43285), the Chicago Community Trust (Searle Scholars Program), the American Cancer Society Institutional Research Grant (IN-13-Y-15), and the University of Minnesota (Office of Alcohol and Other Drug Abuse Programming).

Registry No. 1, 124513-37-7; 2, 26555-40-8; 4, 2812-72-8; 5, 79598-17-7; 6, 79598-16-6; 7, 89264-59-5; 8, 124535-50-8; 9, 5813-75-2; 10, 1468-37-7; CH_3Cl, 74-87-3; CH_3SH, 74-93-1; MeOC(=S)SH, 2667-20-1; MeOC(=S)OMe, 1115-13-5; MeOC(=S)N(Me)Ph, 87463-11-4; PhNHMe, 100-61-8; $MeOCCl_2SCl$, 87463-08-9; PhN(Me)Ac, 579-10-2; MeOCOOMe, 616-38-6; $MeOCOS_2CO_2Me$, 26555-41-9; CH_3SCl, 5813-48-9; MeOC(=S)SMe, 19708-81-7.

Decyanation of Tertiary Nitriles by Alkyllithium Reagents Observed during the Synthesis of Imidazoles Pendant to a Quaternary Carbon Center

George B. Gregory, Alexander L. Johnson,* and William C. Ripka

E. I. duPont deNemours & Co., Inc., Medical Products Department, Experimental Station, E353/304, Wilmington, Delaware 19880-0353

Received June 16, 1989

We have devised a five-step synthesis of the new chemical entities **7a–d** from 5-methoxytetralone, **1**, via unsaturated nitrile **3**, the reductive alkylation products **4a–d**, and ketones **5a–d** and **6a–d**. Structures **7a–d** are distinguished by the presence of a 4-imidazolyl moiety pendant to a quaternary center of the 1,2,3,4-tetrahydronaphthalene nucleus. The tertiary nitriles **4a–d** can produce either the desired ketones **5a–d**, **10a,b**, or **11** in reactions in benzene or diethyl ether, or the decyanation products **12a,b,d** and **13a**, in reactions in THF. Apparently fragmentation in 4-centered transition state **9b** to the decyanation products is favored as the Lewis base strength of the solvent increases. Synthetically, it is preferable to use CH_3MgBr in benzene in the conversion of **4a–d** to **5a–d**.

Introduction

In the design of nonpeptide antagonists of the angiotensin II receptor,[1,2] we concluded from computer modeling studies that O-alkylation products derived from structures **7a–d** would be interesting molecules for biological evaluation. Naphthalenoid systems bearing a pendant carbon-linked imidazole substituent are not readily accessible by substitution reactions. Therefore, we selected 5-methoxy-1-tetralone (**1**) as a readily available starting material and are pleased to report that we have devised a five-step synthesis to construct compounds **7a–d**.

Synthesis

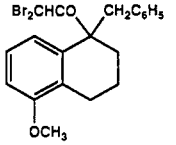
Treatment of **1** with TMSCN and ZnI_2 in benzene solution[3,4] at 25 °C for 3 h gave a quantitative yield of the O-TMS cyanohydrin (**2**) (Scheme I). Conversion of **2** to α,β-unsaturated nitrile **3** can be done stepwise by deprotection to the cyanohydrin with dilute acid[3] followed by dehydration with $POCl_3$–pyridine.[5] However, we found Oda's modification[4] to be most convenient in this synthesis: upon completion of formation of **2** (TLC), it is converted in situ into key intermediate **3** by the addition of $POCl_3$ and pyridine to the reaction vessel followed by heating the mixture at reflux for 5 h.

Nitrile **3** is the key structure in our synthesis because the cyano group serves as the stub from which the imidazole ring is constructed, and provides direction for the α-introduction of the aralkyl group by an extension of the enoate reductive alkylation reaction.[6] Concomitant treatment of nitrile **3** with L-Selectride (Aldrich) and the appropriate aralkyl bromide at −78 °C in THF, followed by warming to room temperature, gave the respective reductive alkylation products **4a–d**.

The imidazole ring attached to the 1-position of the 1,2,3,4-tetrahydrophthalene nucleus was now elaborated from the nitrile group in structures **4a–d** through the methyl ketones **5a–d** and bromomethyl ketones **6a–d** to the desired products **7a–d**.

The respective methyl ketones **5a–d** were prepared by Grignard reaction of **4a–d** with CH_3MgBr at reflux in benzene, followed by an acidic workup. The yields of these ketones were high, as judged by TLC, IR, and ^1H NMR data, but their purification on a multigram scale was not easy. When the organometallic reagent is CH_3Li, both ketone and decyanation products are obtained from **4a–d**; this is discussed in detail below.

The α-bromination reaction of **5a–d** with Br_2 in CH_2Cl_2/ether used to form **6a–d** is not especially clean. The major products, monobromides **6a–d**, are accompanied by small amounts of starting ketones and dibromination products such as **8**. Modification of the bromination conditions, such as lowering the reaction temperature,



8

* Please address correspondence in care of A. L. Johnson, Medical Products Department, E. I. du Pont de Nemours & Co., Inc. Experimental Station, 353 Building, Wilmington, DE 19880-0353. Contribution No. 86-P27/28.

(1) Presented in preliminar form: Johnson, A. L.; Gregory, G. B.; Ripka, W. C. 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 7–12, 1986, Paper No. ORGN-186.

