7.04 (d, J = 2.2 Hz, 1 H), 6.87 (dd, J = 2.2 and 8.9 Hz, 1 H), 3.86 (s, 3 H), 3.76 (s, 3 H); LRMS (m/z, rel intensity) 264 (48), 263 (M^+, 100), 262 (68), 248 (30), 220 (36), 204 (18). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.98; H, 6.47; N, 5.06.

5-Methoxy-1-methyl-2-(*trans*-1-pentenyl)indole (8e). The reaction time was 4 h. Evaporation of the methylene chloride/hexanes filtrate under reduced pressure afforded **8e** (93%) as a white, crystalline solid: mp 84.0–85.0 °C; IR (KBr) 1615, 1575, 1520, 1480, 1455, 1430, 1400, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (d, J = 8.9 Hz, 1 H), 7.00 (d, J = 2.3 Hz, 1 H), 6.81 (dd, J = 2.3 and 9.0 Hz, 1 H), 6.48 (s, 1 H), 6.41 (d, J = 15.8 Hz, 1 H), 6.32–6.21 (m, 1 H), 3.83 (s, 3 H), 3.67 (s, 3 H), 2.27–2.19 (m, 2 H), 1.56–1.48 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.2, 139.3, 134.2, 128.3, 119.0, 111.3, 109.7, 101.8, 97.3, 55.9, 35.5, 29.9, 22.5, 18.7; LRMS (m/z, rel intensity) 230 (27), 229 (M^+, 100), 214 (62), 200 (66), 185 (17), 174 (23), 169 (28), 169 (29), 156 (27), 114 (21). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.50; H, 8.31; N, 6.04.

5-Methoxy-1-methyl-2-((8-methyl-8-azabicyclo[3.2.1]octan-3-ylidene)methyl)indole (8g). A solution of **5g** (1.50 g, 4.41 mmol), sodium hydride (60% in oil, 0.27 g, 6.75 mmol, 1.5 equiv), and isopropyl alcohol (25 mL) was heated at reflux (82 °C) under nitrogen for 3 h. The reaction solution was cooled, glacial acetic acid was added (1 mL), and the reaction mixture was evaporated under reduced pressure. The residual solid was triturated with ether to afford a white solid (2.00 g). An NMR spectrum[18] of this solid was consistent with 5-methoxy-1-methyl-2-((8-methyl-8-azabicyclo[3.2.1]octyliden-3-yl)methyl)indole-3-carboxylic acid (**6g**, 100% crude) and sodium acetate. Crude **6g** (0.53 g) was placed in bromobenzene (10 mL), and this mixture was heated at reflux (156 °C) under nitrogen for 8 h. The resulting reaction solution was passed through a silica gel filter (approximately 25 g) followed first by ethyl acetate (250 mL) and then by a solution of ethyl acetate/methanol/triethylamine (18:1:1, 250 mL). This latter filtrate was then evaporated under reduced pressure to yield **8g** (0.35 g, 99% for two steps) as a clear, pale yellow oil: IR (neat) 1620, 1575, 1520, 1480, 1450, 1430, 1400, 1345, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 1 H), 7.02 (d, J = 2.4 Hz, 1 H), 6.83 (dd, J = 2.5 and 8.8 Hz, 1 H), 6.27 (s, 1 H), 6.23 (br s, 1 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.31–3.26 (m, 1 H), 3.22–3.17 (m, 1 H), 2.85–2.80 (br d, 1 H), 2.74–2.69 (br d, 1 H), 2.52–2.47 (br d, 1 H), 2.38 (s, 3 H), 2.16–2.11 (br d, 1 H), 2.04–1.86 (m, 2 H), 1.64–1.60 (m, 1 H), 1.41–1.37 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.1, 140.3, 137.2, 132.3, 128.1, 116.4, 111.4, 109.7, 101.9, 101.1, 61.8, 61.3, 55.9, 42.1, 39.6, 36.1, 29.9, 26.8, 26.6; LRMS (m/z, rel intensity) 297 (25), 296 (M^+, 64), 215 (69), 200 (18), 174 (16), 162 (58), 148 (15), 82 (100). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.60; H, 8.23; N, 9.30.

***tert*-Butyl (3-(Ethoxycarbonyl)indol-2-yl)-2-methylprop-2-yl Carbonate (9u).** To a stirred solution of lithium diisopropylamide (7.5 mmol made from 1.05 mL of diisopropylamine and 3.0 mL of 2.5 M *n*-butyllithium in hexanes, 1.5 equiv) in anhydrous THF (15 mL) at −78 °C under nitrogen was added rapidly a solution of **3f** (5.00 mmol) in anhydrous THF (10 mL) while the reaction temperature was maintained below −40 °C. The resultant yellow solution was stirred at −78 °C for 15 min, at which time acetone (0.60 mL, 8.17 mmol, 1.6 equiv) was added slowly dropwise. The resultant reaction solution was stirred at −78 °C for 30 min, then a saturated solution of sodium hydrogen carbonate (20 mL) was added, and this mixture was allowed to warm to room temperature. The resultant aqueous mixture was extracted with ethyl acetate (3 × 25 mL), and these extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual solid was triturated in hexanes to afford **9u** (78%) as a white solid: mp 121.0–124.0 °C; IR ($CHCl_3$) 3440, 1740, 1685, 1545, 1455, 1440, 1370, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.95 (br s, NH), 8.14–8.11 (m, 1 H), 7.35–7.32 (m, 1 H), 7.25–7.20 (m, 2 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.71 (s, 2 H), 1.55 (s, 6 H), 1.50 (s, 9 H), 1.45 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 152.1, 143.1, 134.9, 126.5, 122.7, 121.8, 121.6, 110.8, 106.1, 83.6, 82.0, 59.6, 38.1, 27.9, 25.5, 14.6; LRMS (m/z, rel intensity) 361 (M^+, 15), 244 (57), 243 (100, [M^+] − CO_2 − HO-*t*-Bu), 228 (24), 198 (64), 170 (31), 57 (55). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.50; H, 7.47; N, 3.85.

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Supplementary Material Available: X-ray data on compound **5g** (7 pages). Ordering information is given on any current masthead page.

(18) ^1H NMR (DMSO-d_6) 7.65 (d, J = 2.8 Hz, 1 H), 7.30 (d, J = 8.9 Hz, 1 H), 6.76 (dd, J = 2.1 Hz and 9.0 Hz, 1 H), 6.42 (s, 1 H), 3.75 (s, 3 H), 3.53 (s, 3 H), 3.19–3.16 (m, 1 H), 2.99–2.96 (m, 1 H), 2.64–2.59 (m, 1 H), 2.31–2.10 (m, 3 H), 2.22 (s, 3 H), 1.90–1.70 (m, 4 H).

