Identification of a New Scaffold for Opioid Receptor Antagonism Based on the 2-Amino-1,1-dimethyl-7-hydroxytetralin Pharmacophore

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The *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines are a unique class of opioid antagonists that have recently provided selective antagonists for μ-opioid receptors (MOR) and κ-opioid receptors (KOR). Molecular modeling indicated a strong structural similarity between the parent of this series and 2-amino-1,1-dimethyl-7-hydroxytetralin. In binding and in vitro functional assays, the aminotetralin derivatives displayed some overlap in SAR with that previously reported for the phenylpiperidine series, providing evidence for a common binding mode for the two series at opioid receptors. Introduction of a methoxy group in the 3-position increased potency at MOR and KOR receptors, suggesting that this aminotetralin skeleton can be utilized as a new scaffold for the design of selective opioid receptor antagonists.

Introduction

There has been considerable interest over many years in the development of selective ligands with which to study the function of opioid receptors.[1,2] Significant advances have been made with selective agonists and antagonists available for each of the three opioid receptors (μ, MOR; δ, DOR; κ, KOR).[1,3−5] Portoghese has developed both KOR- and DOR-selective antagonists by applying the message−address concept of Schwyzer to the opioid antagonist naltrexone (**1**, Chart 1), which itself is slightly MOR-selective.[6] The prototypic KOR-antagonist, developed in this way, is norBNI (**2**).[7] Portoghese has since shown that the large bimorphinan structure of **2** can be significantly simplified while retaining KOR selectivity and antagonist potency. This has ultimately led to the development of GNTI (**3**).[8]

The undoubted success of this approach means a large number of KOR and DOR antagonists have been synthesized on the basis of the oxymorphone framework. It is now desirable for the range of scaffolds to be increased because this could provide ligands with, for example, differing pharmacokinetic and pharmacodynamic properties or differing receptor subtype selectivity. In this regard, the provision of KOR antagonists that lack the extremely long duration of activity of **2** and **3** would be of particular value.

Carroll and co-workers have been successful in developing selective MOR and KOR antagonists based on an alternative to the oxymorphone framework, *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines, which produced a unique class of opioid antagonists, discovered by Zimmerman.[9−11] It was shown that modification of the N-substituent provided a means to control both the selectivity and potency of the ligands without introducing efficacy. By this approach, the selective MOR antagonist (**4a**)[10] and the highly selective KOR antagonist JDTic (**4b**)[11] were discovered. In these cases the phenylpiperidine unit acts as the message while the cinnamyl phenyl group and 7-hydroxyterahydroisoquinoline moieties provide the MOR and KOR address components, respectively.

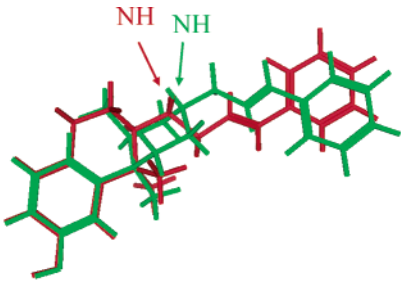

Figure 1. Overlay of **4a** (green) with **9k** (red).

We recognized the structural equivalence of the 14β-amino group in the morphinone series (**5**)[12] and the piperidine basic center in the phenylpiperidine series (**4**) in their spatial relationships to the respective phenolic binding centers. The 14β-alkylaminomorphinone series (**5a**), particularly those members with a side chain terminal aryl group, consistently provides potent opioid receptor antagonism with only low-level agonist activity. This SAR is characteristic also of the phenylpiperidine series (**4**). Though we investigated the 14β-cinnamylaminomorphinone (**5a**) and showed it to have potent noncompetitive MOR antagonist activity,[12] we were not immediately attracted to further investigation of the 14β-amino skeleton as a new message scaffold, particularly for introducing the address component for KOR selectivity because its synthesis from thebaine is multistep and very low yielding.[13] We considered the simpler but closely related aminobenzomorphan structure (**6**), but that too failed our criterion of ready accessibility.[14]

We therefore turned to an even simpler structure, 2-amino-1,1-dimethyl-7-hydroxytetralin (**7**). The 2-aminotetralin skeleton has previously been employed in the development of opioid analgesics.[15−17] A primary amino group was required for good in vivo analgesic activity with dezocine (**8**) the most well characterized example.[18] Because of their reduced analgesic potency, little atten-

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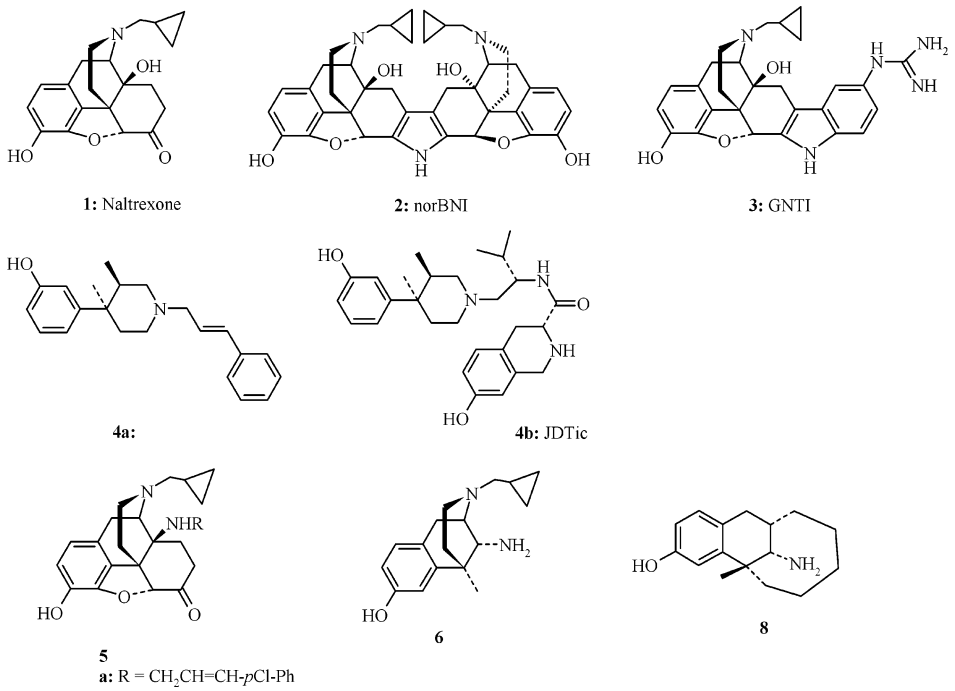
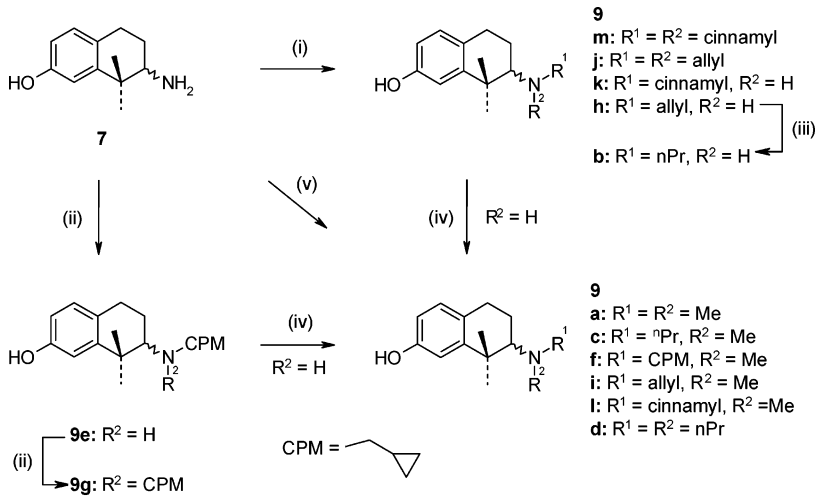
Chart 1