(2) (a) Duncia, J. V.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Wells, G. J.; Chiu, A. T.; Price, W. A.; Timmermans, P. B.; Wong, P. C. *J. Med. Chem.*, in press. (b) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. *J. Med. Chem.*, in press.

(3) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, *29*, 3773–3776.

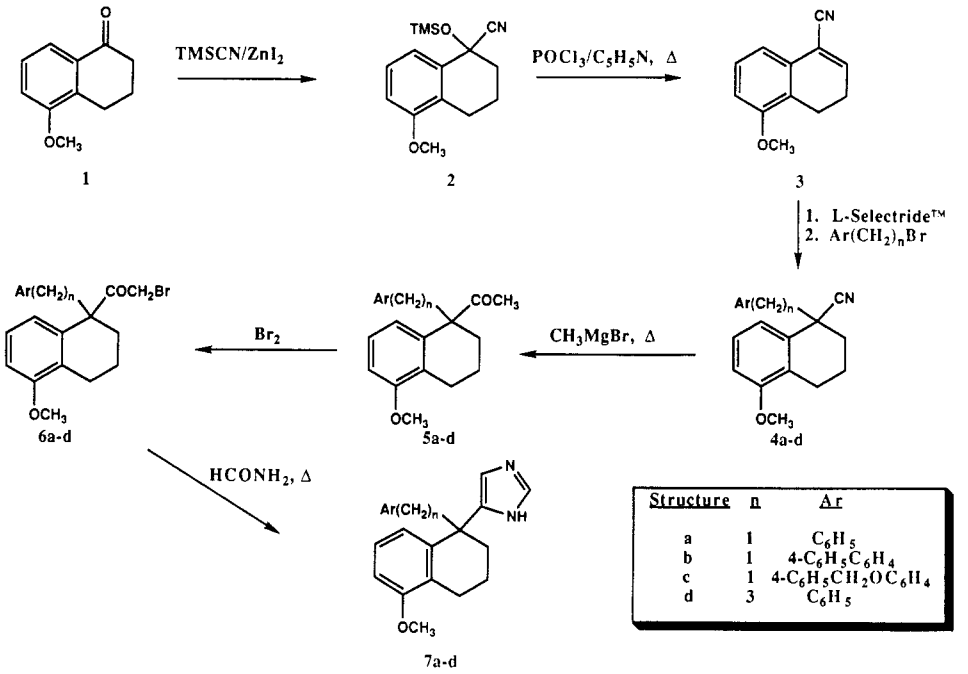
(4) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427–1430.

(5) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 878.

(6) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200.

0022-3263/90/1955-1479$02.50/0 © 1990 American Chemical Society

Scheme I

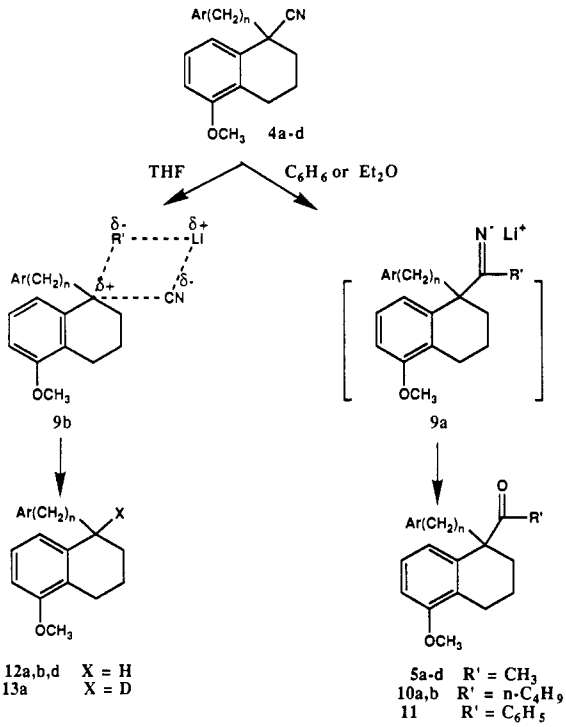


adding an equivalent of base, or using other brominating agents, did not improve the yield of **6a–d**. During preparative work, we found it was adequate to use the crude bromo ketones **6a–d**, which were readily converted to the corresponding 1-(4-imidazolyl)-1,2,3,4-tetrahydronaphthalenes **7a–d** by formamide at reflux.[7] The imidazole products **7a–d** were purified by chromatography or recrystallization. In preparative-scale experiments in which rigorous purification of the intermediate ketones **5a–d** and bromo ketones **6a–d** was not found to be necessary, overall yields of **7a–d** of the order of 40% were obtained from unsaturated nitrile **3**. Our experiments demonstrate that a variety of 1-aralkyl-1-(4-imidazolyl)-1,2,3,4-tetrahydronaphthalenes can be prepared in good yields in few experimental steps.

Decyanation Reaction: Synthetic Use. Nitriles react generally with organometallic reagents to form ketones after hydrolysis.[8,9] As part of the work described above, we have observed decyanation of the tertiary nitrile intermediates **4a–d** when alkyllithiums in ether solvents were substituted for CH_3MgBr, particularly in THF. When **4a–d** were treated at reflux in benzene with CH_3MgBr, followed by acidic workup, the desired ketones **5a–d** were obtained in high yield. However, the reactions did not proceed to completion, even with excess Grignard reagent, and the respective products were not readily separated from the starting materials. When the solvent was changed to THF or diethyl ether in attempts to optimize ketone formation, the reaction slowed and lower yields were observed.