Synthesis of Picenadol via Metalloenamine Alkylation Methodology

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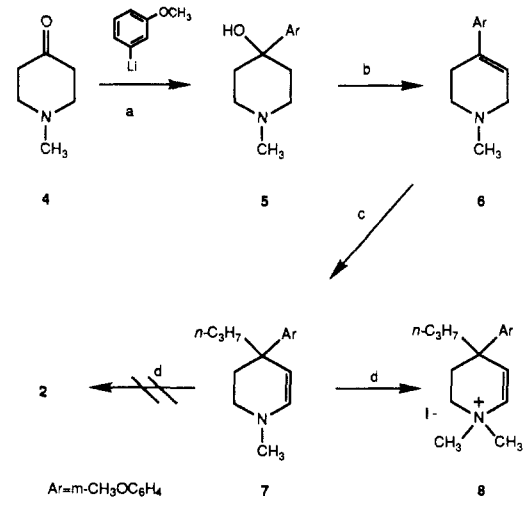
A convenient synthesis of the novel phenylpiperidine analgesic agent picenadol, (±)-**1**, via tetrahydropyridine **2** is described. Tetrahydropyridine **7**, prepared from **6** via metalation (*n*-butyllithium) and alkylation with 1-bromopropane, could not be directly converted to **2**, thus necessitating development of alternative strategies. Dehydration of piperidinol **10** gave a mixture of tetrahydropyridines **11** and **12**. Metalation of **11** followed by alkylation with 1-bromopropane afforded trans-oriented **14**, while **12** provided **2**. Reaction of **7** with excess hot 37% aqueous formaldehyde provided **17** instead of the desired **2**. Exposure of **7** to either Eschenmoser's salt in organic solvent or dimethylamine–formaldehyde (pH 3–3.5) in aqueous solution afforded **15** in high yield. Hydrogenation of **15** to **2** (H_2 Pd/C), demethylation (HBr), and separation of the resulting diastereomeric mixture by recrystallization completed the synthesis of picenadol (**1**).

Extensive investigation of the analgesic activity of 4-alkyl-4-phenylpiperidines and related perhydroisoquinolines has led to the discovery and development of picenadol (*cis*-(±)-3-(1,3-dimethyl-4-propyl-4-piperidinyl)phenol hydrochloride, LY150720, **1**), a unique opioid mixed agonist–antagonist currently undergoing

0022-3263/89/1954-4795$01.50/0

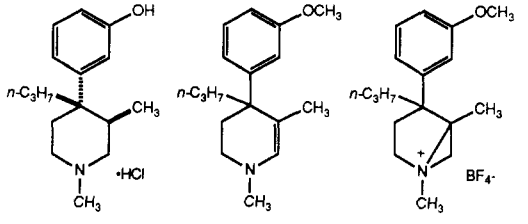
Scheme I[a]



4 5 6 2 7 8

[a] (a) THF, −70 °C; (b) *p*-TsOH, $PhCH_3$, reflux; (c) *n*-BuLi, THF, C_3H_7Br; (d) CH_3I.

clinical evaluation.[1] Interestingly, the mixed opioid properties of (the racemate) picenadol result from agonist activity in the (+) isomer (LY136596) and antagonist activity in the (−) isomer (LY136595).

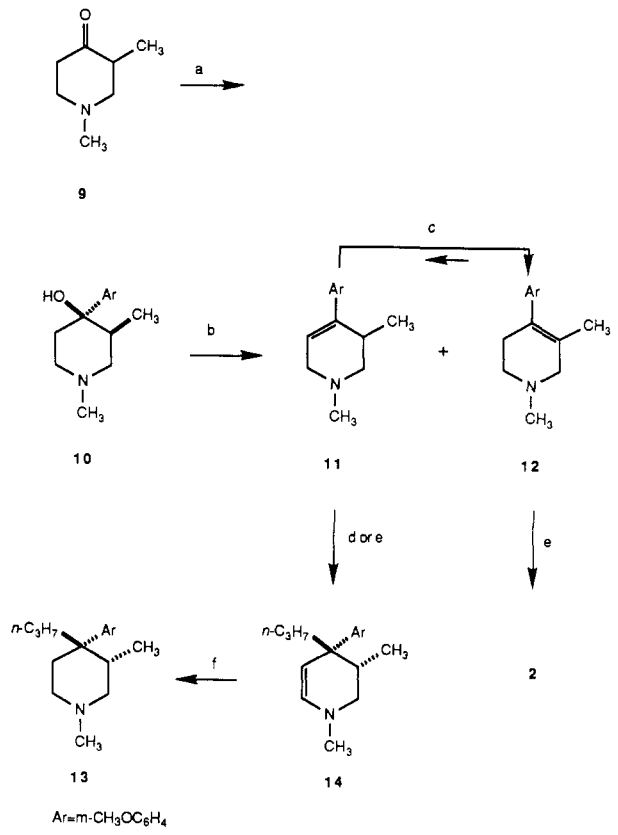


1 2 3

Picenadol was first prepared by catalytic reduction of tetrahydropyridine **2**, derived from thermal rearrangement of bicyclic aziridinium salt **3**.[2] Preparation of **3** from (3-methoxyphenyl)acetone involved a lengthy series of operations concluded by carbene (diazomethane) insertion into the corresponding cyclic iminium salt, providing **3**. The hazardous nature of diazomethane precluded its use in practical-scale syntheses. A more expeditious approach to picenadol was required for larger scale preparations.

Construction of the quaternary center at C-4 is central to the synthesis of phenylpiperidines like picenadol. Evans, in collaboration with a group of Lilly chemists, established that alkylation of lithiated 4-aryl-1,2,3,6-tetrahydropyridines proceeds regiospecifically, providing 4-alkyl-4-aryltetrahydropyridines in good yield.[3] The utility of this approach was illustrated by the synthesis of decahydroisoquinolines bearing angular aryl substituents[3,4] and in an expeditious synthesis of (±)-morphine.[5] In this report we describe an extension of metalated enamine alkylation methodology to the synthesis of 4-alkyl-4-phenylpiperidines bearing a carbon at C-3, as represented by picenadol (**1**).

Scheme II[a]



9 10 11 12 13 14 2

Ar=m-$CH_3OC_6H_4$

[a] (a) 3-$CH_3OC_6H_4Li$, THF, −78 °C; (b) *p*-TsOH, $PhCH_3$; (c) 100% H_3PO_4, 100 °C; (d) *n*-BuLi, THF, C_3H_7Br; (e) *sec*-BuLi, THF, C_3H_7Br; (f) H_2Pd/C.

