DIASTEREOSELECTIVE CONJUGATE ADDITION APPROACH TO PICENADOL AND OXYGENATED ANALOGUES†

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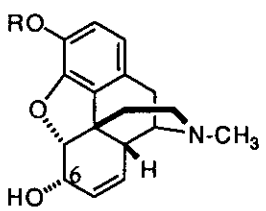
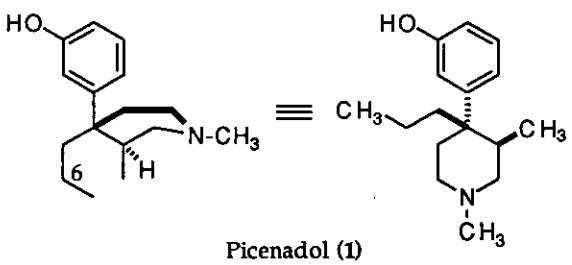
Abstract - *Horner-Emmons-Wadsworth reaction with 1,3-dimethyl-4-piperidone in water afforded an exocyclic enone, with minimal deconjugation of the double bond. Copper catalyzed conjugate addition with an aryl Grignard reagent then afforded an adduct with high stereocontrol. Wolff-Kischner reduction and deprotection proceeded to provide picenadol (1) in excellent overall yield. Access to oxygenated analogues of picenadol was also accomplished with this approach.*

INTRODUCTION.

Picenadol (1) is a racemic mixture in which the *d*-enantiomer exhibits morphine-like agonist activity, and the *l*-enantiomer shows nalorphine-like antagonist activity.[1] Picenadol has high affinity for the μ and δ receptors, but low affinity for the κ receptor, and low potential to produce opiate-like side effects, including abuse and dependence. The pharmacology of both picenadol enantiomers and diastereomers was studied in detail.[1,2] This unique opioid, resulting from extensive investigations on the analgesic properties of the 4-phenylpiperidine



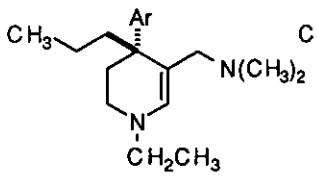
R = H Morphine
R = OCH_3 Codeine



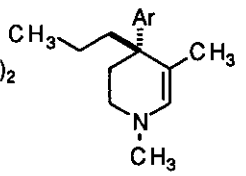
Picenadol (1)

series, underwent thorough clinical evaluation. The structural similarities of picenadol with morphine is shown above, and substantial structure-activity-relationship research has been reported.[3]

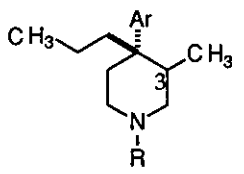
Previous syntheses of picenadol (**1**) have been reported.[1b,4] The tetrahydro-pyridines (**2**) and (**3**), for example, served as a pivotal intermediates in some synthetic strategies. Catalytic hydrogenation of **2** or **3**, however, afforded diastereomeric mixtures of piperidines epimeric at C-3 in varying ratios, thereby necessitating a diastereomer separation protocol. For example, optimal reduction conditions for **2** with 10% Pd/C in heptane provided **4** with 59:31 (α:β-CH_3) selectivity, whereas reduction of **3** with 10% Pd/Al_2O_3 in $(C_2H_5)_3N$ provided **5** with 67:27 (α:β-CH_3) selectivity. The occurrence of this stereorandom step so late in the synthesis was strategically undesirable. Furthermore, the published synthesis of enamine (**3**) employed the bicyclic aziridinium salt (**6**), prepared through a linear multistep scheme utilizing diazomethane and a thermolytic rearrangement thereof.