Alkyllithiums were tried as an alternative to Grignard reagents. The addition of methyllithium to nitrile **4a** in 1:1 ether–THF mixture gave a quantitative yield of decyanation product, **12a**. Similar results were obtained for nitriles **4b,d** in THF alone, producing 100% isolated yields

Scheme II



of the respective compounds **12b,d**. In diethyl ether alone, the same nitriles produced methyl ketones **5a–d** in 81–90% yields with less than 10% decyanation product being formed. Similar results were observed with *n*-butyllithium, except that the ratio of butyl ketones **10a,b** to decyanation products **12a,b** was lower than that for methyllithium (see Table I). None of the decyanation products **12a,b,d** are reported in the literature.

(7) Bredereck, H.; Theilig, G. *Chem. Ber.* **1953**, *86*, 88.
(8) Grignard reactions: (a) Cullen, J. E.; Dornfeld, C. A.; Coleman, G. H. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 26. (b) Moffett, R. B.; Shriner, R. L. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 562.
(9) Alkyllithium Reactions: (a) van Leusen, A. M.; van Leusen, D. *Synth. Commun.* **1978**, *8*, 397. (b) Pawson, B. A. et al. *J. Am. Chem. Soc.* **1970**, *92*, 336.

Table I. Product Distribution for the Reaction of Alkyllithium Reagents with Tertiary Nitriles

nitrile	organometallic reagent	solvent	products (% yield) ketone	decyanation
4a	CH_3MgBr	C_6H_6	94	–
4b			99	–
4c			90	–
4a	CH_3Li	Et_2O	85	6
4b			90	9
4c			81	6
4a	CH_3Li	THF	0	100
4b			0	100
4c			0	100
4a	CH_3Li	1:1 THF–Et_2O	0	100
4a	*n*-BuLi	Et_2O	65	33
4b			40	50
4a	*n*-BuLi	THF	0	100
4b			0	100
4a	C_6H_5Li	Et_2O	98	0
4b		THF	33–47	33

These results show that a tertiary nitrile can be efficiently converted into either a ketone or a decyanation product, depending on the organometallic reagent and the solvent.

Decyanation Reaction: Mechanistic Studies. There are literature reports of the decyanation of certain tertiary nitriles by ethylmagnesium bromide[10] and *n*-butyllithium,[11] but experiments to support a mechanism were not done in these cases. The results discussed below are consistent with a existence of different intermediate forms **9a** and **9b** as precursors to the ketone and decyanation products, respectively. In benzene and ether, the usual intermediate imine salt **9a** persists until it undergoes hydrolysis to the ketone product in aqueous acidic medium.[8,9] In THF, it is unlikely that decyanation products **12a,b,d** arise from fragmentation of **9a**; we explain their formation through 4-membered transition state **9b**, the collapse of which is accompanied by hydride ion abstraction from alkyl radical R′ by the incipient benzylic carbonium ion at the 1-position of the tetrahydronaphthalene nucleus. Such a mechanism has been invoked by Marr and Ronayne[11] to explain the decyanation of α,α-dibenzylferrocenylacetonitrile by *n*-butyllithium.

The following experimental results support this proposed mechanism of formation of **12a,b,d**: (a) quenching the reaction in THF with DCl or other electrophiles *does not* change the product, i.e., no incorporation of deuterium or electrophile is seen, indicating an internal source of the entering benzylic hydrogen atom; (b) monodeutero compound **13a** was identified (HRMS, ^1H, and ^{13}C spectra) as the sole decyanation product in an experiment with CD_3Li, consistent with deuteride capture by the incipient benzylic carbonium ion from the CD_3 group within the 4-center transition state; (c) the deliberate addition of THF to an ether solution of the reactants caused slow fragmentation to the decyanation product, and eventually no ketone could be observed in these reactions (Table II). This last observation can be explained by irreversible conversion of imine salt **9a** to the decyanation products through 4-center transition state **9b**.

In the HRMS of **13a**, the parent ion for monodeutero product $C_{18}H_{19}DO$ (m/z 253.1576) is detected along with the debenzylated ion $C_{11}H_{12}DO$ (m/z 162.1029), indicating attachment of the entering deuterium to the tetrahydronaphthalene fragment during the formation of **13a**. In the proton NMR spectrum of **12a**, the multiplets at 3.08 and 2.85 ppm in an intensity ratio of 2:1 are attributed to the proton at the 1-position and the CH_2 group of the pendant benzyl group; in structure **13a**, these signals reduce to a pair of doublets of equal intensity at 3.08 and 2.85 ppm, characteristic of the benzyl protons found in other tetrasubstituted tetrahydronaphthalenes such as **4a–c** and **5a–c**. The assignment of the 1-H of **12a** as part of the 3.08 ppm multiplet is consistent with the observed changes in intensity and multiplicity of these signals. Finally, the carbon atom at the 1-position of **12a** appears as a sharp triplet at 39.67 ppm in the proton-decoupled ^{13}C NMR spectrum, but becomes a low-intensity triplet at 39.19 ppm for **13a**, other signals in the ^{13}C spectra of **12a** and **13a** being unchanged. These data clearly indicate that methyllithium is the hydrogen source in **12a,b,d** and **13a**, and that it is delivered to the 1-position of the tetrahydronaphthalene nucleus during fragmentation of **9b** in THF.