The synthesis of tetrahydropyridine **7** via alkylation of the metalloenamine of **6** is shown in Scheme I. It was presumed that a methyl substituent at C-3 could be introduced by alkylation, affording the previously reported picenadol precursor **2**. Despite a lack of complete stereoselectivity in the reduction of **2**,[6] this strategy was attractive because it utilized readily available starting materials and appeared to involve a minimum of processing steps.

Dehydration of piperidinol **5**, prepared by arylation of 1-methyl-4-piperidinone (**4**) by a modified literature procedure,[7] afforded, as expected, the known tetrahydropyridine **6**.[8] Metalation of **6** with *n*-butyllithium in THF followed by addition of 1-bromopropane (−10 °C), essentially according to the literature method,[3a] gave tetrahydropyridine **7** in 78% yield (corrected for assay), 60% after distillation. An alternative workup involving silica gel treatment of crude **7** provided an improved yield of material suitable for further processing. In contrast to

(1) Zimmerman, D. M.; Smits, S. E.; Hynes, M. D.; Leander, J. D.; Mendelsohn, L. G.; Nickander, R. *Drug Alcohol Depend.* **1985**, *14*, 381. The cis/trans nomenclature refers to the relative stereochemistry of the C-3 methyl and C-4 propyl substituents in picenadol and analogues.

(2) Zimmerman, D. M. U.S. Pat. 4 081 450, 1978; *Chem. Abstr.* **1978**, *89*, 109113c.

(3) (a) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. (b) Zimmerman, D. M.; Robey, R. L. U.S. Pat. 4 236 009, 1980; *Chem. Abstr.* **1981**, *94*, 121345t.

(4) Zimmerman, D. M.; Cantrell, B. E.; Swartzendruber, J. K.; Jones, N. D.; Mendelsohn, L. G.; Leander, J. D.; Nickander, R. C. *J. Med. Chem.* **1988**, *31*, 555.

(5) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, 285.

(6) The catalytic reduction of **2** was studied extensively by J. B. Campbell, B. E. Cantrell, and D. M. Zimmerman of these laboratories, and the stereochemical outcome was found to be dependent upon catalyst, purity of substrate, and reaction media. Palladium was the only catalyst found to provide a predominance of the cis (picenadol series) diastereomer. Predominantly trans product was obtained with Pt, Rh, and Ni. In acetic acid, all catalysts gave trans/cis ratios of ca. 2:1, owing to control of relative stereochemistry by the thermodynamics of iminium salt formation prior to reduction (see ref 3a). Reduction of purified **2** with Pd/C or $Pd/CaCO_3$ in triethylamine afforded the best cis–trans product ratio, 75:25. These results are in accord with our own observations.

(7) Ziering, A.; Berger, L.; Heineman, S. D.; Lee, J. *J. Org. Chem.* **1947**, *12*, 894.

(8) Lee, J.; Ziering, A.; Berger, L.; Heineman, S. D. *Jubilee Vol. Emil Barell* **1946**, 264; *Chem. Abstr.*, **1947**, *41*, 6246i.

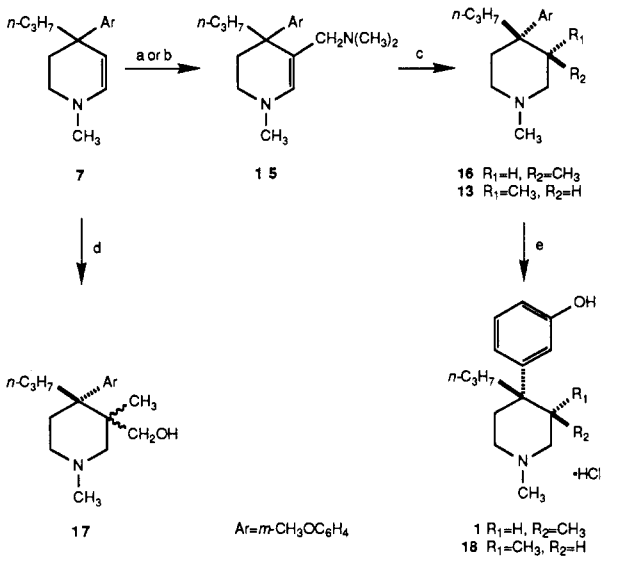
other less highly substituted 1,2,3,4-tetrahydropyridines,[9] **7** was found to be a relatively stable, distillable oil which could be isolated and manipulated without special precautions.[10] Despite previously reported intramolecular β-alkylations[3-5] of compounds analogous to **7**, however, direct introduction of a methyl group at C-5 by intermolecular alkylation could not be accomplished. Reaction of **7** with methyl iodide under a variety of conditions led to formation of N-quaternary iodide **8** instead of the desired C-alkylation product **2**.[11]

It was apparent that the C-3 methyl might be introduced alternatively by utilizing 1,3-dimethyl-4-piperidone (**9**) as starting material (Scheme II). The asymmetry of **9**, however, introduced regio- and stereochemical ambiguities, not all of which were fully appreciated at the outset. Arylation of **9** with *m*-anisyllithium gave a mixture of diastereomeric piperidinols, of which crystalline **10** predominated. While the stereochemistry in **10** would be lost in the subsequent dehydration step, it was of practical importance to be able to purify **10** by crystallization. Careful control of the temperature of arylation (−70 °C) minimized formation of the oily diastereomer of **10** (diastereomeric ratio 9:1), providing crystalline **10** in 84% yield. The relative stereochemistry of **10** was assigned by comparison of its carbon-13 NMR spectrum to that of the known desmethoxy analogue.[12]

Dehydration of **10** with *p*-toluenesulfonic acid in toluene gave a 7:3 mixture of tetrahydropyridines **11** and **12**, respectively, in 94% yield. Alternatively, exposure of **10** to hot, anhydrous phosphoric acid promoted equilibration of the unsaturated products, giving a 1:9 mixture (NMR) in favor of **12** in 75% yield.[13] Recovery of **11** and **12** from the phosphoric acid conditions tended to be erratic, however, possibly due to O-demethylation and loss of the phenolic products upon workup. Although **11** and **12** could be separated chromatographically, it was necessary for practical scale preparative purposes to process the unseparated mixture.