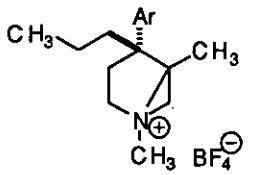
2, Ar = *m*-$CH_3OC_6H_4$



3, Ar = *i*-$C_3H_7OC_6H_4$



4, Ar = *m*-$CH_3OC_6H_4$, R = CH_2CH_3
5, Ar = *i*-$C_3H_7OC_6H_4$, R = CH_3



6, Ar = *m*-$CH_3OC_6H_4$

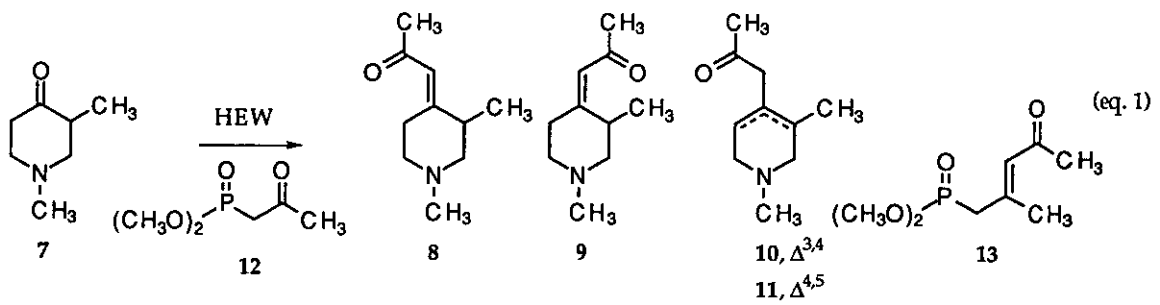
In order to minimize the number of processing steps and obviate undesired diastereomer production, a short, highly stereoselective synthesis of picenadol was sought. Protecting group utilization or interchange at N-1 and the phenol OH would therefore be carefully selected. Additionally, a hidden aspect of the synthetic design was avoidance of neurotoxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) like intermediates, known to induce Parkinson's disease.[5] We envisioned formation of the quaternary center C-4 of picenadol from the well-precedented[6] arylcuprate conjugate addition to an exocyclic enone, and moreover, wanted to exploit the C-3 methyl group directing effect. Thus, since 1,3-dimethyl-4-piperidone (**7**) was a logical and commercially available starting material, a picenadol (**1**) synthesis from this precursor is described.

RESULTS AND DISCUSSION.

As a first goal, the synthesis of the requisite α,β-unsaturated ketones (**8**) and (**9**) was investigated (eq. 1). The reluctance of the 4-piperidone carbonyl moiety to undergo Wittig olefination was established in 1960 by Sugasawa and Matsuo.[7] The reported Wittig reaction of substituted piperidones with ylides required several days at ambient temperature. The more reactive

Horner-Emmons-Wadsworth (HEW) phosphonoacetate ester reagents, however, have been shown to react readily with a variety of piperidones[8] although yields were moderate and olefin isomerization was significant. Only limited examples of the reaction of piperidones with keto phosphonate (**12**) have appeared,[8a] perhaps due to facile olefin isomerization under the reaction conditions described above.[9] Bosch and coworkers obtained a 1:1 to 4:1 double bond mixture from reaction of 1-benzyl-4-piperidone or 1-methyl-4-piperidone with **12** (NaOH / EtOH / 5 °C → ambient), and reported that the *N*-benzyl substrate gave less olefin isomerization.[8c] A 1:1 endocyclic:exocyclic olefin mixture (**8** + **9** : **10** + **11**) was obtained under the classical conditions of NaH/DME with keto phosphonate (**12**) and piperidone (**7**) in 40% yield. NaH in dipolar aprotic solvents or metal alkoxides in alcohol produced similar results. Replacement of the *N*-methyl moiety with an *N*-toluenesulfonyl group afforded higher yields and improved endo:exo olefin ratios, as did alternative *N*-protecting groups which made N-1 less basic. Furthermore, competing self-condensation of the keto phosphonate (**12**) occurred to produce enone phosphonate isomers (**13**).