Scheme 1[a]



[a] Reagents and conditions: (i) RBr, $NaHCO_3$, DMF, 80 °C; (ii) cyclopropylcarbonyl chloride, then $LiAlH_4$; (iii) Pd, H_2; (iv) formaldehyde (1 equiv), $NaB(OAc)_3H$, CH_2Cl_2; (v) formaldehyde or propionaldehyde (2 equiv), $NaB(OAc)_3H$, CH_2Cl_2.

tion had previously been paid to secondary or tertiary amines.[16]

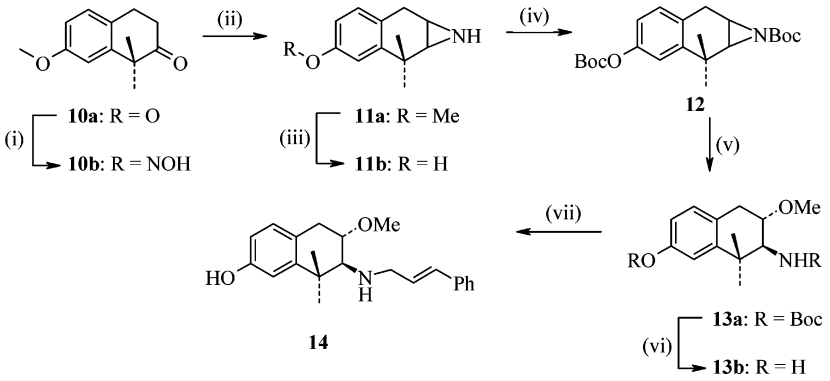
The validity of the choice of the aminotetralin (**7**) as a message scaffold for the design of selective antagonist ligands for MOR and KOR was confirmed by molecular modeling. Figure 1 shows the cinnamylphenylpiperidine derivative (**4a**) and the *R* enantiomer of the cinnamylaminotetralin derivative (**9k**) with the phenolic rings overlaid. In this orientation C_3, C_4, and the C_3 methyl group of the piperidine (**4a**) can overlay the reduced ring carbons of the tetralin while the latter's *gem*-dimethyl groups can overlay well with the C_4 methyl group and C_5 ring carbon of the piperidine. Importantly, this also allows the hydrogens of the protonated nitrogens to assume a common location, and the phenyl rings of the cinnamyl moieties are also in proximity to one another.

Our first targets were secondary and tertiary amine derivatives of (**7**) including those with cinnamyl groups. The secondary cinnamyl derivative (**9k**) had good MOR binding affinity and had moderate MOR and KOR antagonist potency. At the completion of this phase of the work, Roy et al. reported their work, based on the analgesic Dezocine, toward development of the aminotetralin pharmacophore for MOR agonist activity.[19] Their findings showed that a two-atom side chain α to the primary amino function gave optimal agonist potency. We resynthesized the published lead compound (**13b**) and a new cinnamyl derivative (**14**). The latter had high binding affinity particularly for MOR and high antagonist potency for MOR and KOR.

Chemistry

As depicted in Scheme 1, the synthesis of the substituted aminotetralins (**9a**−**m**) was accomplished by several methods. The tertiary amines (**9m**,**j**) and the secondary amines (**9k**,**h**) were prepared by direct alky-

Scheme 2[a]



[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, H_2O, MeOH; (ii) SMEAH, Bu(Me)NH, toluene; (iii) BBr_3, CH_2Cl_2; (iv) Boc_2O, DMAP, NEt_3, CH_2Cl_2; (v) MeOH, pyridinium *p*-toluenesulfonate; (vi) TFA, CH_2Cl_2; (vii) PhCH=CHCHO, CH_2Cl_2, then $NaBH_4$, MeOH.

Table 1. Binding Affinities to Opioid Receptors[a]

			$K_i \pm$ SEM (nM)		
compd	R^1	R^2	[^{3}H]DAMGO μ	[^{3}H]Cl-DPDPE δ	[^{3}H]U69,593 κ
9a	Me	Me	114 ± 31.7	4010 ± 399	333 ± 65.8
9b	^{n}Pr	H	491 ± 48.0	>10000	251 ± 55.0
9c	^{n}Pr	Me	85.0 ± 14.7	2090 ± 22.8	184 ± 29.4
9d	^{n}Pr	^{n}Pr	482 ± 61.1	2720 ± 780	552 ± 42.5
9e	CPM	H	312 ± 45.0	3830 ± 159	232 ± 4.80
9f	CPM	Me	104 ± 24.5	601 ± 84.0	146 ± 13.7
9g	CPM	CPM	422 ± 46.7	5770 ± 591	1830 ± 517
9h	allyl	H	202 ± 0.92	5830 ± 682	63.7 ± 6.60
9i	allyl	Me	1080 ± 142	2220 ± 484	263 ± 5.10
9j	allyl	allyl	105 ± 0.89	672 ± 127	55.8 ± 18.6
9k	cinnamyl	H	10.7 ± 2.73	472 ± 108	82.3 ± 18.0
9l	cinnamyl	Me	39.7 ± 11.7	591 ± 27.3	207 ± 29.6
9m	cinnamyl	cinnamyl	268 ± 53.4	>10000	1250 ± 143
13b			17.5 ± 5.90	2430 ± 422	149 ± 2.15
14			1.63 ± 0.58	22.4 ± 6.70	7.50 ± 0.84
naltrexone			0.2 ± 0.0	10.8 ± 3.0	0.4 ± 0.1
naltrindole			6.3 ± 2.3	0.2±0.05	10.1 ± 0.65
norBNI			21.0 ± 5.0	5.7 ± 0.9	0.2 ± 0.05