Table II. Change in Product Ratio with Time after Addition of THF to Diethyl Ether Solutions of Imine Salt Intermediates

nitrile	organometallic reagent	volume of THF added per volume of ether	time, h	products (% yield) ketone	decyanation
4a	CH_3Li	0	1.5	85	6
		1	0.5	56	41
		1	2.0	–	82
		2	15.0	0	99
4b	CH_3Li	0	1.5	90	9
		1	0.5	71	27
		2	15.0	0	98

The reaction of **4a** with phenyllithium in ether gave only the phenyl ketone **11** and no decyanation product. In THF, some fragmentation was observed, and a mixture of ketone **11** (up to 35%), decyanation product **12a** (33–47%), and several minor products was produced. Table I summarizes these results.

Formation and fragmentation of 4-centered transition state **9b** in THF probably occurs because THF is a stronger Lewis base than diethyl ether or benzene and is better able to solvate the lithium cation.[12,13] The observed internal hydride capture is more consistent with the 4-centered mechanism than frank fragmentation of imine salt **9a** to an anion and alkyl cyanide, a pathway which would be analogous to the methyllithium-induced rearrangement of the α,β-unsaturated carboxylic acid described by Dalton and co-workers.[13]

Experimental Section

Spectra were determined as follows: ^1H NMR in $CDCl_3$/TMSi, IBM 200 MHz; ^{13}C NMR in $CDCl_3$, IBM 270 MHz operating at 67.92 MHz; IR in film or KBr pellet, Nicolet 7199 and PE 1710FT; UV in THF or EtOH, Cary 17; HRMS by direct injection, Consolidated CEC-110.

1-Cyano-5-methoxy-3,4-dihydronaphthalene (3). A mixture of 5-methoxy-1-tetralone (1, 3.52 g, 20 mmol), benzene (20 mL), trimethylsilyl cyanide (2.28 g, 23 mmol), and zinc iodide (0.10 g) was stirred at 25 °C for 3 h, at which time reaction was judged to be complete by TLC (7:3 petroleum ether–ether). The solvent was removed by rotary evaporator to leave 5.9 g (ca. 100%) of intermediate 1-cyano-1-(trimethylsilyl)oxy)-5-methoxy-1,2,3,4-tetrahydronaphthalene (**2**) as a colorless oil with ν_{max} 2230 cm^{-1}; ^1H NMR δ 7.27 (m) and 6.80 (d, J = 6, each d, J = 1) (aromatic), 3.80 (s, OCH_3), 2.67 (t, J = 7, CH_2), 2.10 (m, CH_2), 0.20 (s, $(CH_3)_3Si$). The crude TMS–cyanohydrin was stirred at reflux

(10) Schultz, E. M. *J. Am. Chem. Soc.* **1952**, *74*, 5793.
(11) Marr, G.; Ronayne, J. *J. Chem. Soc., Chem. Commun.* **1970**, 350.
(12) (a) Benkeser, R. A.; Broxterman, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162. (b) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307.
(13) (a) Dalton, J. C.; Chan, H. F. *Tetrahedron Lett.* **1973**, 3145. (b) Dalton, J. C.; Stokes, B. G. *Tetrahedron Lett.* **1975**, 3179.

temperature in a mixture of benzene (20 mL), pyridine (20 mL), and $POCl_3$ (4.7 mL, 7.7 g, 50 mmol). Removal of the solvents by rotary evaporator gave 3.42 g (18.5 mmol, 92%) of unsaturated nitrile, **3**. In subsequent experiments it was most convenient to add the pyridine and $POCl_3$ directly to the benzene solution after checking by TLC that TMS–cyanohydrin formation was complete. The product was recrystallized from a mixture of petroleum ether and ether with Darco (Aldrich) treatment as fine colorless needles. 1-Cyano-5-methoxy-3,4-dihydronaphthalene (**3**) was obtained from the "one-pot" reaction in 68% yield: mp 63–64 °C; ν_{max} 2219 cm^{-1}; λ_{max} 275 nm (ϵ 8000); ^1H NMR δ 7.27 (t, J = 7), 7.11 (d, J = 7), and 6.90 (m) (aromatic, vinyl), 3.85 (s, OCH_3), 2.83 (t, J = 8, CH), 2.47 (m, CH_2); HRMS calcd for $C_{12}H_{11}NO$ m/z 185.0840, found 185.0836. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.08, 77.86; H, 5.93, 5.89; N, 7.77, 7.78.

General Procedure for Preparing Reductive Alkylation Products 4a–d. A 500-mL round-bottomed flask fitted with magnetic stirrer, reflux condenser, addition funnel, septum, and −78 °C bath was charged with L-Selectride [LiB(*s*-Bu)$_3$H, 1 M in THF, 86 mL, 86 mmol], the stirrer was started, and a solution of nitrile **3** (15.57 g, 84.1 mmol) in THF (105 mL) was added dropwise. The mixture was stirred for 60 min at −78 °C and then treated with benzyl bromide (13.0 mL, 18.69 g, 109 mmol). The bath was removed, and the mixture was stirred at 25 °C for 3 h. The mixture was then cooled to 0 °C and treated dropwise in turn with 10% NaOH (35 mL, 87.5 mmol) and 30% H_2O_2 (30 mL). The mixture was stirred at 25 °C for 20 h, and the crude white solid was filtered. Additional solid was obtained on further standing. The combined air-dried solid was recrystallized from acetone to give 20.28 g (73.2 mmol, 87%) of colorless needles of **4a**. For products **4b–d**, obtained by using equimolar amounts of 4-(bromomethyl)biphenyl, 4-(benzyloxy)-α-bromotoluene and 3-phenyl-1-bromopropane, respectively, in place of benzyl bromide, the aqueous THF solution containing H_2O_2 was diluted with ether and separated. The ether layer was washed twice with a 1:2 solution of saturated $NaHSO_3$–H_2O and then with brine, dried (Na_2SO_4), and evaporated to leave a residue, which was recrystallized from cyclohexane containing sufficient EtOAc to effect solution at the boiling point.