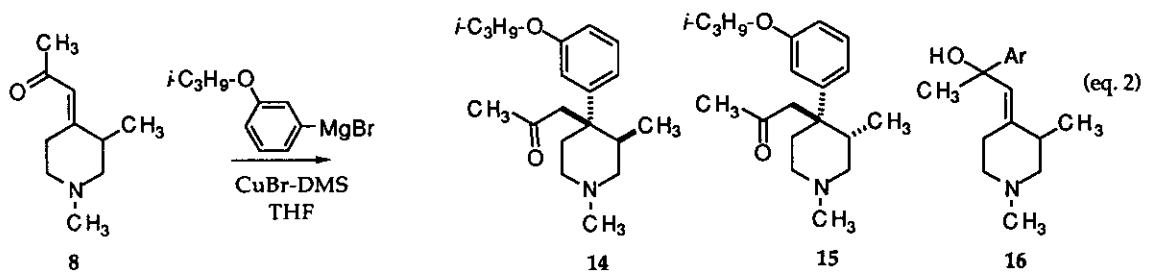
In alcohol medium, hydrated metal hydroxides (MOH, M = Li, Na, K) afforded slightly better yields and enhanced endo:exo ratios than the anhydrous forms, thereby suggesting water added to the reaction mixture might be advantageous. Thus, HEW reaction in 20% aqueous EtOH propagated the observed trend, up to pure water as the solvent medium, which provided an optimal product profile. Addition of the keto phosphonate (**12**)[10] to an aqueous KOH solution at -5 °C (±3 °C), followed by 1,3-dimethyl-4-piperidone (syringe pump) with continued stirring at -5 °C for 40 h provided, in nearly quantitative yield, enone (**8**) as a 9 : 1 mixture of **8** : **7**, and <3% total endocyclic compounds **10** + **11**. Formation of the undesired self-condensation by-product (**13**) was also suppressed under these conditions. Interestingly, exocyclic enone geometry was maintained during the course of the HEW reaction when the temperature was kept at -5 °C. Extended reaction times were not detrimental to the double bond integrity however, and the reaction could almost be driven to completion. The enone (**8**) was stable under neutral



(eq. 1)

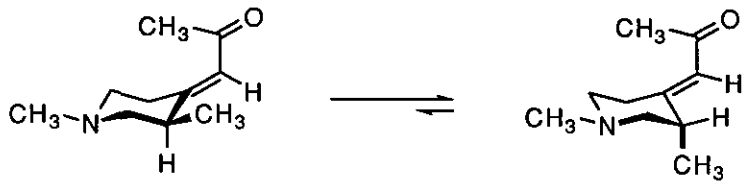
conditions and could be stored at -15 °C for month periods. Thermodynamic equilibration under basic conditions afforded the $\Delta^{3,4}$-olefin (**10**). The use of water in HEW reactions has been reported to enhance the rate and chemical yield, with some limitations,[11] as has phase transfer catalysis.[12]

Attention was next focussed on the conjugate additions with the enone (**8**) now in hand. The Grignard reagent prepared by reaction of *m*-bromo-*iso*-propoxybenzene with magnesium turnings in THF at reflux for 1.5 h was treated with purified CuBr-S(CH_3)2 compex[13] (15 wt %) at ambient temperature, and the mixture then cooled to 0 °C. The enone was dissolved in THF and added to the freshly generated cuprate at 0 °C, with continued stirring for 30 min. The major isolated product was the desired 1,4-adduct (**14**), which contained <6% of the 1,2-adduct (**16**). We have not been able to isolate and characterize any of the the undesired diastereomer (**15**) (eq. 2). Although the conjugate addition could be conducted at a range of temperatures from -30 °C to 0 °C, it was convenient to operate at 0 °C. Furthermore, the optimal chemical yield of 80% for adduct (**14**) was obtained by using the crude enone (**8**). Added TMSCl / HMPA,[14] $BF_3 \bullet (C_2H_5)_2O$,[15] or the use of a variety of other organocopper reagents[16] proved less satisfactory, often resulting in dismal yields (5-20%) and / or poor 1,4 : 1,2 selectivity.