Treatment of the equilibrated mixture of **11** and **12** with *sec*-butyllithium in THF (*n*-butyllithium gave incomplete deprotonation) followed by reaction with 1-bromopropane afforded the tetrahydropyridines **14** and **2** and a small amount of a third isomeric substance (GCMS) which was not identified but presumed to be the product of alkylation of the metalloenamine of **12** at the 2-position. The relative stereochemistry of **14**, arising from alkylation of **11**, was shown to be trans by the following experiment. A purified sample of **11** (preparative HPLC) was subjected to metalation (*n*-butyllithium) and alkylation with 1-bromopropane, and the exclusive product, **14**, obtained in 93% yield, was reduced to provide **13**, previously obtained as a byproduct of the earlier picenadol synthesis. Thus contamination of **2** by **14** would decrease the ultimate diastereomeric purity of crude picenadol. The observed

Scheme III[a]



[a] (a) Eschenmoser's salt; (b) CH_2O, $(CH_3)_2NH$, H_2SO_4; (c) H_2/Pd/C, Et_3N; (d) aqueous CH_2O (excess), 100 °C; (e) HBr, base, HCl.

isomer ratio was even lower than expected because **12** is being selectively converted to products other than **2**, perhaps because of less regiospecific alkylation of the metalloenamine of **12** as compared to **11**. Thus reduction of mixtures of **2** and **14** derived from this sequence provided products in which the cis/trans ratio was 60:40 at best, as compared with 75:25 from the reduction of purified **2** under similar conditions.

The further deterioration of stereochemical control encountered in Scheme II prompted us to reconsider the problem of introducing a methyl substituent into **7** at the enamine β-position. Indirect methods of alkylation have been devised to circumvent the regiochemical ambiguities associated with the direct alkylation of enamines. One method,[14] involving enamine bromination, lithium–halogen exchange, and alkylation of the resulting β-lithio enamine with methyl iodide has, for example, been successfully applied in the tetrahydropyridine series. We utilized this procedure to prepare **2** from **7** in approximately 60% overall yield, but found that exacting control of reaction conditions and substantial excesses (250 mol %) of both metalation and alkylation reagents were necessary for satisfactory results. The ideal replacement for direct alkylation would, in our view, be a process capable of accomplishing the desired result without increasing the overall number of steps in the synthesis.

The reported formal methylation of a conjugated endocyclic enamine by aqueous formaldehyde,[15] a most economical source of a single carbon atom, appeared to provide an unambiguous method of C-alkylation in a single processing step. Exposure of **7** to 37% aqueous formaldehyde at 100 °C according to the literature procedure (see the Experimental Section), however, led only to formation of the 3-methyl-3-hydroxymethyl derivative **17** (as a mixture of diastereomers) instead of **2** (Scheme III). In this case, methylation must have been followed by attack of a second mole of formaldehyde, with subsequent reduction of the resulting iminium species. Reaction of **7** with formaldehyde under mild conditions afforded an oily hydroxymethyl derivative (not fully characterized), which

(9) Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336. See also Blaha, K.; Cervinka, O. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1966; Vol. 6, p 219.

(10) Discoloration of **7** and its analogues was observed upon exposure to air or storage in clear glass at room temperature. Samples of these compounds were usually stored cold.

(11) The tendency for endocyclic enamines to be alkylated at nitrogen with alkyl halides has been documented in a number of cases. See: Szmuszkovicz, J. In *Advances in Organic Chemistry*; Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1963; Vol. 4, p 58 and references cited therein.

(12) Jones, A. J.; Casy, A. F.; McErlane, K. M. J. *Can. J. Chem.* **1973**, *51*, 1782.

(13) The desmethoxy *N*-benzyl analogues of **11** and **12** were obtained in ratio 1:6, respectively, from equilibration in HCl–acetic acid. Casy, A. F.; Beckett, A. H.; Iorio, M. A. *Tetrahedron* **1967**, *23*, 1405.

(14) Duhamel, L.; Poirier, J.-M. *J. Am. Chem. Soc.* **1977**, *99*, 8356.

(15) Mollov, N.; Philipov, S. *Chem. Ber.* **1979**, *112*, 3737.

failed to undergo hydrogenolysis to **2** under the basic conditions required for obtaining predominantly cis stereochemistry in the subsequent reduction step.[16]

Alternatively, the sequence of aminomethylation followed by hydrogenolysis has been successfully employed to effect net C-methylation of phenols and certain heterocycles,[17] but there were no published examples of successful application of this protocol to nonconjugated endocyclic enamines, leaving us uncertain as to whether hydrogenolysis of the dimethylamino substituent would occur prior to reduction of the enamine in the present case. We initially employed a preformed Mannich reagent under anhydrous conditions. Thus, treatment of **7** with dimethylmethyleneammonium iodide (Eschenmosers' salt)[18] in methylene chloride gave the desired aminomethylation product **15** in 90% yield (Scheme III). Compound **15**, an oil, could be purified on a small scale by careful distillation under vacuum, but it was marginally stable under these conditions. The structure of **15** was supported by the appearance of a new 6-proton singlet in the ^1H NMR at δ 2.17 due to the dimethylamino group and a vinylic singlet at δ 6.10 attributable to the enamine α-proton, as well as by ^{13}C NMR and mass spectral data. Catalytic hydrogenation of crude **15** (5% $Pd/CaCO_3$) under basic conditions proceeded cleanly via hydrogenolysis of the dimethylamino substituent and in situ reduction of **2**,[19] giving rise to picenadol methyl ether (**16**) and its diastereomer **13** (ratio 69:31).

Having demonstrated the utility of **15** as a precursor to picenadol via **2**, we became interested in more practical approaches to its preparation involving an in situ generated aminomethylation reagent, as in the classical Mannich process. Accordingly, treatment of **7** with formaldehyde and dimethylamine hydrochloride in alcoholic solution (typical Mannich conditions) gave mixtures of **15** and other products which were not characterized. Replacement of hydrochloric acid with sulfuric acid simplified the product mixture, suggesting that chloromethylation of **7** was competing with aminomethylation. Optimum results were obtained by exposure of **7** to formaldehyde and dimethylamine sulfate in aqueous solution adjusted to pH 3–3.5 with sulfuric acid, affording **15** in 92% yield.

Separation of the diastereomeric piperidines obtained from the reduction of **15** could be effected chromatographically, but a more convenient approach was desirable for large-scale work. Earlier approaches to this problem utilized differences in solubilities of certain salts of **13** and **16**.[20] We found that picenadol (**1**) itself could be selectively crystallized from mixtures containing its diastereomer **18** in a much more convenient fashion than was the case with the methyl ether. Thus, demethylation of the mixture of diastereomeric piperidines from reduction of **15** with hydrobromic acid afforded upon neutralization a mixture of picenadol base (**1**) and **18**, from which picenadol hydrochloride dihydrate could be obtained in high purity by neutralization with aqueous hydrochloric acid and crystallization (as the dihydrate) from water. Alternatively, **1** could be separated from **18** as the free base by recrystallization from acetonitrile–ethyl acetate (5:1) prior to hydrochloride formation. Recrystallization of picenadol (**1**) as the hydrochloride or hydrochloride dihydrate from ethanol served to remove remaining small amounts of isomeric material, affording the purified anhydrous hydrochloride as a stable, nonhygroscopic, crystalline solid.