[a] Data provided through NIDA (OTDP).

lation of the known 7-amino-8,8-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**7**)[14] using the appropriate alkyl bromide. The most reliable method for synthesis of the monopropyl analogue (**9b**) proved to be hydrogenation of the allyl group of **9h**. The cyclopropylmethylamines (**9e**,**g**) were prepared by sequences of acylation with cyclopropylcarbonyl chloride and subsequent reduction with $LiAlH_4$. The methylamines (**9a**,**c**,**f**,**i**,**l**) and the dipropylamine (**9d**) were synthesized by reductive amination using sodium triacetoxyborohydride as the reducing agent.

The synthesis of **13b** has been reported previously (Scheme 2).[19] While the use of $LiAlH_4$ in the presence of DEA was reported to give good yields (60%) of aziridine (**11a**) from the oxime (**10b**), we were unable to carry out the reaction in a reproducible manner. An alternative method utilizing RedAl with *N*-methylbutylamine gave **11a** in lower, but reproducible, 40% yield (Scheme 2). Ring opening with MeOH under acid catalysis followed by removal of the Boc protecting group gave **13b**. The cinnamyl group was introduced by reaction with cinnamaldehyde and subsequent reduction with $NaBH_4$ (**14**).

Results and Discussion

The ligands were evaluated in competition binding assays in Chinese hamster ovary (CHO) cells transfected with cloned human opioid receptors (Table 1).[20] The displaced radioligands were [^{3}H]DAMGO (MOR), [^{3}H]Cl-DPDPE (DOR), and [^{3}H]U69,593 (KOR). The simplest tertiary amino derivative (**9a**) had modest affinity for MOR and KOR but very low affinity for DOR. Replacement of one of the methyl groups of **9a** by *n*-propyl, allyl, or cyclopropylmethyl (piperidine N-substituents that give antagonist activity in the epoxymorphinan, morphinan, and benzomorphan series) had variable effects on opioid receptor affinity. The *n*-propyl analogue (**9c**) had affinity similar to that of **9a** for all opioid receptors. The allyl analogue (**9i**) had KOR and DOR affinity similar to that of **9a** but an order of magnitude lower affinity for MOR. The cyclopropylmethyl (CPM) derivative (**9f**) had MOR affinity similar to that of **9a** but somewhat higher KOR affinity and substantially higher DOR affinity. The effect of replacing the *N*-methyl group in **9c** by a second propyl group (**9d**) was to reduce KOR and MOR affinity. Similar replacement of the *N*-methyl group in **9f** by a second CPM group (**9g**) had an equivalent but more pronounced effect having 4-fold lower MOR affinity and an order of magnitude lower KOR and DOR affinity. Surprisingly the bis-allylamine (**9j**) had substantially higher affinity than the monoallyl tertiary amine (**9i**) for all opioid receptor types but particularly for MOR.

Table 2. Antagonist Potencies in [^{35}S]GTPγS Assays Performed in Cloned Human Opioid Receptors[a]

			$K_e \pm$ SEM (nM)		
compd	R^1	R^2	vs DAMGO μ	vs DPDPE δ	vs U69,593 κ
9k	cinnamyl	H	67.7 ± 7.59	NT	42.7 ± 2.75
13b			agonist[b]	NT	49.3 ± 4.3
14			2.62 ± 0.40	26.3 ± 3.90	2.12 ± 0.11
naltrexone			0.59 ± 0.04	5.44 ± 0.75	1.86 ± 0.16
naltrindole			4.26 ± 0.33	0.11 ± 0.005	4.95 ± 0.32
norBNI			18.9 ± 1.80	4.42 ± 0.38	0.039 ± 0.004

[a] Data provided by NIDA (OTDP). [b] Agonist $IC_{50} = 234 \pm 55$ nM, 31.6% stimulation relative to the standard μ agonist DAMGO.

The propyl and CPM secondary amines (**9b**,**e**) had lower affinity than the equivalent *N*-methyl tertiary amines, but the secondary allylamine (**9h**) had substantially higher affinity for MOR than the tertiary amine (**9i**). The secondary allylamine (**9h**) and the bisallylamine (**9j**) had higher KOR affinity than any of the other new ligands. The tertiary cinnamylamine (**9l**) had higher MOR affinity than any of the other tertiary amines, together with modest selectivity for MOR over KOR and substantial selectivity for MOR over DOR. The bis-cinnamylamine (**9m**) had lower affinity than **9l**, but the secondary cinnamylamine (**9k**) had higher affinity than **9l**, and its MOR affinity ($K_i = 10.6$ nM) was the highest recorded for any opioid receptor by ligands of structure **9**. It had 8-fold selectivity for MOR over KOR and 45-fold selectivity for MOR over DOR. This is reminiscent of the findings of Zimmerman who showed that a phenyl ring separated by a three-atom chain from their phenylpiperidine scaffold was optimal for MOR affinity and antagonist activity.[9] In the present series, in no case was significant affinity seen for the DOR, with the highest affinity ($K_i = 471$ nM) displayed by **9k**.