1-Benzyl-1-cyano-5-methoxy-1,2,3,4-tetrahydronaphthalene (4a): mp 153–154 °C (from acetone); ν_{max} 2221, 1585, 1460 cm^{-1}; λ_{max} 274 nm (ϵ 2040), 281 (2040); ^1H NMR δ 7.10–7.30 (m) and 6.78 (d, J = 8) (aromatic), 3.83 (s, OCH_3), 3.35 and 3.03 (2 d, J = 13, $ArCH_2$), 2.70 (m) and 1.93 (m) (CH_2); HRMS calcd for $C_{19}H_{19}NO$ m/z 277.1467, found 277.1459. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.66, 82.17; H, 6.81, 6.68; H, 5.05, 5.23.

1-(4-Biphenylylmethyl)-1-cyano-5-methoxy-1,2,3,4-tetrahydronaphthalene (4b): mp 111–113 °C (from cyclohexane–EtOAc); ν_{max} 2225, 1600, 1584, 1468 cm^{-1}; λ_{max} 256 nm (ϵ 24 200); ^1H NMR δ 7.13–7.67 (m) and 6.80 (d, J = 8) (aromatic), 3.85 (s, OCH_3), 3.40 and 3.07 (2 d, J = 13, $ArCH_2$), 2.73 (m) and 2.00 (m) (CH_2); HRMS calcd for $C_{25}H_{23}NO$ m/z 353.1779, found 353.1776. Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.67; H, 6.48; N, 3.98.

1-(4-(Benzyloxy)benzyl)-1-cyano-5-methoxy-1,2,3,4-tetrahydronaphthalene (4c): mp 134–135 °C (from cyclohexane–hexane); ν_{max} 2227, 1610, 1584, 1513, 1468 cm^{-1}; λ_{max} 228 nm (ϵ 29 750), 275 (3550), 282 (3325); ^1H NMR δ 7.45 (m), 7.18 (m), 6.93 and 6.78 (2 d, J = 8) (aromatic), 5.06 (s, OCH_2), 3.83 (s, OCH_3), 3.27 and 2.96 (2 d, J = 13, $ArCH_2$), 2.69 (m) and 1.93 (m) (CH_2); HRMS calcd for $C_{26}H_{25}NO$ m/z 383.1885, found 383.1902. Anal. Calcd for $C_{26}H_{25}NO$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.37, 81.25; H, 6.71, 6.68; N, 4.12, 4.11.

1-(3-Phenylpropyl)-1-cyano-5-methoxy-1,2,3,4-tetrahydronaphthalene (4d): mp 73–75 °C (from cyclohexane); ν_{max} 2227, 1603, 1584, 1470, 1464 cm^{-1}; λ_{max} 273 nm (ϵ 2020), 280 (2010); ^1H NMR δ 7.33–7.05 (d, J = 5, m) and 6.75 (d, J = 7) (aromatic), 3.82 (s, OCH_3), 2.65 (m) and 2.23–1.87 (m) (CH_2); HRMS calcd for $C_{21}H_{23}NO$ m/z 305.1779, found 305.1782. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.62, 82.84; H, 7.49, 7.51; N, 4.60, 4.51.

General Procedure for Preparing Ketones 5a–d. A 500-mL round-bottomed flask equipped with magnetic stirrer, reflux condenser, distillation head, and rubber septum was charged under dry N_2 with ethereal 3 M CH_3MgBr (29 mL, 25 mmol) and a solution of nitrile **4a** (6.93 g, 25 mmol) in C_6H_6 (200 mL). The mixture was stirred and heated, and the ether was removed by distillation before the benzene solution was allowed to stir at reflux overnight. The mixture was cooled to 0 °C, acidified with 6 N HCl (30 mL), and separated. The organic layer was washed with H_2O and saturated $NaHCO_3$, dried (Na_2SO_4), and then evaporated to leave 7.6 g of yellow oil. This crude product was purified by flash chromatography (20% hexane–CH_2Cl_2) to give 6.94 g (23.6 mmol, 94%) of **5a** as a pale yellow oil. Compounds **5b,c,d** were obtained similarly in yields of 82, 90, and 90%, respectively.

1-Benzyl-1-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (5a): ν_{max} 1704, 1600, 1582, 1462 cm^{-1}; λ_{max} 275 nm (ϵ 1820) 282 (1830); ^1H NMR δ 7.10 (m), 6.92 (br s), 6.72 and 6.61 (2 d, J = 7) (aromatic), 3.81 (s, OCH_3), 3.31 and 3.15 (2 d, J = 13, $ArCH_2$), 2.53 (m, CH_2), 1.92 (s, CH_3CO), 1.83 and 1.68 (m) (CH_2); HRMS calcd for $C_{20}H_{22}O_2$ m/z 294.1620, found 294.1624. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.30, 82.01; H, 7.46, 7.51.