In conclusion, aminomethylation of **7**, available from metalloenamine alkylation methodology, and reduction of the resulting intermediate **15** provides a concise and practical means for conversion of C-4 quaternized tetrahydropyridines into 3-methyl-4-alkyl-4-phenylpiperidines. This sequence has provided a useful synthesis of picenadol itself and should find additional utility in the synthesis of analogous compounds.

Experimental Section

General Considerations. ^1H (90 MHz) and ^{13}C NMR spectra were obtained on a JEOL FX90Q instrument and are reported as ppm downfield from internal tetramethylsilane. Certain ^1H NMR spectra were measured at 300 MHz (where noted) on a General Electric QE-300 instrument. IR, UV, and mass spectral measurements and elemental analyses were acquired by standard techniques in the Molecular Structure Research Laboratory, Lilly Research Laboratories. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected.

(±)-4-(3-Methoxyphenyl)-1-methyl-4-piperidinol (5). To a solution of 250 g (1.34 mol) of 3-bromoanisole (Aldrich Chemical Co.) in 675 mL of dry THF cooled to −50 to −55 °C under nitrogen was added 1357 mL of *sec*-butyllithium in cyclohexane (1.27 M, 1.7 mol) at a rate such that the reaction temperature did not exceed −50 °C. The resulting white suspension was stirred at −50 °C for 1 h followed by addition of 174.2 g (1.54 mol) of 1-methyl-4-piperidone in 440 mL of THF at a rate such that the temperature was maintained below −40 °C. When addition was complete the mixture was allowed to warm, with stirring, to −20 °C over 1.5 h, then to room temperature over 1 h. Saturated NaCl solution, 350 mL, and water, 525 mL, were added, and the phases were separated. The aqueous layer was extracted with 2 × 350 mL of methylene chloride. The combined organic extracts were in turn extracted with 2 × 1250 mL of 1 N HCl. The combined acidic aqueous phases were made alkaline (pH 10) by addition of concentrated ammonium hydroxide, and the resulting suspension was extracted with 3 × 350 mL of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residual solid was slurried in 1 L of hot hexanes and filtered, affording 225.6 g (74%) of **5**, mp 111–113 °C. A pure sample was obtained by recrystallization from EtOAc/hexanes: mp 113–114 °C (lit.[7] mp 112–113 °C); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H, NCH_3), 2.40 (s, 1 H, OH), 1.6–2.8 (m, 8 H), 3.78 (s, 3 H, OCH_3), 6.8–7.3 (m, 4 H, aryl).

1,2,3,6-Tetrahydro-4-(3-methoxyphenyl)-1-methylpyridine (6). ***Warning***! *The product (**6**) of this preparation is an analogue of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which has been found to possess neurotoxic activity similar to MPTP itself.*[21] *Workers should exercise appropriate caution to avoid exposure to **6**.* A mixture of 110.5 g (0.5 mol) of piperidinol **5** and 190.5 g (1.0 mol) of *p*-toluenesulfonic acid monohydrate in 750 mL toluene was heated to reflux under a Dean–Stark trap for 2 h, the theoretical amount of water having been collected. Water, 400 mL, was added after cooling below 100 °C, and the resulting two phases were thoroughly mixed and separated. The toluene phase was extracted with 300 mL of water, and the combined (cooled) aqueous extracts were made basic with

(16) Reduction under acidic conditions (acetic acid–ethanol, Pd/C) afforded piperidines **13** and **16** (ratio 85:15). The higher ratio of trans product as compared to the 2:1 ratio from reduction of **2** in acetic acid (see note 4) represents more efficient trapping of the kinetic iminium ion. We found that the hydrobromide of **2**, obtained by precipitation from ether, was reduced entirely to **13** by sodium borohydride.

(17) A notable example of this transformation is the preparation of skatole from indole via gramine. Marchand, B. *Chem. Ber.* **1962**, *95*, 577. See also: Tramontini, M. *Synthesis* **1973**, 703 and references cited therein.

(18) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(19) The intermediacy of **2** could be demonstrated by HPLC analysis of aliquots from reduction runs, but 10–15% reduction of **2** usually occurred before hydrogenolysis was complete. We did not observe products arising from preferential reduction of the enamine linkage.

(20) Picenadol methyl ether (**16**) forms the less soluble picrate, while the trans diastereomer **13** affords the less soluble hydrobromide. Zimmerman, D. M.; Cantrell, B. E., unpublished observations.

(21) For a discussion of the neurotoxicity of MPTP and **6**, and recommendations for circumventing this problem, see: Zimmerman, D. M.; Cantrell, B. E.; Reel, J. K.; Hemrick-Luecke, S. K.; Fuller, R. W. *J. Med. Chem.* **1986**, *29*, 1517 and references cited therein.

aqueous NaOH and extracted with 1 × 400 and 2 × 300 mL of hexane. The combined hexane extracts were washed (saturated NaCl), dried (Na_2SO_4), and evaporated under vacuum, affording 88.5 g (87%) of **6** as an oil. Material thus obtained was suitable for further processing but could be purified by distillation: bp 98–99 °C (0.04–0.05 Torr) [lit.[8] bp 142 °C (6 torr)]; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H, NCH_3), 2.62 (m, 4 H), 3.10 (m, 2 H), 3.80 (s, 3 H, OCH_3), 6.05 (br t, 1 H, vinyl), 6.7–7.3 (m, 4 H, aryl); UV λ (EtOH) 285 nm (ε 2860), 247 (ε 10784), 224 (ε 11890).