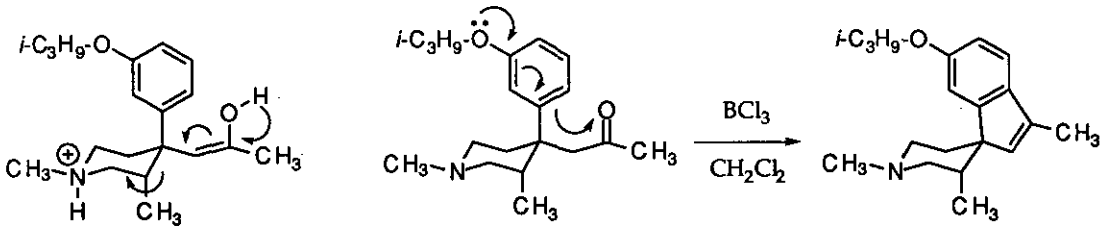
8 **14** **15** **16**

The α, β, β-trisubstituted enone (**8**) would be expected to undergo a slow conjugate addition due to its steric requirements.[17] Therefore, the normal mode for Grignard reaction, a competing 1,2-addition, would be expected to occur as noted above. The analogous *t*-butylcyclohexylidene series, in fact, afforded a 3:1 ratio of 1,4-addition : 1,2-addition with CH_3MgBr and Cu(I) catalysis.[17] Since diastereomeric adduct (**15**) could not be detected, the C-3 methyl group directability proved to be very significant for enone (**8**). Thus, the 1,3-interaction between the C-3-methyl group and the enone moiety forces the methyl group into an axial orientation, thereby blocking one face (eq. 3). Attack from the face anti to the C-3-methyl results in the observed stereochemistry. Alternatively, the conformation with an equatorial C-3-methyl substituent could allow equatorial attack onto the enone with an effectively large cuprate reagent.



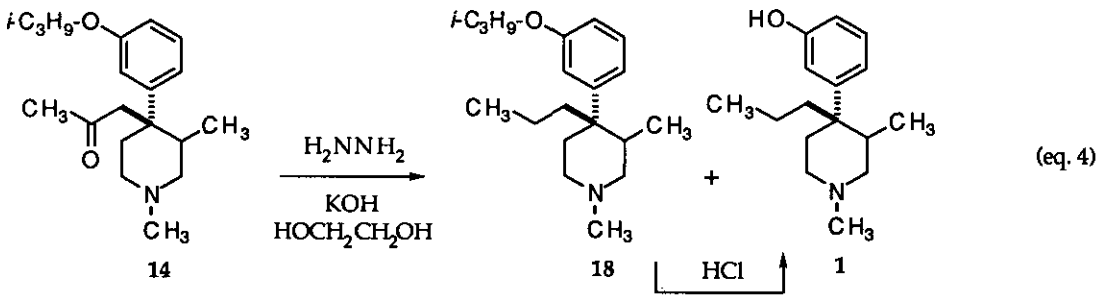
(eq. 3)

Ketone (**14**) proved to be sensitive to acidic conditions at elevated temperatures resulting in degradation, although at ambient temperatures there was no observable reaction. This observation precluded a deoxygenation protocol such as the Clemmensen reduction which utilizes Zn/HCl. One possible explanation for this mode of reactivity could result from the disposition between the ketone and the *N*-methylammonium moiety (**14H**$^+$, protonated under acidic conditions). Enolization, followed by degradative fragmentation would be entropically favored and irreversible. As an alternative, the thioketalization-desulfurization strategy was investigated. Attempted thioketalization of **14** with $BF_3 \cdot (C_2H_5)_2O$ and $HSCH_2CH_2SH$ formed the interesting spirocycle (**17**), resulting from a Friedel-Crafts type reaction, followed by dehydration. BCl_3[18] also effected this intramolecular Friedel-Crafts cyclization in good yield upon attempted deprotection of the phenol moiety.



