=6-OMe, R^2=3-thienyl)** as a 4:1 mixture of *Z* and *E* isomers 17 g, (88%) as an orange oil.

All of the product from the previous reaction (17 g, 63 mmol) was dissolved in 500 mL methanol with stirring. Ammonium acetate (74.81 g, 970.6 mmol) and sodium cyanoborohydride (20.48 g, 325.9 mmol) was added to the methanol solution and the mixture was heated to reflux for 2.5 h. The solvent was evaporated in vacuo to yield a residue, that was suspended as a slurry in 500 mL water and then made basic with 50 mL 50% NaOH. This aqueous mixture was extracted three times with 250 mL methylene chloride. The combined organics were washed twice with 100 mL brine and dried over $MgSO_4$. The crude material was purified via silica gel chromatography using a gradient of DCM to DCM/MeOH/NH_4OH (90/10/1), to give the aminotetralin as a dark oil. The oil was dissolved in ethyl ether and treated with an excess of ethereal HCl. Evaporation of the solvent gave a solid which was triturated in 200 mL hot ethyl acetate, cooled, filtered, and dried in vacuo to yield the product HCl salt, **1 (R^1=6-OMe, R^2=3-thienyl)**, as a powder 10.43 g, (53%). NMR (DMSO-d_6): δ 75% cis, 25% trans, 8.43 (br s, 3H), 7.50 (m, 1H), 7.02 (m, 2H), 6.68 (m, 1H), 6.47 (dd, 1H), 6.18 (d, 1H), 3.67 (s, 3H), 3.58–3.12 (m, 3H), 3.11–2.55 (m, 3H), and 2.12–1.90 (m, 2H). MS: *m*/*z* 274.1 (MH^+). HRMS; $C_{16}H_{19}NOS$ Calcd. for 274.126561 (obs. 274.125985).

***cis*-6-Fluoro-1-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-naphthalen-2-ylamine (1, R^1=6-F, R^2=3-pyridyl).** 6-Fluoro-β-tetralone (4.14 g, 25.2 mmol) was dissolved in 100 mL benzene with stirring. Pyridine-3-carboxaldehyde (2.2 mL, 23.3 mmol) and catalytic piperidine (0.062 mL, 0.63 mmol) was added and, the solution was heated under Dean-Starke conditions under a nitrogen atmosphere for 21 h. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel using a gradient of hexanes to ethyl acetate/Et_3N(200/1 to yield the product, **5 (R^1=6-F, R^2=3-pyridyl)** as a 4:1 mixture of *Z*:*E* isomers 4.74 g (74%) as a yellow–orange waxy solid. *Z* isomer (faster running): NMR ($CDCl_3$): δ 8.62 (d, 1H), 8.51 (dd, 1H), 7.69 (d, 1H), 7.61 (s, 1H), 7.29–7.16 (m, 2H), 7.02 (dd, 1H), 6.76 (dt, 1H), 3.07 (t, 2H), and 2.67 (t, 2H). MS: *m*/*z* 254.5 (MH^+). *E* isomer (slower running):

NMR ($CDCl_3$): δ 8.74 (d, 1H), 8.55 (dd, 1H), 8.16 (d, 1H), 7.53 (dd, 1H), 7.32 (dd, 1H), 7.10–6.94 (m, 3H), 3.07 (t, 2H), and 2.70 (t, 2H). MS: m/z 254.5 (MH^+).

The product from the previous reaction, **5 (R^1=6-F, R^2=3-pyridyl)**, (4.61 g, 18.2 mmol) was dissolved in 150 mL methanol with stirring. Ammonium acetate (21.09 g, 273.6 mmol) and sodium cyanoborohydride (5.97 g, 95.0 mmol) was added to the methanol solution and the mixture was heated to reflux under nitrogen for 1.5 h. The reaction was evaporated in vacuo to yield a residue, that was suspended in 300 mL water and then made basic by the addition of 200 mL 1 N NaOH. This aqueous mixture was extracted three times with 200 mL methylene chloride. The combined organics were washed twice with 200 mL brine then extracted four times with 100 mL 1 N HCl. These acidic extracts were made basic with 500 mL 1 N NaOH solution and then extracted six times with 100 mL methylene chloride. The combined organics were dried over $MgSO_4$, to yield the crude aminotetralin. This crude material was subjected to silica gel chromatography eluted with a gradient of DCM to DCM/MeOH/NH_4OH (86/14/1.4) to yield the product as its free base as a green oil. The oil was dissolved in methanol and an excess of ethereal HCl was added. Evaporation of the solvents yielded a solid, which was dried in vacuo to yield the product bis HCl salt as a light yellow powder 3.83 g (64%). NMR (DMSO-d_6): 8.83 (d, 2H), 8.73 (br s, 3H), 8.32 (d, 1H), 7.97 (t, 1H), 7.05 (dd, 1H), 6.68 (dt, 1H), 6.11 (dd, 1H), 3.62 (m, 1H), 3.52–3.33 (m, 2H), 3.14–3.02 (m, 1H), 3.01–2.85 (m, 1H), 2.84–2.67 (m, 1H), and 2.18–1.96 (m, 2H). MS: m/z 257.2 (MH^+). HPLC (220 nm): 83% cis, 17% trans. HRMS; $C_{16}H_{18}FN_2$ Calcd. for 257.145402 (obs. 257.145652).