1,2,3,4-Tetrahydro-4-(3-methoxyphenyl)-1-methyl-4-propylpyridine (7). To a solution of 90 g (0.443 mol) of **6** (*see warning statement in preceding procedure*) in 1.08 L of dry THF cooled to −10 °C under nitrogen was added 304 mL of *n*-butyllithium (1.6M, hexane, 0.486 mol) at a rate such that the temperature was maintained below −5 °C. After 15 min 57.2 g (0.465 mol) of *n*-propyl bromide in 240 mL of THF was slowly added to the resulting deep red solution so that the temperature remained below −5 °C. The reaction was stirred for 10 min and then quenched with 150 mL of water. The organic phase was separated, washed with 150 mL of water and 150 mL of saturated NaCl, and dried (Na_2SO_4). Evaporation of the solvent afforded 112.6 g (104%) of crude **7** as an oil, purity 75% (GC analysis), corrected yield 78%. Distillation of the crude product [bp 113 °C (0.2 torr)] provided 65 g (60%) of purified product: ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 0.9–1.4 (m, 2 H), 1.56–1.83 (m, 2 H), 2.01 (m, 2 H), 2.57 (s, 3 H, NCH_3), 2.64 (m-obscured, 1 H), 2.75 (m, 1 H), 3.80 (s, 3 H, OCH_3), 4.58 (d, J = 8 Hz, 1 H, vinyl), 5.95 (d, J = 8 Hz, 1 H, vinyl), 6.8–7.3 (m, 4 H, aryl); ^{13}C ($CDCl_3$) 14.64, 17.30, 37.08, 40.21, 42.28, 46.01, 46.39, 54.95, 102.95, 109.83, 114.11, 119.58, 128.57, 136.38, 151.76, 159.24; IR (film) 1581, 1597, 1610, 1639(s) cm^{-1}; MS 245 (M^+), 202 (100). As an alternative to distillation, the crude product could be purified by slurry with silica gel in hexane–ethyl acetate. Treatment of 65 g of crude **7** (GC 75%) with 135 g of silica gel (Woelm) in 680 mL of hexane–ethyl acetate (65:35) followed by filtration and washing the silica with 700 mL of the same solvent mixture gave 50.6 g of purified **7** (78% based on weight of crude **7**, GC 87%). The tetrafluoroborate crystallized from EtOAc–ether, mp 87.5–89 °C. Anal. Calcd for $C_{16}H_{24}BF_4NO$: C, 57.68; H, 7.26; N, 4.20. Found: C, 57.56; H, 6.92; N, 4.11.

1,4,5,6-Tetrahydro-1,1-dimethyl-4-(3-methoxyphenyl)-4-propylpyridinium Iodide (8). A mixture of 0.5 g (2.04 mmol) of **7**, 4.5 g (32 mmol) of methyl iodide, and 5 mL of tetrahydrofuran was heated to 50–55 °C for 2 h. Material which crystallized from the reaction mixture on cooling was collected by filtration and dried, affording 630 mg (80%) of **8**, mp 177–181 °C. The filtrate was evaporated to dryness under vacuum, affording 100 mg of solid residue. The residue was identified by NMR as (impure) **8** with no resonances attributable to the C-alkylation product **2**. An analytical sample was obtained by recrystallization from 2-propanol: mp 179–181 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3 H), 1.02 (m, 1 H), 1.22 (m, 1 H), 1.78 (m, 1 H), 2.26 (br t, 1 H), 3.22 (m, 1 H), 3.62 (s, 3 H, NCH_3), 3.70 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 4.16 (br d, 1 H), 6.19 (d, J = 8 Hz, 1 H, vinyl), 6.66 (m, 1 H, aryl), 6.75 (m, 2 H, aryl), 6.97 (d, J = 8 Hz, 1 H, vinyl), 7.25 (t, 1 H, aryl). Anal. Calcd for $C_{17}H_{26}INO$: C, 52.72; H, 6.77; N, 3.62; I, 32.77. Found: C, 52.96; H, 6.91; N, 3.80; I, 32.50. Reactions conducted similarly in ethanol, acetonitrile, and ether also gave **8**.

(±)-4-(3-Methoxyphenyl)-1,3-dimethyl-4-piperidinol (10). 3-Anisyllithium prepared from reaction of 85 g (0.45 mol) of 3-bromoanisole (Aldrich Chemical Co.) in 200 mL of dry THF and 590 mL of *sec*-butyllithium (0.97 M in cyclohexane, 0.57 mol) according to the preceding procedure (for **5**) was cooled to −78 °C, and 50 g (0.39 mol) of 1,3-dimethyl-4-piperidone (**9**)[22] in 125 mL of THF was added slowly so as to keep the temperature below −70 °C. After being stirred for 15 min the reaction mixture was allowed to warm to −20 °C over 1 h and then quenched with brine. The product was isolated by aqueous extractive workup (methylene chloride) as described for **5**. Crystallization from about 400 mL of hexane afforded 72.7 g (84%) of piperidinol **10**, mp 128.5–130 °C. An analytical sample was obtained from EtOAc–hexane: mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 0.61 (d, 3 H, CCH_3), 1.7 (m, 1 H), 2.0–2.34 (m, 4 H), 2.28 (s, 1, OH), 2.32 (s, 3 H, NCH_3), 2.46–2.81 (m, 2 H), 3.79 (s, 3 H, OCH_3), 6.8–7.3 (m, 4 H, aryl); ^{13}C ($CDCl_3$) δ 12.2(q), 39.2 (d), 40.5 (t), 46.1 (q), 51.5 (t), 55.1 (q), 58.6 (t), 73.2 (s), 110.1 (d), 111.7 (d), 117.1 (d), 129.1 (d), 149.2 (s), 159.6 (s). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95. Found: C, 71.68; H, 8.79; N, 5.85.

(±)-1,2,3,6-Tetrahydro-4-(3-methoxyphenyl)-1,3-dimethylpyridine (11).[23] A mixture of 5.0 g (21 mmol) of **10** and 10.1 g (53 mmol) of *p*-toluenesulfonic acid in 100 mL of toluene was heated under reflux for 5 h. TLC ($CHCl_3$–MeOH, 10:1, silica gel) of an aliquot indicated complete conversion of starting material. The basic products were extracted into water. The combined aqueous phase was made alkaline with 5 N NaOH (pH 11) and extracted with hexane. The hexane layers were combined, washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent afforded 4.32 g (94%) of a mixture of **11** and **12**, 7:3 by NMR integration of the *C*-methyl signals. HPLC purification of 4.3 g of the crude product (silica gel, preconditioned with $CHCl_3$–MeOH–diethylamine, 97:3:0.2; elution with $CHCl_3$–MeOH, 97:3) afforded 2.24 g of purified **11**: bp 100–104 °C (0.2 Torr); ^1H NMR ($CDCl_3$) δ 1.00 (d J = 7 Hz, 3 H, CCH_3), 2.38 (s, 3 H, NCH_3), 2.4 (m, partially obscured, 1 H), 2.66 (m, 1 H), 2.8 (m, 1 H), 3.04 (br d, J = 3.4 Hz, 2 H), 3.80 (s, 3 H, OCH_3), 5.85 (t, 1 H, vinyl), 6.7–7.3 (m, 4 H, aryl). Hydrobromide, mp 145–146 °C (EtOH–Et_2O). Anal. Calcd for $C_{14}H_{20}BrNO$: C, 56.39; H, 6.76; N, 4.70; Br, 26.79. Found: C, 56.29; H, 6.52; N, 4.83; Br, 26.58.