14H$^+$ **14** **17**

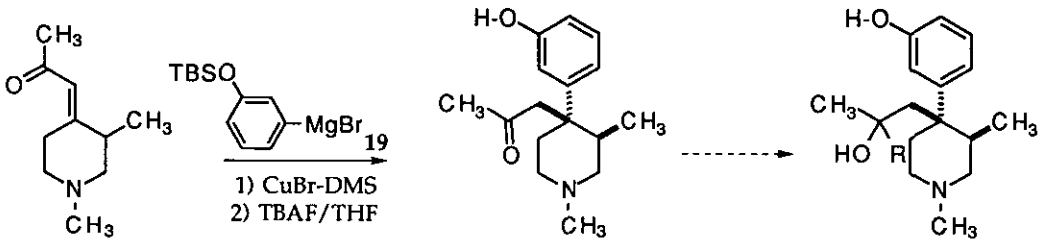
Finally, under basic conditions **14** was well-behaved and Wolff-Kishner reduction[19] proceeded smoothly to afford **18** in excellent yield (eq. 4). Concomitant partial deprotecion of the *i*-propyl moiety had occurred under these conditions, however. Therefore, complete deprotection of **18** with 12N HCl at reflux then provided picenadol (**1**), isolated by direct crystallization of the HCl salt from the reaction mixture. Picenadol itself was obviously quite stable to acid at elevated temperatures, supporting the hypothesis that acid instability of ketone (**14**) was related to the



14 18 1 (eq. 4)

carbonyl moiety disposition. Thus, a four step, highly diastereoselective synthesis for picenadol was accomplished.

The biological activity of these opioid analogues is severely reduced by protection or substitution of the phenolic oxygen. Furthermore, as part of an ongoing structure-activity program, access to 6-keto picenadol and analogues was desirable. However, due to the difficulties with deprotection at the *i*-propyl moiety while maintaining the ketone functionality as described above, an alternative phenol protecting group was implemented. The *t*-butyldimethylsilyl ether of *m*-bromophenol was converted to the corresponding Grignard reagent as before, and subjected to the conjugate addition, followed by desilylation with tetrabutylammonium fluoride (TBAF) to afford keto picenadol (**20**) in 74% overall yield (eq. 5). The keto analogue thus formed could be further derivatized (eg., **21**, R = H, CH_3, Ph) to afford new compounds for biological evaluation.[20]



8 20 21 (eq. 5)

CONCLUSION.

In summary, a facile and highly diastereoselective synthesis of picenadol (**1**) was developed from commercially available starting materials. The chemistry provides a very convergent route with a low number of transformations and no protecting group interchange. The selectivity in the cuprate addition obviates the need for a diastereoisomer separation protocol. Furthermore, the new route has allowed access to a keto-picenadol analogue (**20**), as well as other oxygenated analogues, not heretofore available due to synthetic limitations.

EXPERIMENTAL PART.

General Experimental Procedures. Melting points were determined on a hot-stage microscope and are uncorrected. All experiments were conducted under an atmosphere of nitrogen, unless otherwise noted, and monitored by thin layer chromatography using Merck F254 silica gel plates. All solvents and reagents were used as obtained. ^1H and ^{13}C nmr spectra were obtained on either a GE QE-300 or a Bruker ACP-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Microanalyses were conducted by the Physical Chemistry Department of Lilly Research Laboratories. 1,3-Dimethyl-4-piperidone and 3-bromophenol were obtained from Aldrich Chemical Company; dimethyl 2-oxopropyl phosphonate was obtained from Lancaster Synthesis, Inc.