For ligands having K_i values of 200 nM or better in the binding assays, opioid agonist and antagonist activity was determined using the [^{35}S]GTPγS assay in cloned human opioid receptors transfected into CHO cells.[20] Only one of the new ligands of type **9**, the secondary cinnamylamine (**9k**), had significant activity in this assay (Table 2) with no other ligand displaying a K_e, at any receptor, better than 500 nM. **9k** was a moderately potent antagonist of MOR and KOR with no selectivity. Nevertheless, it was of great significance that **9k** was an antagonist in the in vitro functional assays, thus further confirming the relationship of this series to the phenylpiperidines. As was to be expected there was little similarity in the effect of N-substitution between the aminotetralins (**9**) and the basic N-atom in the epoxymorphinan, morphinan, and benzomorphan series.[21] In these series arylalkyl substitution, particularly phenethyl, enhanced agonist (antinociceptive) activity. Though antinociceptive potency was substantially lower for cinnamyl, phenylpropyl, and phenylbutyl substitution, there was no evidence of morphine antagonist activity.

The *trans*-3-methoxy-substituted analogue **14** had much higher affinity for all opioid receptor types than the lead compound **9k** from the aminotetralin series (Table 1). MOR affinity for **14** was 6.5-fold higher, KOR affinity 11-fold higher, and DOR affinity 21-fold higher than for **9k**. Compared with the previously reported primary amine (**13b**),[19] the cinnamylamino derivative **14** also had much higher affinity, 11-fold for MOR, 20-fold for KOR, and 108-fold for DOR. In [^{35}S]GTPγS assays **14** showed potent MOR and KOR antagonist activity, and in each case potency was ~20-fold greater than for **9k**. Interestingly, though the primary amine was reported to have potent antinociceptive activity,[19] in the GTPγS assay it was a low potency, low efficacy MOR partial agonist and a KOR antagonist.

Conclusions

In conclusion, it is clear that the 2-amino-1,1-dimethyl-7-hydroxytetralin skeleton, particularly when incorporating an appropriate functional group (e.g., OMe) in the 3-position and trans to the C_2 amine, offers an alternative scaffold for the design of receptor selective opioid ligands. The ligands produced were comparable to their *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine analogues in opioid binding affinity and antagonist potency. We are currently investigating the use of this skeleton in the preparation of KOR selective antagonists.

Experimental Section

Column chromatography was performed under gravity over silica gel 60 (35−70 μm) purchased from Merck. Preparative TLC was performed on plates made with Kieselgel 60 $PF_{254+366}$, obtained from Merck. The thickness of the silica layer was approximately 1 mm. Analytical TLC was performed using aluminum-backed plates coated with Kieselgel 60 F_{254}, from Merck. The chromatograms were visualized using either UV light (UVGL-58, short wavelength), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High- and low-resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzyl alcohol. High- and low-resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. ^{1}H NMR and ^{13}C NMR spectra were recorded using JEOL EX 400 (operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C) or JEOL GX270 (operating at 270 MHz for ^{1}H and 68 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are measured in ppm relative to TMS. Coupling constants (J) are expressed in Hz. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Anhydrous THF, DMF, DCM, and MeOH were purchased from Aldrich. All other solvents used were GPR grade, purchased from Merck or Fisher Scientific. Chemicals were purchased from Aldrich, Fluka, Lancaster, and Acros chemical companies.

General Methods. Procedure A. To a solution of the appropriate amine (1.0 mmol) in CH_2Cl_2 (10 mL) was added formaldehyde (75 μL, 1 mmol, 37 wt %) followed by a spatula tip of $MgSO_4$ to remove excess water. This mixture was then treated with solid sodium triacetoxyborohydride (0.29 g, 1.4 mmol) and stirred at room temperature overnight under an atmosphere of nitrogen. The mixture was quenched by the addition of saturated aqueous Na_2CO_3 solution, and the product was extracted into CH_2Cl_2. The combined extracts were dried ($MgSO_4$) to give the crude free base that was purified by thin-layer chromatography or flash chromatography followed by crystallization from methanolic HCl/Et_2O.

Procedure B. A suspension of 0.19 g (1.0 mmol) of 2-amino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (**7**), sodium bicarbonate (0.21 g, 2.5 mmol), and the appropriate alkyl bromide (1.2 mmol) in 10 mL of DMF was heated at 80 °C for 16 h. Upon completion of the reaction, the volatiles were removed in vacuo and the residue was purified by flash chromatography or thin-layer chromatography followed by cystallization from methanolic HCl/Et_2O.

2-(Dimethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9a). 9a was prepared from **7** with procedure A, using double the amount of formaldehyde and sodium triacetoxyborohydride. Yield: 59%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.34. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.36 (s, 3H), 1.68 (m, 1H), 1.96 (m, 1H), 2.36 (s, 6H), 2.50 (dd, *J* 11.9, 2.9, 1H), 2.71−2.89 (m, 2H), 6.37 (br, 1H), 6.60 (dd, *J* 8.2, 2.7, 1H), 6.81 (d, *J* 2.3, 1H), 6.88 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 18.62, 26.67, 29.21, 30.56, 40.83, 44.55, 69.61, 113.43, 113.97, 127.16, 129.73, 148.27, 154.07. EIMS (CI) *m*/*z* (%): 219 (100). HRMS ($C_{14}H_{21}NO$): calcd 219.1623, found 219.1617. Anal. ($C_{14}H_{21}NO$·HCl) C, H, N.

1,1-Dimethyl-2-propylamino-1,2,3,4-tetrahydronaphthalen-7-ol (9b). A suspension of 0.25 g (1.08 mmol) of **9h** and 0.11 g of Pd/C (10%) in EtOH (50 mL) was stirred in a hydrogen atmosphere for 24 h. The catalyst was removed by filtration over Celite, and the crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 100:10:1) to give 0.18 g (77%) of **9b** as a solid. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* 7.4, 3H), 1.19 (s, 3H), 1.32 (s, 3H), 1.54 (sext, *J* 7.4, 2H), 1.74 (m, 1H), 2.01 (m, 1H), 2.50−2.87 (m, 5H), 4.34 (br, 2H), 6.55 (d, *J* 8.2, 2.3, 1H), 6.77 (d, *J* 2.3, 1H), 6.85 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.30 23.42, 24.19, 26.02, 28.12, 29.47, 39.00, 50.76, 63.76, 113.77, 113.92, 126.55, 129.83, 146.63, 154.73. EIMS *m*/*z* (%): 234 (7), 233 (37), 148 (100). HRMS ($C_{15}H_{23}NO$): calcd 233.1780, found 233.1772. Anal. ($C_{15}H_{23}NO$·HCl) C, H, N.