1,2,3,6-Tetrahydro-4-(3-methoxyphenyl)-1,5-dimethylpyridine (12).[23] A mixture of 30 g of 85% H_3PO_4 and 33 g of P_2O_5 was mixed with warming until homogeneous. Then 5.0 g (23 mmol) of **10** was added, and the mixture was heated to 100 °C for 5 h. The mixture was poured into excess water and stirred until clear, then made basic (pH 9) with 28% ammonium hydroxide and extracted with hexane. The extract layers were washed with water and brine and dried (Na_2SO_4). Evaporation of solvent afforded 3.46 g (75%) of crude **12**, shown by NMR analysis (integral of ring methyl signals) to be a 9:1 mixture of **12** and **11**. Preparative HPLC of 3.4 g (silica, $CHCl_3$–MeOH, 97:3, 0.2% Et_2NH) afforded 1.5 g of purified **12**: ^1H NMR ($CDCl_3$) δ 1.57 (s, 3 H, CCH_3), 2.39 (s, 3 H, NCH_3), 2.4 (m, 2 H), 2.58 (d, J = 4.3 Hz, 2 H), 2.93 (br s, 2 H), 3.79 (s, 3 H, OCH_3), 6.75 (m, 3 H, aryl), 7.19 (m, 1 H, aryl). Picrate (EtOH) mp 140–141 °C. Anal. Calcd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 53.56; H, 4.85; N, 12.54.

Alkylation of 11 with *n*-Butyllithium–Propyl Bromide. (±)-*trans*-1,2,3,4-Tetrahydro-1,3-dimethyl-4-(3-methoxyphenyl)-4-propylpyridine (14). To a solution of 435 mg (2.0 mmol) of **11** in 6 mL of THF cooled to −15 to −20 °C was added 2.0 mL of *n*-butyllithium in hexane (1.5 M, 3.0 mmol). After 15 min, the dark red solution thus obtained was cooled to −60 °C and treated with 370 mg (3.0 mmol) of 1-bromopropane. After being stirred for 45 min the mixture was allowed to warm to about −10 °C and then quenched with water. The mixture was concentrated under vacuum, and the residue was partitioned between hexane and water. The hexane layers were combined, washed with brine, and dried (Na_2SO_4). The solution was filtered through a short column of silica gel, eluting with $CHCl_3$–MeOH, 9:1 (100 mL). Evaporation of the solvent afforded 482 mg of **14** (93%, oil), purity estimated to be >90% by NMR and TLC ($CHCl_3$–MeOH, 9:1); microdistillation of a 330-mg portion of the crude afforded 220 mg: bp 90–98.5 °C (0.05 Torr); ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (d, J = 7 Hz, 3 H), 0.87 (t, 3 H), 1.1 (m, 1 H), 1.36 (m, 1 H), 1.68 (m, 1 H), 1.95 (m, 2 H), 2.40 (m, 1 H), 2.65 (s, 3 H), 2.69 (m, 1 H), 3.80 (s, 3 H), 4.46 (d, J = 8 Hz, 1 H), 6.01 (d, J = 8 Hz, 1 H), 6.70 (m, 1 H), 6.95 (m, 2 H), 7.20 (t, 1 H); IR ($CHCl_3$) 1648, 1667 cm^{-1}; MS 259 (M^+), 216 (100). Tetrafluoroborate (EtOH), mp 150–151 °C. Anal. Calcd for $C_{17}H_{26}BF_4NO$:

(22) Howton, D. R. *J. Org. Chem.* **1945**, *10*, 277.

(23) The neurotoxic potential of **11** and **12** was compared to **6** in a study in mice according to the protocol of ref 21. Doses of 80 mg/kg of **11** or **12** did not cause depletion of striatal dopamine levels, although **12** showed slight depletion of two dopamine metabolites, (3,4-dihydroxyphenyl)acetic acid and homovanillic acid. At the same dose, **6** caused 82% depletion of striatal dopamine and comparable effects on dopamine metabolite levels. Fuller, R. W.; Hemrick-Luecke, S. K., Lilly Research Laboratories, unpublished data.

C, 58.81; H, 7.55; N, 4.03. Found: C, 59.09; H, 7.30; N, 4.02.

(±)-1,2,3,4-Tetrahydro-4-(3-methoxyphenyl)-1,5-dimethyl-4-propylpyridine (2) via Alkylation of 12. To a solution of 45.7 g (0.21 mol) of crude **12** (containing about 10% of **11**) in 450 mL of dry THF (−15 °C, under N_2) was slowly added 217 mL (0.315 mol) of 1.46 M *sec*-butyllithium in cyclohexane. After being stirred for 0.5 h the mixture was cooled to −70 °C, and a solution of 51.7 g (0.42 mol) of 1-bromopropane in 750 mL of ether was slowly added. After being stirred 45 min the mixture was warmed to −20 °C and quenched with excess water. The layers were separated, and the aqueous phase was extracted with additional ether. The combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was removed under vacuum, affording 52.3 g of crude **2**, shown to contain 78.6% **2**, 9.4% **14**, 5.8% of an unknown component, and 4.2% **12**, the starting material, by GC analysis. The products were identified by GC and NMR comparison with authentic samples. GCMS analysis of a sample prepared under similar conditions indicated that the unknown component was isomeric with **2**.

Reduction of 2 Prepared from 12. A 1.0-g sample of crude **2** obtained from the previous experiment was subjected to catalytic hydrogenation over 0.5 g of 5% Pd/C in 50 mL of triethylamine in a Parr apparatus at an initial pressure of 50 psi. Filtration of the catalyst and evaporation of the solvent afforded 1 g of crude product. GC analysis indicated that the ratio of the two major components, picenadol methyl ether (**16**) and the trans diastereomer **13**, was 60:40.