1-(1,3-Dimethyl-4-piperidylidene)-2-propanone (8/9). To a -8 °C solution of 1,3-dimethyl-4-piperidone (30.0 ml, 0.224 mol) and 28.90 g of 85% KOH (0.438 mol) in 116 ml of H_2O was added dropwise dimethyl 2-oxopropyl phosphonate (62.1 ml, 0.449 mol) at a rate such that the temperature was maintained below 0 °C. After the reaction was stirred for 74 h at -5±3 °C, it was poured into 500 ml 1 N HCl, rinsed three times with Et_2O, made basic (pH = 10) with 5 N NaOH, and extracted three times with CH_2Cl_2. The solvent was removed after drying over Na_2SO_4, and the subsequent cuprate addition was carried out without further purification. An analytical sample could be obtained by careful column (flash) chromatography: R_f 0.48 (SiO_2, 15% MeOH/CH_2Cl_2); ms 168 (M+1); ir ($CHCl_3$) 3010, 1707, 1684, 1618 cm^{-1}; nmr (^1H, $CDCl_3$) 1.08 (d, 3H, J=6.7 Hz), 1.96 (t, 1H, J=9.8 Hz), 2.13-2.22 (m, 1H), 2.21 (s, 3H), 2.26 (s, 3H), 2.43-2.52 (m, 2H), 2.67-2.79 (m, 2H), 3.48 (dt, 1H, J=4.1, 14.0 Hz), 6.00 (s, 1H); (^{13}C, $CDCl_3$) 15.8, 28.1, 31.4, 38.1, 45.1, 56.3, 63.7, 119.5, 160.2, 198.6; uv λ_{max} 236 (ε=9810, EtOH).

***trans*-4-(3-*iso*-Propoxyphenyl)-1,3-dimethyl-4-(2-propionyl)piperidine (14).** To a 1 l Morton flask equipped with a reflux condenser, mechanical stirrer, and a N_2 inlet was added 1-bromo-3-isopropoxybenzene (90.0 g, 0.418 mol) and 430 ml of THF. Magnesium (20.32 g, 0.836 mol) was added portionwise. The initial 9 g portion was freshly crushed before addition, and an exothermic reaction (reflux) began within 30 min. The remaining Mg was added within 1 h, and the reaction was heated at reflux for another 30 min. After the Grignard solution had cooled to ambient temperature, purified CuBr·DMS complex (3.2 g) was added. The mixture was stirred for 3 min at ambient temperature and then cooled to 0 °C. The unpurified enone (32.0 g, estimated by nmr to be 66% pure) in 200 ml of THF was added dropwise over 40 min and then stirred an additional 30 min at 0 °C. An aqueous solution of concentrated NH_4OH (250 ml) and saturated NH_4Cl (250 ml) was added, and the resulting emulsion was filtered through Hyflo before extracting with Et_2O. The product was extracted into the aqueous layer with 1 N HCl and reextracted three times with CH_2Cl_2 after basifying (pH=10-11) with 50% NaOH. The organic

solution was rinsed with brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (SiO_2, 15% MeOH/CH_2Cl_2) provided 55.0 g (81% yield from 1,3-dimethyl-4-piperidone). R_f 0.26 (SiO_2, 15% MeOH/CH_2Cl_2); ms 303 (M^+); ir ($CHCl_3$) 2978, 1719, 1605, 1580 cm^{-1}; nmr (^1H, $CDCl_3$) 0.94 (br s, 3H), 1.31 (d, 6H, J=6.1 Hz), 1.83 (br s, 3H), 2.23 (s, 3H), 2.23-2.43 (m, 7H), 2.68 (d, 1H, J=15.8 Hz), 2.85 (d, 1H, J=15.7 Hz), 4.51 (sept, 1H, J=6.1 Hz), 6.73 (dd, 1H, J=1.7, 8.0 Hz), 6.88-6.91 (m, 2H), 7.21 (t, 1H, J=7.9 Hz); (^{13}C, $CDCl_3$) 14.4, 21.9, 31.8, 31.9, 38.2, 42.0, 46.0, 46.9, 52.0, 58.9, 69.8, 113.1, 115.5, 119.1, 128.9, 146.3, 157.8, 207.4; uv λ_{max} 275 (ε=1610, EtOH).