1,1-Dimethyl-2-(propylmethylamino)-1,2,3,4-tetrahydronaphthalen-7-ol (9c). 9c was prepared from **9b** with procedure A. Yield: 46%. Mp (hydrochloride): 192 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* 7.4, 3H), 1.18 (s, 3H), 1.35 (s, 3H), 1.53 (m, 1H), 1.69 (m, 1H), 1.89 (m, 1H), 2.29 (s, 3H), 2.35 (m, 1H), 2.49−2.56 (m, 2H), 2.68−2.84 (m, 3H), 4.72 (br, 1H), 6.57 (dd, *J* 8.2, 2.7, 1H), 6.79 (d, *J* 2.7, 1H), 6.86 (d. *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.25, 19.68, 21.60, 26.78, 28.97, 30.91, 40.16, 40.79, 60.00, 68.63, 113.26, 114.04, 127.47, 129.77, 148.72, 153.76. EIMS *m*/*z* (%): 247 (59), 148 (100), 42 (99). HRMS ($C_{16}H_{25}NO$): calcd 247.1936, found 247.1934. Anal. ($C_{16}H_{25}NO$·HCl·0.5H_2O·0.25CH_3OH) C, H, N.

2-(Dipropylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9d). 9d was prepared from **7** with procedure A, using double the amount of propionaldehyde and sodium triacetoxyborohydride. Yield: 0.18 g (45%). Mp (hydrochloride): 119 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* 7.4, 6H), 1.15 (s, 3H), 1.32 (s, 3H), 1.36−1.54 (m, 4H), 1.75 (m, 1H), 1.86 (m, 1H), 2.40 (t, *J* 7.4, 4H), 2.54 (dd, *J* 12.3, 2.5, 1H), 2.68−2.86 (m, 2H), 4.3 (br, 1H), 6.57 (dd, *J* 8.2, 2.7, 1H), 6.81 (d, *J* 2.7, 1H), 6.87 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.04, 19.81, 21.87, 26.59, 28.59, 31.01, 40.32, 54.70, 66.57, 112.79, 113.68, 127.31, 129.51, 148.82, 153.41. EIMS *m*/*z* (%): 275 (39), 148 (52), 43 (100). HRMS ($C_{18}H_{29}NO$): calcd 275.2249, found 275.2245. Anal. ($C_{18}H_{29}NO$·HCl·0.25H_2O) C, H, N.

2-(Cyclopropylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9e). A solution of 7-amino-8,8-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (**7**) (0.19 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was treated with cyclopropylcarbonyl chloride (2.2 mmol) followed by triethylamine (0.5 mL). The resulting mixture was stirred at room temperature overnight. After this time the reaction mixture was washed with water and brine and the solvent was evaporated. The residue was redissolved in anhydrous THF (10 mL), and $LiAlH_4$ (0.1 g) was added carefully. After 3 h, excess $LiAlH_4$ was destroyed with Glauber's salt and the reaction mixture was filtered. The crude product was purified by flash chromatography followed by cystallization from methanolic HCl/Et_2O. Yield: 69%. Mp (hydrochloride): >200 °C. Signs of decomposition: >175 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (m, 2H), 0.48 (m, 2H), 1.04 (m, 1H), 1.21 (s, 3H), 1.34 (s, 3H), 1.73 (m, 1H), 2.01 (m, 1H), 2.42 (dd, *J* 12.1, 7.4, 1H), 2.59 (dd, *J* 10.2, 2.7, 1H), 2.63−2.82 (m, 3H), 3.91 (br, 2H), 6.55 (dd, *J* 8.2, 2.7, 1H), 6.78 (d, *J* 2.7, 1H), 6.84 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 3.42, 3.89, 11.29, 23.85, 25.65, 27.72, 29.14, 38.68, 53.63, 63.20, 113.34, 113.52, 126.36, 129.52, 146.37, 154.23. EIMS *m*/*z* (%): 245 (62), 148 (100). HRMS ($C_{16}H_{23}NO$): calcd 245.1780, found 245.1774. Anal. ($C_{16}H_{23}NO$·HCl·0.25CH_3OH) C, H, N.

2-(Cyclopropylmethylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9f). 9f was prepared from **9e** with procedure A. Yield: 57%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (m, 2H), 0.51 (m, 2H), 0.95 (m, 1H), 1.24 (s, 3H), 1.39 (s, 3H), 1.71 (m, 1H), 1.95 m, 1H), 2.42 (dd, *J* 12.9, 6.6, 1H), 2.42 (s, 3H), 2.59 (dd, *J* 12.8, 5.9, 1H), 2.61−0.88 (m, 3H), 5.91 (br, 1H), 6.62 (dd, *J* 8.2, 2.7, 1H), 6.85 (d, *J* 2.7, 1H), 6.89 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 3.42, 4.81, 9.73, 19.47, 26.46, 28.69, 30.51, 39.80, 40.62, 62.94, 67.45, 113.15, 113.85, 126.90, 129.41, 148.20, 153.58. EIMS *m*/*z* (%): 260 (10), 259 (51), 204 (34), 148 (89), 55 (100). HRMS ($C_{17}H_{25}NO$): calcd 259.1936, found 259.1921. Anal. ($C_{17}H_{25}NO$·HCl·0.25$CHCl_3$) C, H, N.

2-(Bis-cyclopropylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9g). 9g was prepared from **9e**. The sequence for the formation of **9e** was repeated. Yield: 64%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.60. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (m, 4H), 0.43 (m, 2H), 0.57 (m, 2H), 0.94 (m, 2H), 1.23 (s, 3H), 1.42 (s, 3H), 1.76 m, 1H), 1.93 (m, 1H), 2.42 (m, 2H), 2.69−2.93 (m, 4H), 5.11 (br, 1H), 6.62 (dd, *J* 8.2, 2.7, 1H), 6.85 (d, *J* 2.7, 1H), 6.90 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 2.47, 5.74, 10.11, 20.23, 26.55, 28.71, 30.95, 40.57, 56.89, 65.63, 112.87, 113.80, 127.28, 129.50, 148.71, 153.33. EIMS *m*/*z* (%): 299 (17), 244 (10), 55 (100). HRMS ($C_{20}H_{29}NO$): calcd 299.2249, found 299.2237. Anal. ($C_{20}H_{29}NO$·HCl·0.25$CHCl_3$·0.25H_2O) C, H, N.