1-(4-Biphenylylmethyl)-1-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (5b): ν_{max} 1704, 1600, 1583, 1467 cm^{-1}; λ_{max} 257 nm (ϵ 27 400); ^1H NMR δ 7.55 (d, J = 7), 7.33 (m), 7.13 (t, J = 7), 7.00 (d, J = 2), 6.75 and 6.67 (2 d, J = 7) (aromatic), 3.83 (s, OCH_3), 3.37 and 3.20 (2 d, J = 10, $ArCH_2$), 2.50 (m, CH_2), 1.93 (s, CH_3CO), 1.9–1.5 (m, CH_2); HRMS calcd for $C_{26}H_{26}O_2$ m/z 370.1932, found 370.1937. Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.29; H, 7.07. Found: C, 84.11, 84.03; H, 7.35, 7.36.

1-(4-(Benzyloxy)benzyl)-1-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (5c): ν_{max} 1700, 1600, 1580, 1510, 1464 cm^{-1}; λ_{max} 227 nm (ϵ 26 160), 277 (3400), 283 (3110); ^1H NMR δ 7.47 (m), 7.13 (d, J = 8), 6.60 (m) and 6.65 (d, J = 7) (aromatic), 5.01 (s, OCH_2), 3.85 (s, OCH_3), 3.30 and 3.13 (2 d, J = 10, $ArCH_2$), 2.60 (m, CH_2), 1.97 (s, CH_3CO), 2.0–1.7 (m, CH_2); HRMS calcd for $C_{27}H_{28}O_3$ m/z 400.2038, found 400.2031. Anal. Calcd for $C_{27}H_{28}O_3$: C, 80.96; H, 7.05. Found: C, 81.28, 80.99; H, 7.15, 6.91.

1-(3-Propylphenyl)-1-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (5d): ν_{max} 1702, 1601, 1581, 1497, 1460 cm^{-1}; λ_{max} 274 nm (ϵ 1800), 281 (1810); ^1H NMR δ 7.13 (m), 6.70 and 6.56 (2 d, J = 7) (aromatic), 3.82 (s, OCH_3), 2.67 (m, CH_2), 1.95 (s, CH_3CO), 2.0–1.5 (m, CH_2); HRMS calcd for $C_{22}H_{26}O_2$ m/z 322.1933, found 322.1934. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.71, 81.67; H, 7.98, 8.07.

1-Benzyl-1-(bromoacetyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (6a). A mixture of **5a** (1.1 g, 3.7 mmol) and CH_2Cl_2 (6 mL) was treated with 1.6 mL (5.2 mmol) of 14% Br_2 in CH_2Cl_2. The mixture was stirred for 30 min at 25 °C, and then the solvents were evaporated to leave a brown oil which showed three TLC spots (CH_2Cl_2, SiO_2) with R_f 0.74, 0.68, 0.50. These materials were separated by flash chromatography and identified as follows. The major spot, R_f 0.68, was **6a** (0.86 g, 2.31 mmol, 62%); the minor spots were starting material (R_f 0.50) and dibromide **8** (R_f 0.74). Bromo ketone **6a** is an oil: ν_{max} 1719, 1583 cm^{-1}; ^1H NMR δ 7.13 (m), 6.95 (m), 6.78 and 6.58 (2 d, J = 7) (aromatic), 3.83 (s, OCH_3), 3.80 (m, $BrCH_2$), 3.38 and 3.25 (2 d, J = 13, $ArCH_2$), 2.78–2.38 (m), 1.91 (t J = 7), 1.70 (m) and 1.42 (m) (CH_2); HRMS calcd for $C_{20}H_{21}O_2Br$: m/z 372.0725, found 372.0757.

1-Benzyl-1-(dibromoacetyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (8): ^1H NMR δ 7.47 (m), 6.97 (m), 6.80 and 6.67 (2 d, J = 10) (aromatic), 5.70 (s, $CHBr_2$), 3.87 (s, OCH_3), 3.43 and 3.23 (2 d, J = 10, $ArCH_2$), 2.60 (m) and 2.0–1.7 (m) (CH_2). The following modified bromination conditions were used unsuccessfully to attempt to improve the conversion of **5a** to **6a** and prevent formation of **8**: addition of ether; cooling to −5 °C; use of pyrrolidone hydrotribromide in CH_2Cl_2, THF, or Et_3N/CH_2Cl_2; Me_3SiNLi in THF at −78 °C or 25 °C with NBS or Br_2. Similar results were obtained in the Br_2/CH_2Cl_2 bromination of ketones **5b–d**. We found it most convenient to use the crude bromination products for conversion to the imidazole derivatives in preparative-scale experiments.

General Procedure for Preparing Imidazoles 7a–d. The bromo ketone **6a** prepared by bromination of **5a** (4.18 g, 14.2 mmol) was dissolved in formamide (30 mL), and the mixture was stirred at reflux for 2.5 h. The mixture was cooled to 100 °C, treated with water (30 mL), and allowed to stand at 25 °C overnight. The crude product was filtered and recrystallized twice from 1,2-dichloroethane, yield 1.84 g (5.78 mmol, 41%) of fine needles, mp 183–184 °C.