***trans*-4-(3-*iso*-Propoxyphenyl)-1,3-dimethyl-4-(*n*-propyl)piperidine (18).** To a solution of the ketone (0.970 g, 3.20 mmol) in ethylene glycol (5 ml) was added anhydrous hydrazine (1.0 ml, 32.0 mmol) at ambient temperature. NaOH pellets (1.28 g, 32.0 mmol) were added and the temperature was raised to 150 °C, with vigorous stirring. After 1 h the condenser was removed to allow H_2O to evaporate. The condenser was replaced after the reaction had been heated to 210 °C. Following a 3 h reflux period at 210 °C, the solution was cooled to ambient temperature overnight. The reaction mixture was dissolved in H_2O and 1 N HCl, rinsed with Et_2O (3 x), and the pH adjusted to 10, the product was extracted with CH_2Cl_2 (3 x), dried over Na_2SO_4, and concentrated *in vacuo*. The product was used directly in the following deprotection reaction without further purification.

Spirocyclization of 14. The ketone (**14**) (160 mg, 0.527 mmol) was dissolved in CH_2Cl_2 (1 ml) and cooled to 0 °C under N_2 atmosphere. BCl_3 (1M in CH_2Cl_2, 2.1 ml, 2.1 mmol) was then added dropwise with stirring to afford a dark brown reaction mixture. After stirring for 2.25 h at 0 °C, the reaction was quenched with 1N HCl (2 ml), extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction mixture was chromatographed (SiO_2, 10% CH_3OH/CH_2Cl_2) to afford the spirocyclic indene (**17**) as a white solid (113 mg, 75%). R_f 0.64 (SiO_2, 20% MeOH/CH_2Cl_2); ms 285 (M^+); nmr (^1H, $CDCl_3$) 0.39 (d, 3H, J=6.2 Hz), 1.28 (d, 6H, J=6.2 Hz), 1.46 (m, 1H), 2.09 (s, 3H), 2.87 (m, 7H), 3.40 (m, 1H), 3.60 (m, 1H), 4.57 (sept, 1H, J=6.2 Hz), 6.05 (br s, 1H), 6.78 (dd, 1H, J=2.0, 9.3 Hz), 6.96 (d, 1H, J=2.0 Hz), 7.12 (d, 1H, J=9.3 Hz); uv λ_{max} 270 (ε=10200, EtOH); Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.67; H, 9.51; N, 4.55.

Picenadol (1). To 0.826 g of substrate **18** (3.0 mmol) was added 2 ml of 12 N HCl. After stirring at 120 °C for 2 h and cooling to ambient temperature, the mixture was diluted with H_2O. After rinsing twice with Et_2O, the pH was adjusted to 10-11 with aqueous NaOH. Extraction with CH_2Cl_2 (3 x), desiccation with Na_2SO_4, and concentration gave 0.642 g of crude picenadol. The crude product was dissolved by warming in 2.75 ml of 1 N HCl and cooled slowly overnight to give 0.460 g (54% yield for the reduction and deprotection) of pure, crystalline, picenadol hydrochloride. Nmr (^1H, DMSO-d_6) 0.45 (d, 3H, J=6.8 Hz), 0.96 (br t, 3H, J=6.8 Hz), 1.10 (m, 2H),