2-Diallylamino-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9j) and 2-(Allylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9h). 9j and **9h** were prepared from **7** and allyl bromide with procedure B.

Fraction 1 Containing 9j. Yield: 15%. Mp (hydrochloride): 99 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.60. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.33 (s, 3H), 1.73 (m, 1H), 1.84 (m, 1H), 2.69−2.84 (m, 3H), 2.99 (dd, *J* 14.6, 8.0, 2H), 3.26 (m, 2H), 5.08 (dd, *J* 10.2, 1.6, 2H), 5.16 (m, 1.2, 2H), 5.86 (m, 2H), 6.56 (dd, *J* 8.2, 2.3, 1H), 6.80 (d, *J* 2.7, 1H), 6.88 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.23, 26.27, 28.71, 30.63, 40.45, 55.12, 64.32, 112.85, 113.71, 116.20, 127.25, 129.51, 137.06, 148.41, 153.33. EIMS *m*/*z* (%): 271 (23), 122 (42), 41 (100). HRMS ($C_{18}H_{25}NO$): calcd 271.1936, found 271.1933. Anal. ($C_{18}H_{25}NO$·HCl·0.75H_2O) C, H, N.

Fraction 2 Containing 9h. Yield: 41%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.32 (s, 3H), 1.72 (m, 1H), 2.02 (m, 1H), 2.62 (dd, 10.5, 2.7, 1H), 2.67−2.82 (m, 2H), 3.24 (dd, *J* 13.7, 7.0, 1H), 3.51 (dd, *J* 13.7, 5.5, 1H), 4.34 (br, 2H), 5.11 (d, *J* 10.2, 1H), 5.20 (dd, *J* 17.2, 1.6, 1H), 5.92 (m, 1H), 6.55 (dd, *J* 8.2, 2.3, 1H), 6.76 (d, *J* 2.7, 1H), 6.85 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.87, 26.10, 27.98, 29.58, 39.01, 51.10, 62.67, 113.89, 113.97, 117.47, 126.73, 129.95, 136.45, 146.61, 154.53. EIMS *m*/*z* (%): 232 (3), 231 (17), 159 (27), 148 (94), 41 (100). HRMS ($C_{15}H_{21}NO$): calcd 231.1623, found 231.161. Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

2-(Allylmethylamino)-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9i). 9i was prepared from **9h** with procedure A. Yield: 71%. Mp (hydrochloride): >200 °C. Signs of decomposition: >150 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.36 (s, 3H), 1.73 (m, 1H), 1.90 (m, 1H), 2.33 (s, 3H), 2.62 (dd, *J* 12.1, 2.7, 1H), 2.72−2.88 (m, 2H), 3.02 (dd, *J* 14.1, 7.0, 1H), 3.29 (dd, *J* 14.1, 5.5, 1H), 5.10 (dd, *J* 10.9, 0.8, 1H), 5.19 (dd, *J* 17.0, 1.8, 1H), 5.35 (br, 1H), 5.85 (m, 1H), 6.59 (dd, *J* 8.2, 2.7, 1H), 6.82 (d, *J* 2.3, 1H), 6.89 (d, *J* 8.2, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.37, 26.37, 28.67, 30.43, 40.29, 40.61, 60.18, 67.30, 113.01, 113.75, 116.32, 127.15, 129.47, 136.84, 148.23, 153.37.

EIMS *m*/*z* (%): 245 (35), 41 (100). HRMS ($C_{16}H_{23}NO$): calcd 245.1780, found 245.1775. Anal. ($C_{16}H_{23}NO \cdot HCl \cdot H_2O$) C, H, N.

2-{Bis-[(*E*)-3-phenylprop-2-enyl]amino}-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (9m) and 1,1-Dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydronaphthalen-7-ol (9k). 9m and **9k** were prepared from **7** and cinnamyl bromide with procedure B.

Fraction 1 Containing 9m. Yield: 7%. Mp (hydrochloride): 148 °C (dec). R_f (EtOAc): 0.89. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.39 (s, 3H), 1.79 (m, 1H), 1.92 (m, 1H), 2.71−2.86 (m, 3H), 3.23 (m, 2H), 3.49 (m, 2H), 4.08 (br, 1H), 6.29 (ddd, *J* 16.0, 8.2, 4.7, 2H), 6.53 (d, *J* 14.8, 2H), 6.54 (dd, *J* 8.2, 2.3, 1H), 6.79 (d, *J* 2.7, 1H), 6.86 (d, *J* 8.2, 1H), 7.20 (m, 2H), 7.29 (m, 4H), 7.37 (d, *J* 7.8, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.45, 26.47, 28.86, 30.68, 40.57, 54.67, 64.68, 112.89, 113.67, 126.12, 127.09, 127.15, 128.43, 128.96, 129.53, 131.40, 137.22, 148.21, 153.39. EIMS *m*/*z* (%): 423 (4), 307 (66), 35 (100). HRMS ($C_{30}H_{33}NO$): calcd 423.2562, found 423.2573. Anal. ($C_{30}H_{33}NO \cdot HCl$) C, H, N.

Fraction 2 Containing 9k. Yield: 60%. Mp (hydrochloride): >200 °C. Signs of decomposition: >175 °C. R_f (EtOAc): 0.70. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.34 (s, 3H), 1.74 (m, 1H), 2.08 (m, 1H), 2.61−2.82 (m, 3H), 3.38 (ddd, *J* 13.7, 7.0, 0.8, 1H), 3.42 (br, 1H), 3.62 (ddd, *J* 13.7, 5.9, 1.6, 1H), 6.32 (m, 1H), 6.53−6.59 (m, 2H), 6.78 (d, *J* 2.7, 1H), 6.88 (d, *J* 8.5, 1H), 7.19−7.37 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.10, 26.16, 28.07, 29.68, 39.12, 50.73, 62.79, 113.98, 114.10, 126.61, 126.89, 127.75, 128.42, 128.82, 130.03, 132.29, 137.19, 146.78, 154.53. EIMS *m*/*z* (%): 307 (7), 173 (19), 148 (17), 117 (29), 82 (100). HRMS ($C_{21}H_{25}NO$): calcd 307.1936, found 307.1927. Anal. ($C_{21}H_{25}NO \cdot HCl$) C, H, N.