1-Benzyl-1-(4-imidazolyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (7a): mp 183–184 °C (from 1,2-dichloroethane); ν_{max} 1584 cm^{-1}; λ_{max} 273 nm (ϵ 1520), 281 (1540); ^{1}H NMR δ 7.57 (s) and 6.50 (s) (imidazole), 7.18 (m), 6.91 (m), 6.73 (d, J = 7) (aromatic), 2.70–1.48 (m, CH_2); HRMS calcd for $C_{21}H_{22}N_2O$ m/z 318.1732, found 318.1724.

1-(4-Biphenylylmethyl)-1-(4-imidazolyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (7b): mp 201–203 °C (from CH_2Cl_2–hexane, 28% yield); ν_{max} 1580 cm^{-1}; λ_{max} 257 nm (ϵ 21 800); ^{1}H NMR δ 7.52 (d, J = 8), 7.43–7.12 (m), 6.94 (d, J = 7), 6.61 (d, J = 7) and 6.48 (s) (aromatic, imidazole), 3.77 (s, OCH_3), 3.53 and 3.43 (2 d, J = 13, $ArCH_2$), 2.68–1.45 (m, CH_2); HRMS calcd for $C_{27}H_{26}N_2O$ m/z 394.2045, found 394.2051. Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 82.49; 82.25; H, 6.72, 6.72; N, 6.79, 6.90.

1-(4-(Benzyloxy)benzyl)-1-(4-imidazolyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (7c): mp 82–84 °C (chromatographed, 38% yield); ν_{max} 1662, 1609, 1581 cm^{-1}; λ_{max} 275 nm (ϵ 3310); ^{1}H NMR δ 7.53 (s), 7.43–7.13 (m), 6.77 (m) and 6.49 (s) (aromatic, imidazole), 4.97 (s, OCH_2), 3.80 (s, OCH_3), 3.45 and 3.33 (2 d, J = 13, $ArCH_2$), 2.69–1.47 (m, CH_2); HRMS calcd for $C_{28}H_{28}N_2O_2$ m/z 424.2150, found 424.2198.

1-(3-Phenylpropyl)-1-(4-imidazolyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (7d): glassy solid (chromatographed, yield 40%); ν_{max} 1600, 1580, 1495, 1460 cm^{-1}; λ_{max} 271 nm (ϵ 1880), 280 (1770); ^{1}H NMR δ 7.45 (s) and 6.47 (s) (imidazole), 7.27 (m), 6.78 and 6.67 (2 d, J = 7) (aromatic), 3.80 (s, OCH_3), 2.75 (m), 2.10 (m), and 1.80 (m) (CH_2); HRMS calcd for $C_{23}H_{26}N_2O$ m/z 346.2045, found 346.2031.

Alkyllithium Method for Preparing Ketones 5a–d, 10a,b, 11. A slurry of nitrile **4a** (345 mg, 1.24 mmol) in ether (35 mL) was cooled to 0 °C and treated dropwise with 0.6 M methyllithium in ether (5.0 mL, 3.0 mmol). The reaction was monitored by TLC (3:7 ether–petroleum ether). A further 0.5 mL of 0.6 M methyllithium was added after the reaction mixture had stirred at 25 °C for 1 h, and the stirring was continued for a further 0.5 h. The reaction mixture was quenched with 6 mL of 2:1 concentrated HCl–H_2O, followed by overnight stirring and isolation of the crude product from the ether layer as a yellow oil. Flash chromatography (5–12% ether–petroleum ether) gave the decyanation product **12a** (20 mg, 6%) and ketone **5a** (310 mg, 85%) in turn. When the imine salt **9a** is insoluble in ether, heating is required to hydrolyze it to the ketone (**5b**, **10b**, **15**). Compounds **5a–d** prepared by this method were identical with those obtained by the reaction of methylmagnesium bromide on nitriles **4a–d**. Substitution of *n*-butyllithium or phenyllithium for methyllithium gave compounds **10a,b** and **11**, respectively.

1-Benzyl-1-pentanoyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (10a): ν_{max} 1703, 1600, 1582 cm^{-1}; ^{1}H NMR δ 7.13 (m), 6.95 (m), 6.75 and 6.63 (2 d, J = 7) (aromatic), 3.23 (s, OCH_3), 3.37 and 3.17 (2 d, J = 10, $ArCH_2$), 2.50 (m), 2.19 (m), 1.80 (m), 1.57 (m), and 1.10 (m) (CH_2), 0.80 (t, J = 7, CH_3). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 81.75; H, 8.45.

1-(4-Biphenylylmethyl)-1-pentanoyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (10b): colorless oil; ν_{max} 1703, 1600, 1582, 1475, 1460 cm^{-1}; ^{1}H NMR δ 7.55 (d, J = 7), 7.30 (m), 7.13 (t, J = 7), 7.02 (d, J = 7), 6.75 and 6.65 (2 d, J = 7) (aromatic), 3.82 (s, OCH_3), 3.40 and 3.19 (2 d, J = 10, $ArCH_2$), 2.68 (m), 2.50 (m), 2.20 (m), 1.75 (m), and 1.30 (m) (CH_2), 0.80 (t, J = 7, CH_3). Anal. Calcd for $C_{29}H_{32}O_2$: C, 84.42; H, 7.82. Found: C, 83.56, 83.44; H, 7.89, 7.92 (could not be purified further).