1.60 (m, 1H), 1.70 (m, 1H), 1.84 (m, 1H), 2.25 (m, 1H), 2.43 (m, 1H), 2.74 (s, 3H), 2.82-3.35 (m, 3H), 3.26 (m, 1H), 3.49 (s, 3H), 6.62 (m, 1H), 6.75 (m, 2H), 7.10 (m, 1H), 9.42 (br s, 1H); (^{13}C, DMSO-d_6) 12.2 (C_3-CH_3), 14.7 (Pr-CH_3), 16.9 (Pr-CH_2), 26.8 (Pr-CH_2), 30.9 (C_5), 39.1 (C_3), 41.1 (C_4), 42.4 (N-CH_3), 49.7 (C_6), 54.9 (C_2), 113.3 (Ar-C), 114.3 (Ar-C), 117.5 (Ar-C), 129.3 (Ar-C), 146.5 (Ar-C_i), 157.5 (Ar-C-OH); ir (KBr) 3354 (br), 2694 (br), 1600 (w), 1470, 1458, 1253 cm^{-1}; Anal. Calcd for $C_{16}H_{26}NOCl$: C, 67.70; H, 9.23; N, 4.93. Found: C, 67.70; H, 9.24; N, 5.00. This material was identical in all respects to material previously prepared: (see reference 4).

1-*t*-Butyldimethylsilyloxy-3-bromobenzene (19). A solution of *t*-butyldimethylsilyl chloride (15.07 g, 0.10 mol) and imidazole (9.53 g, 0.14 mol) in anhydrous DMF (75 ml) was treated dropwise at ambient temperature with a solution of *m*-bromophenol (17.3 g, 0.10 mol) in DMF (25 ml) under a $CaCl_2$ filled drying tube. A slight exotherm was noted, and after 20 h at ambient temperature the reaction was diluted with hexane (200 ml) and washed successively with water (3 x 100 ml) and brine (100 ml), and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the product thus obtained was used directly in the subsequent reaction.

***trans*-4-(3-Hydroxyphenyl)-1,3-dimethyl-4-(2-propionyl)piperidine (20).** The bromide **19** (5.60 g, 19.5 mmol) was dissolved in THF (20 ml) and treated with Mg turnings (950 mg, 39.0 mmol). The mixture was brought to reflux under N_2 atmosphere for 5 h. After the Grignard solution had cooled to ambient temperature, purified CuBr·DMS complex (151 mg, 15 wt %) was added. The deep purple heterogeneous mixture was stirred for 3 min at ambient temperature and then cooled to 0 °C. The unpurified enone (1.51 g, estimated by nmr to be 66% pure) in 10 ml of THF was added dropwise over 45 min and then stirred an additional 30 min at 0 °C. An aqueous solution of concentrated NH_4OH (250 ml) and saturated NH_4Cl (250 ml) was added, and the resulting emulsion was filtered through Hyflo before extracting with Et_2O. The product was extracted into the aqueous layer with 1 N HCl and reextracted three times with CH_2Cl_2 after basifying (pH=12) with 50% NaOH. The organic solution was rinsed with brine, dried over Na_2SO_4, and concentrated. Since the product was a mixture of partially desilylated compounds, the crude mixture was subjected to excess tetrabuylammonium fluoride in THF solution. Upon complete desilylation (45 min), the THF was evaporated and the residue was redissolved in CH_2Cl_2. The organic phase was rinsed with aqueous saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the product was purified by column chromatography (SiO_2, 15% MeOH/CH_2Cl_2) to provide 1.15 g (74% overall yield). Nmr (^{1}H, $CDCl_3$) 0.79 (br s, 3H), 1.91 (br s, 3H), 2.04-2.41 (m, 4H), 2.94 (s, 3H), 2.61 (m, 4H), 2.92 (m, 1H), 6.64 (d, 1H, J=7.5 Hz), 6.67 (d, 1H, J=7.5 Hz), 6.82 (s, 1H), 7.07 (m, 1H), 7.58 (br s); (^{13}C, DMSO-d_6) 14.2, 32.1, 31.5, 39.0, 41.8, 45.7, 51.8, 58.4, 113.1, 114.4, 117.6, 129.0, 146.7, 157.4, 207.2 (one CH_2 not observed); Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.70; H, 8.54; N, 5.01.

†Dedicated to Professor E. C. Taylor on the occasion of his 70th birthday.

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