1,1-Dimethyl-2-{methyl-[(*E*)-3-phenylprop-2-enyl]amino}-1,2,3,4-tetrahydro-naphthalen-7-ol (9l). 9l was prepared from **9k** with procedure A. Yield 45%. Mp (hydrochloride): >200 °C. R_f (CH_2Cl_2/MeOH/NH_4OH, 100:10:1): 0.85. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.40 (s, 3H), 1.76 (m, 1H), 1.93 (m, 1H), 2.38 (s, 3H), 2.63−2.89 (m, 3H), 3.19 dd, 4.1, 7.4, 1H), 3.44 (dd, *J* 14.1, 5.1, 1H), 6.32 (ddd, *J* 15.6, 7.0, 5.5, 1H), 6.52 (d, *J* 15.6, 1H), 6.59 (dd, *J* 8.2, 2.7, 1H), 6.83 (d, *J* 2.7, 1H), 6.89 (d, *J* 8.2, 1H), 7.24 (m, 1H), 7.32 (t, *J* 7.6, 2H), 7.39 (d, *J* 8.2, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.80, 26.78, 29.03, 30.79, 40.80, 41.02, 59.82, 67.70, 113.17, 113.92, 126.44, 127.42, 127.49, 28.73, 129.15, 129.80, 131.58, 137.50, 148.53, 153.73. EIMS *m*/*z* (%): 321 (1), 188 (45), 173 (69), 162 (100). HRMS ($C_{22}H_{28}ClNO$): calcd 321.2093, found 321.2090. Anal. ($C_{22}H_{28}ClNO \cdot 0.5H_2O$) C, H, N.

7-Methoxy-1,1-dimethyl-3,4-dihydronaphthalen-2-one Oxime (10b). To a vigorously stirred solution of hydroxylamine hydrochloride (3.79 g, 54.5 mmol) and sodium acetate (4.47 g, 54.5 mmol) in H_2O (30 mL) was added a solution of **10a** (3.71 g, 18.2 mmol) in MeOH (30 mL). Stirring was continued for 10 min at 60 °C and then for a further 15 h at room temperature. After this time the solid oxime was collected by suction filtration and washed with ice-cold MeOH (2 × 5 mL), leaving the title product as a white solid (2.13 g, 54%). R_f (50% EtOAc/50% hexane): 0.59. Mp 140−142 °C. IR, ν_{max} (KBr): 1628 (C═N). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.50 (s, 6H), 2.79−2.92 (m, 4H), 3.81 (s, 3H), 6.71 (dd, *J* 8.4, 2.6, 1H), 6.94 (d, *J* 2.6, 1H), 7.06 (d, *J* 8.4, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.23, 27.05, 27.99, 41.20, 55.41, 111.13, 111.51, 128.62, 129.22, 145.07, 158.61, 165.10. EIMS *m*/*z* (%): 219 (65).

7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphtho[2,3]-azirene (11a). To a stirred solution of **10b** (1.50 g, 6.85 mmol) and *N*-methylbutylamine (0.1 mL) in toluene at 0 °C was added sodium bis(2-methoxyethoxy)aluminum hydride (70% solution in toluene, 10.7 mL, 34.2 mmol) dropwise over 10 min. The mixture was heated to reflux for 15 h and then allowed to cool to room temperature. The reaction was quenched by the dropwise addition of 2 M HCl (50 mL), and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 70 mL) and then basified to pH 10 with 10 M NH_4OH. The free base was extracted into CH_2Cl_2 (3 × 70 mL), and the combined organic layers were washed with H_2O (2 × 150 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave a brown oil. Column chromatography (5% MeOH/94% DCM/1% NH_4OH) afforded the title product as a yellow oil (0.48 g, 35%). R_f (10% MeOH/89% DCM:/1% NH_4-OH): 0.51. IR, ν_{max} (film): 3300 (N−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.51 (s, 3H), 2.12 (d, *J* 6.2, 1H), 2.47 (d, *J* 5.7, 1H), 3.14 (s, 2H), 3.78 (s, 3H), 6.69 (dd, *J* 8.2, 2.5, 1H), 6.85 (d, *J* 2.5, 1H), 6.96 (d, *J* 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 26.90, 29.36, 29.49, 29.54, 35.94, 41.31, 55.09, 111.38, 111.81, 122.58, 130.43, 142.83, 158.64. EIMS *m*/*z* (%): 203 (60).

1,1-Dimethyl-1,2,3,4-tetrahydronaphtho[2,3]aziren-7-ol (11b). A solution of **11a** (0.47 g, 2.31 mmol) in DCM (10 mL) was treated with boron tribromide (1 M solution in DCM, 4.6 mL, 4.60 mmol) at −78 °C. After 15 h the reaction was quenched by dropwise addition of MeOH (5 mL). The solvent was evaporated, and the residue was redissolved in MeOH (10 mL). After the mixture was stirred for 15 min, the solvent was again evaporated and the residue made basic (pH 10) with 10 M NH_4OH. H_2O (10 mL) was added followed by extraction with $CHCl_3$/EtOH (3:1, 3 × 15 mL). The combined organics were washed (H_2O), dried ($MgSO_4$), and evaporated. Column chromatography (4% MeOH/95% DCM/1% NH_4OH) afforded the title product as a brown foam (0.32 g, 73%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.39. IR, ν_{max} (film): 3284 (O−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.45 (s, 3H), 2.16 (d, *J* 6.2, 1H), 2.51 (d, *J* 6.0, 1H), 3.12 (d, *J* 7.9, 2H), 5.25 (s, 1H), 6.55 (dd, *J* 8.2, 2.5, 1H), 6.71 (d, *J* 2.5, 1H), 6.82 (d, *J* 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.18, 28.87, 29.59, 30.63, 35.84, 42.09, 113.14, 114.68, 119.93, 130.90, 141.82, 156.92. EIMS *m*/*z* (%): 189 (20).