Reaction of 7 with Excess Formaldehyde. (±)-4-(3-Methoxyphenyl)-1,3-dimethyl-4-propyl-3-piperidinemethanol (17). A 10-g sample of **7** was mixed with 150 mL of 37% formalin and heated to 100 °C for 5 h, according to a literature procedure.[15] Upon cooling, basification (NaOH), and extractive workup there was obtained 12.29 g of **17** as a viscous oil. TLC indicated two similar components, NMR (partial, $CDCl_3$) 0.61 (s), 0.66 (s), ratio of integrals 37:63; 2.24 (s) and 2.26 (s), similar ratio. The predominant component was isolated by flash chromatography (silica gel, EtOAc–MeOH, 6:4) or by formation of the picrate salts of the crude material, repeated recrystallization (EtOH), and recovery of the base (**17**) by neutralization: mp (free base) 93–95 °C; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3 H), 0.85 (m, 1 H), 0.87 (t, 3 H), 1.10 (m, 1 H), 1.67 (dt, 1 H), 1.85 (br t, 1 H), 1.95–2.08 (m, 1 H), 2.26 (s, 3 H), 2.28 (m, partially obscured, 1 H), 2.55 (dd, J = 12, 1 Hz, 1 H), 2.68 (dd, J = 12, 1 Hz, 1 H), 2.80 (m, 1 H), 3.05–3.30 (m, 1 H), 3.21 (s, 2 H), 3.80 (s, 3 H), 5.86 (br s, 1 H), 6.74–7.25 (m, 4 H, aryl); MS 291 (M^+), 276 ($M - CH_3$), 260 ($M - CH_2OH$), 114 (base peak). Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 73.90; H, 10.17; N, 4.52. The minor isomer was not obtained in completely purified condition, MS 291 (M^+).

(±)-1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-*N*,*N*,1-trimethyl-4-propyl-3-pyridinemethanamine (15) via Eschenmoser's Salt. To a slurry of 0.91 g (5.1 mmol) of Eschenmoser's salt (N,N-dimethylmethyleneammonium iodide, Aldrich Chemical Co.)[18] in 7 mL of dichloromethane stirred under nitrogen at room temperature was added 1.0 g (4.08 mmol) of **7** in 3 mL of dichloromethane. The mixture was stirred for 2.5 h, whereupon TLC (silica gel, MeCN/28% NH_3/MeOH, 8:1:1) indicated complete reaction. Excess solid $NaHCO_3$ was added to neutralize HI. The resulting mixture was washed with 1 N NaOH, water, and saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded 1.11 g of **15** as an oil: bp (short path) 117–138 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H), 2.17 (s, 6 H, $N(CH_3)_2$), 1.34–2.57 (m, 7 H), 2.46–2.78 (m, partially obscured, 3 H), 2.63 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.10 (s, 1 H, vinyl), 6.7–7.2 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.9 (q), 18.1 (t), 36.3 (t), 40.2 (t), 43.0 (q), 43.5 (s), 45.8 (q), 46.3 (t), 55.1 (q), 60.8 (t), 109.0 (s), 110.3 (d), 114.3 (d), 120.7 (d), 128.5 (d), 136.6 (d), 151.7 (s), 159.2 (s); MS m/z calcd for $C_{19}H_{30}N_2O$ 302.2376, found 302.2394.

Preparation of 15 by a Modified Mannich Procedure. To a solution of 10 g (0.123 mol) of 37% formalin and 15 g (0.133 mol) of aqueous dimethylamine in 100 mL of H_2O was adjusted to pH 3–4 by addition of concentrated sulfuric acid. A solution of 25 g (0.102 mol) of **7** in 50 mL of hexane was extracted with 40 mL of 2.5 M sulfuric acid, and the aqueous extract was added to the formaldehyde–dimethylamine solution. The pH was adjusted to 3–3.5 by addition of sulfuric acid or dimethylamine as necessary, and the mixture was heated to 65–70 °C for 2 h while maintaining pH in the desired range 3–3.5. The mixture was cooled, made basic with NaOH, and extracted with 2 × 50 mL of hexane. The hexane extracts were washed with 5 × 50 mL of water and 1 × 50 mL of saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent under vacuum afforded 28.4 g (92%) of **15** as an oil, found to be identical in all respects with material prepared by reaction of **7** with Eschenmoser's salt.

Reduction of 15. A Parr hydrogenation bottle was charged with 5 g of 5% Pd on $CaCO_3$ (5% Pd/C was also suitable) followed by a solution of 10 g of **15** in 200 mL of triethylamine. The vessel was pressurized with 60 psi of H_2 and agitated for 16 h. The catalyst was removed by filtration, and the solvent was removed by concentration under reduced pressure, affording 8.08 g of crude product found by GC analysis (FFAP 3% on G C Q, 5 ft × 4 mm, program temperature 190–240 °C at 8 °C/min) to contain 67.2% of picenadol methyl ether (**16**) and 30.8% of the trans diastereomer **13**, ratio 69:31. The products were identified by chromatographic comparison with authentic samples of **16** and **13** prepared by literature methods.[2]

Demethylation of 13–16. A mixture of 5 g of picenadol methyl ether (**16**) and its trans diastereomer **13** (ratio 69:31) in 12.5 mL of 48% aqueous hydrobromic acid was heated at reflux for 6 h. The mixture was cooled and neutralized to pH 8 with ammonium hydroxide. The resulting suspension was extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation under vacuum afforded 3.6 g of crude picenadol base (**1**) and its trans diastereomer (**18**) (cis/trans = 7:3 by GC). The yield of **1** was about 76% based on the amount of **16** contained in the starting material.

Separation of Picenadol as the Free Base. A 3.64-g mixture of **1** and **18** (63% **1**, 32.3% **18**; 66:34 by GC analysis), prepared as in the preceding experiment, was dissolved in 20 mL of EtOAc, the volume was reduced to about 8.5 mL, and 25 mL of acetonitrile was added. The mixture was cooled to room temperature with stirring and then cooled to 5 °C overnight. Filtration of the crystals and drying afforded 1.4 g (61% based on analysis of crude) of picenadol base (**1**), mp 156–160 °C (lit.[2] mp 167–169.5 °C). HPLC analysis revealed the presence of 2% of **18**. Further purification could be effected by recrystallization as either the free base (EtOAc/MeCN) or the hydrochloride salt (water or ethanol).

Separation and Purification of Picenadol via the Hydrochloride Dihydrate. A mixture of the bases **1** and **18** (7:3), 3.6 g, was dissolved in 15 mL of 1 N HCl with warming to 80 °C and filtered hot. Upon cooling, the precipitated material was collected by filtration and dried, affording 2.3 g of picenadol (**1**) hydrochloride dihydrate (70% of **1** available from the crude product), mp 100 °C dec. HPLC analysis indicated that less than 0.5% of **18** was present. Recrystallization of the dihydrate from about 4 vol of EtOH afforded crystals of picenadol (**1**) as the anhydrous hydrochloride, mp 215–217 °C, determined to be identical in both chemical properties and biological activity with material prepared by literature methods.[2]

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