1-Benzyl-1-benzoyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (11): mp 126–127 °C (chromatographed); ν_{max} 1669, 1596, 1582, 1459 cm^{-1}; ^{1}H NMR δ 7.33 (m), 7.02 (m), 6.73 and 6.58 (2 d, J = 7) (aromatic), 3.87 (s, OCH_3), 3.58 and 3.22 (2 d, J = 10, $ArCH_2$), 2.87 (m), 2.50 (m), 2.07 (m), and 1.80 (m) (CH_2). Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 83.99, 83.98; H, 6.88, 6.96.

General Procedure for Preparing Decyanation Products 12a,b,d and 13a: A solution of nitrile **4a** (280 mg, 1.0 mmol) in anhydrous THF (20 mL) was cooled to 0 °C and treated with 0.53 M methyllithium in ether (4 mL, 2.1 mmol). The ice bath was removed, and the reaction mixture was stirred until only the product spot was evident by TLC. The product was isolated in similar manner to that used for the ketones **5a–d** to give decyanation product **12a** as a pale yellow oil (270 mg), which was purified by flash chromatography as described above.

Decyanation products **12a,b** were also formed by the addition of THF to an ethereal solution of the imine salts used in the ketone procedure. Thus, in the preparation of **5a** described above, if 70 mL of THF is added to the reaction solution and stirring is continued until only the decyanation product spot is observable, then decyanation product **12a** can be isolated in 99% yield.

The above procedure was also used to prepare **12b,d** and the deuterated material **13a**. For the latter compound, CD_3Li was prepared in ether solution from CD_3I (Aldrich) and lithium metal.[14]

1-Benzyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (12a): colorless oil; ν_{max} 1602, 1584, 1467 cm^{-1}; λ_{max} 270 nm (ϵ 1530), 274 (1500); ^{1}H NMR δ 7.07–7.37 (m), 6.86 and 6.68 (2 d, J = 7) (aromatic), 3.82 (s, OCH_3), 3.08 (m, CH), 3.08 and 2.85 (2 m, $ArCH_2$), 2.57 (m) and 1.95–1.50 (m) (CH_2); ^{13}C NMR 39.67 ppm (s, CH); HRMS calcd for $C_{18}H_{20}O$ m/z 252.1514, found 252.1511. Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.57, 85.42; H, 8.08, 8.07.

1-Benzyl-1-deuterio-5-methoxy-1,2,3,4-tetrahydronaphthalene (13a): ν_{max} 1602, 1583, 1502, 1462 cm^{-1}; ^{1}H NMR δ 3.08 and 2.85 (2 d, J = 10, $ArCH_2$); ^{13}C NMR 39.19 ppm (t, C-D); HRMS calcd for $C_{18}H_{19}DO$ m/z 253.1576, found 253.1606; calcd for $C_{11}H_{12}DO$ $(M - C_7H_7)^+$ m/z 162.1029, found 162.1027.

1-(4-Biphenylylmethyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (12b): ν_{max} 1601, 1584, 1520, 1485, 1467 cm^{-1}; λ_{max} 256 nm (ϵ 27 400); ^{1}H NMR δ 7.50 (m), 7.23 (m), 7.15 (t, J = 7), 6.87 and 6.71 (2 d, J = 7) (aromatic), 3.83 (s, OCH_3), 3.16 (m, CH), 3.10 and 2.85 (2 m, $ArCH_2$), 2.60 (m) and 1.90–1.60 (m) (CH_2); HRMS calcd for $C_{24}H_{24}O$ m/z 328.1827, found 328.1841. Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.20, 87.20; H, 7.55, 7.64.

1-(3-Phenylpropyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (12d): ν_{max} 1602, 1583, 1498, 1467 cm^{-1}; λ_{max} 269 nm (ϵ 1470), 278 (1410); ^{1}H NMR δ 7.20 (m), 7.03 (t, J = 7), 6.77 and 6.65 (2 d, J = 7) (aromatic), 3.80 (s, OCH_3), 2.60 (m, CH, CH_2), 1.73 (m, CH_2); HRMS calcd for $C_{20}H_{24}O$ m/z 280.1827, found 280.1831. Anal. Calcd for $C_{20}H_{24}O$: C, 85.66; H, 8.63. Found: C, 85.14; H, 8.80.

Registry No. **1**, 33892-75-0; **2**, 124921-27-3; **3**, 98218-37-2; **4a**, 124921-28-4; **4b**, 124921-29-5; **4c**, 124921-30-8; **4d**, 124921-31-9; **5a**, 124921-32-0; **5b**, 124921-33-1; **5c**, 124921-34-2; **5d**, 124921-35-3; **6a**, 124942-73-0; **6b**, 124921-36-4; **6c**, 124921-37-5; **6d**, 124921-38-6; **7a**, 124921-39-7; **7b**, 124921-40-0; **7c**, 124921-41-1; **7d**, 124921-42-2; **8**, 124921-50-2; **10a**, 124921-47-7; **10b**, 124921-48-8; **11a**, 124921-49-9; **12a**, 124921-43-3; **12b**, 124921-44-4; **12d**, 124921-45-5; **13a**, 124921-46-6; $HCONH_2$, 75-12-7; $C_6H_5CH_2Br$, 100-39-0; 4-$C_6H_5C_6H_4CH_2Br$, 2567-29-5; 4-$C_6H_5CH_2OC_6H_4CH_2Br$, 5544-60-5; $C_6H_5(CH_2)_3Br$, 637-59-2.

(14) Schollkopf, U. et al. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 859.