***cis*-1-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine (1, R^1=6-OMe, R^2=*c*-C_3H_5).** A solution of 6-methoxy tetralone (2.70 g, 15.3 mmol), cyclopropanecarboxaldehyde (1.03 mL, 13.8 mmol) and piperidine (38 μL, 0.38 mmol) in benzene (75 mL) was heated to reflux under Dean-Stark conditions for 17 h. Solvent was evaporated in vacuo, and the product was preabsorbed onto silica gel, and purified by flash chromatography using ethyl acetate in hexanes (0–20%) to give the products, **7 (R^1 = 6-OMe, R^2 = *c*-C_3H_5)** a mixture of *E* and *Z* isomers, 2.91 g (92%). MS: m/z 229 (MH^+).

A solution of the tetralone **7 (R^1 = 6-OMe, R^2 = *c*-C_3H_5)** (2.91 g, 12.7 mmol), ammonium acetate (14.7 g, 0.191 mol), and sodium cyanoborohydride (4.0 g, 63.7 mmol) in methanol (600 mL) was heated at reflux for 21 h. The reaction mixture was concentrated in vacuo, and DCM (400 mL) was added. Aqueous sodium hydroxide (1 N) was added with stirring, until the aqueous layer remained basic. The organic layer was separated, washed successively with aqueous sodium hydroxide (1 N),

and water, and dried over sodium sulfate. The solvent was evaporated in vacuo. The product was dissolved in diethyl ether and treated with an excess of ethereal hydrochloric acid (1 N). The aminotetralin **1 (R^1=6-OMe, R^2=*c*-C_3H_5)** crystallized on standing to give 1.75 g (52%) of a colorless solid, a single peak by analytical HPLC. NMR(DMSO-d_6): δ −0.06–0.02 (m, 1H), 0.17–0.28 (m, 1H), 0.42–0.53 (m, 2H), 0.65–0.78 (m, 1H), 1.27–1.55 (m, 2H), 1.88–2.00 (m, 2H), 2.75–3.10 (m, 3H), 3.48 (br m, 1H), 3.70 (s, 3H), 6.67 (s, 1H), 6.70 (d, 1H), 7.13 (d, 1H), and 8.20 (br s, 3H). MS: m/z 232.2 (MH^+). HRMS; $C_{15}H_{22}NO$ Calcd. for 232.171218 (obs. 232.171218).

***bis*-(1-benzyl-6-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-amine (6, R^1-OMe, R^2=Ph).** 6-Methoxy-α-benzyl-β-tetralone (3.64 g, 13.7 mmol) was dissolved in 700 mL methanol with stirring. Ammonium acetate (10.67 g, 138 mmol) and sodium cyanoborohydride (4.29 g, 68.3 mmol) was added to the methanol solution and the mixture was heated at reflux under nitrogen for 21 h. At this point the ratio of the desired aminotetralin to the bis-alkylated contaminant based on HPLC analysis of the crude reaction mixture at 220 nm was 79:21. The solvent was evaporated in vacuo to yield a residue which was suspended in 600 mL diethyl ether and washed twice with 225 mL 0.1 N NaOH. The combined aqueous washes were back-extracted three times with 100 mL diethyl ether. The combined organics were dried over $MgSO_4$ to yield the crude aminotetralin. This crude material was dissolved in ethyl ether and an excess of ethereal HCl was added. Evaporation of this mixture yielded a solid that was stirred with 25 mL hot ethyl acetate, cooled, and filtered. The filtrate was found to contain a large portion of the bis-alkylated contaminant. Treatment of the filtrate with additional ethereal HCl and MeOH followed by partial evaporation yielded a solid that was filtered off, dried, and found to be the bis-alkylated HCl salt (0.034 g). NMR (DMSO-d_6): δ 9.16 (br s, 2H), 7.24 (m, 6H), 7.12 (d, 4H), 6.70 (d, 2H), 6.33 (dd, 2H), 5.89 (d, 2H), 3.78 (br, 2H), 3.66 (s, 6H), 3.48 (br d, 2H), 3.30 (m, 2H), 3.17–2.88 (m, 4H), 2.58 (m, 2H), and 2.32 (br, 4H). MS: m/z 518.9 (MH^+).

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Received in the USA November 8, 2002

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