***tert*-Butyl 7-[(*tert*-Butoxycarbonyl)oxy]-1,1-dimethyl-1,2,3,4-tetrahydronaphtho[2,3]azirene-1′-carboxylate (12).** To a stirred solution of **11b** (0.38 g, 2.01 mmol), 4,4-(dimethylamino)pyridine (0.07 g, 0.57 mmol), and triethylamine (0.56 mL, 4.02 mmol) in DCM (8 mL) was added di-*tert*-butyl dicarbonate (0.88 g, 4.02 mmol). The mixture was allowed to stir at room temperature for 5 h, after which the solvent was evaporated in vacuo. The residue was partitioned between EtOAc (30 mL) and 1 M HCl (30 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Purification by column chromatography (20% EtOAc/80% hexane) afforded the title product as a colorless oil (0.51 g, 65%). R_f (50% EtOAc/50% hexane) 0.70. IR, ν_{max} (film): 1757, 1716 (2 × C═O). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.38 (s, 9H), 1.44 (s, 3H), 1.52 (s, 9H), 2.52 (d, *J* 6.7, 1H), 2.94 (m, 1H), 3.02 (m, 1H), 3.27 (d, *J* 15.6, 1H), 6.92 (dd, *J* 8.2, 2.5, 1H), 6.98 (d, *J* 8.2, 1H), 7.05 (d, *J* 2.5, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.96, 22.84, 24.06, 24.22, 25.25, 25.58, 27.92, 31.88, 33.12, 43.81, 77.00, 79.50, 114.70, 115.54, 124.57, 126.48, 139.61, 146.42. FAB MS *m*/*z* (%): 390 (40).

2-[(*tert*-Butoxycarbonyl)amino]-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-yl *tert*-Butylcarbonate (13a). To a stirred solution of **12** (0.52 g, 1.34 mmol) in MeOH (10 mL) was added pyridinium *p*-toluenesulfonate (0.17 g, 0.68 mmol). The mixture was stirred at room temperature for 15 h under N_2, after which H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with H_2O (70 mL) and brine (50 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (20% EtOAc/80% hexane) afforded the title product as a yellow oil (0.45 g, 80%). R_f (50% EtOAc/50% hexane) 0.59. IR, ν_{max} (film): 1757, 1704 (C═O). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.32 (s, 3H), 1.41 (s, 9H), 1.50 (s, 9H), 2.78 (dd, *J* 16.3, 8.9, 1H), 3.20 (m, 1H), 3.38 (s, 3H), 3.79 (m, 1H), 4.46 (d, *J* 10.2, 1H), 6.92 (d, *J* 2.2, 1H), 6.99 (s, 1H), 7.04 (d, *J* 2.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.19, 22.01, 28.70, 29.42, 35.39, 41.00, 57.44, 59.86, 61.35, 77.00, 80.21, 84.32, 120.21, 120.38, 130.92, 146.39, 150.76, 152.95, 157.64. FAB MS *m*/*z* (%): 422 (35), 322 (20).

2-Amino-3-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (13b). To a stirred solution of **13a** (0.42 g, 1.00 mmol) in DCM (5 mL) was added trifluoroacetic acid (0.7 mL, 9.96 mmol) dropwise. The mixture was allowed to stir for 15 h before removal of the solvent in vacuo in the presence of toluene (0.5 mL) to form an azeotrope with TFA. Purification of the residue by column chromatography (8% MeOH/91% DCM/1% NH_4OH) afforded the title product as a colorless oil (0.13 g, 59%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.15. IR, ν_{max} (film): 3392, 3350 (N−H), 3294 (O−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.38 (s, 3H), 2.56 (dd, *J* 15.4, 9.9, 1H), 2.84 (d, *J* 9.9, 1H), 3.22 (dd, *J* 15.4, 5.5, 1H), 3.37 (m, 1H), 3.46 (s, 3H), 6.61 (dd, *J* 8.2, 2.5, 1H), 6.78 (d, *J* 2.5, 1H), 6.88 (d, *J* 8.2, 1H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.22, 27.49, 33.56, 40.00, 56.13, 60.25, 77.00, 112.79, 113.58, 122.82, 129.61, 145.16, 154.56. FAB MS *m*/*z* (%): 222 (100). HRMS ($C_{13}H_{20}NO_2$) calcd 222.1494, found 222.1506. Anal. ($C_{13}H_{19}NO_2 \cdot HCl \cdot 1.5H_2O$) C, H, N.

3-Methoxy-1,1-dimethyl-2-{[(*E*)-3-phenylprop-2-enyl]-amino}-1,2,3,4-tetrahydronaphthalen-7-ol (14). To a stirred solution of **13b** (69 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (3 mL) was added *trans*-cinnamaldehyde (0.05 mL, 0.37 mmol). The reaction mixture was stirred for 15 h at room temperature after which time the solvent was removed in vacuo. The residue was redissolved in anhydrous MeOH (8 mL), and the solution was cooled to 0 °C. Sodium borohydride (50 mg, 1.23 mmol) was added portionwise over 1 h, and the resulting mixture was stirred for a further 15 h at room temperature. The reaction was quenched by the dropwise addition of 1 M HCl (5 mL), and the solution was adjusted to pH 7 with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. Column chromatography (3% MeOH/96% DCM/1% NH_4OH) afforded the title product as a colorless oil (86 mg, 82%). R_f (10% MeOH/89% DCM/1% NH_4OH): 0.26. IR, ν_{max} (film): 3327 (O−H). ^{1}H NMR (270 MHz, $CDCl_3$): δ1.18 (s, 3H), 1.38 (s, 3H), 2.57−2.71 (m, 2H), 3.25 (m, 1H), 3.48 (s, 3H), 3.50−3.54 (m, 1H), 3.73 (dd, *J* 13.6, 6.2, 2H), 6.33 (m, 1H), 6.54 (m, 1H), 6.61 (dd, *J* 8.2, 2.5, 1H), 6.78 (d, *J* 2.5, 1H), 6.90 (d, *J* 8.2, 1H), 7.26 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$): δ12.73, 19.72, 24.82, 26.61, 33.28, 39.54, 52.43, 55.17, 65.43, 77.00, 111.70, 112.17, 122.78, 124.67, 125.64, 126.89, 127.61, 128.39, 129.53, 135.88, 145.02, 152.98. FAB MS *m*/*z* (%): 338 (80). HRMS ($C_{22}H_{28}NO_2$) calcd 338.2120, found 338.2119.

Molecular Modeling. Structures **4a** and **9k** were drawn using the Builder option in MOE (version 2004.03; Chemical Computing Group Inc.) and minimized using the MMFF94x force field. The Flexible Alignment function was used for the overlay, with the Restraints command ensuring that the phenolic rings remained aligned.

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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