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A CONCISE, STEREOSELECTIVE SYNTHESIS OF PICENADOL

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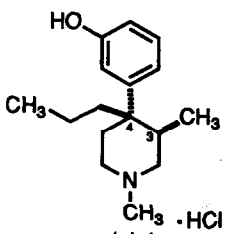
Summary: *A four-step stereoselective synthesis of picenadol (1) is reported. 1,3-Dimethyl-4-piperidone (3) underwent Horner-Wadsworth-Emmons reaction under conditions that did not yield double-bond isomerization, followed by a directed 1,4-addition with an aryl cuprate. Reduction and deprotection then afforded (1).*

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] This unique opioid resulted from extensive investigations on the analgesic properties of the 4-phenylpiperidine series, and is currently undergoing clinical evaluation. Previous syntheses of picenadol (**1**) have been reported.[1b,2] The tetrahydropyridine **2**, for example, has served as a pivotal intermediate in these syntheses. Catalytic reduction of **2**, however, afforded a diastereomeric mixture of piperidines epimeric at C.3 in varying ratios, thereby necessitating a separation protocol. It was desirable to develop a short synthesis of picenadol with a higher degree of stereochemical control. 1,3-Dimethylpiperidone (**3**) was a logical and readily available starting material. We envisioned formation of the quaternary center C.4 of picenadol from the well-precedented[3] conjugate addition of an aryl cuprate to an exocyclic enone, and moreover, wanted to take advantage of the directing effect of the C.3 methyl group. We report herein the successful realization of this strategy.



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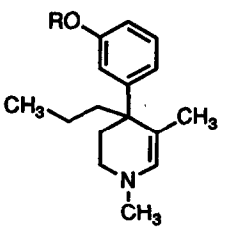

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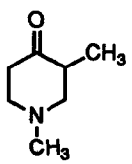

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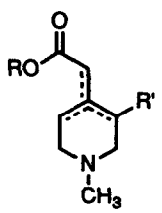

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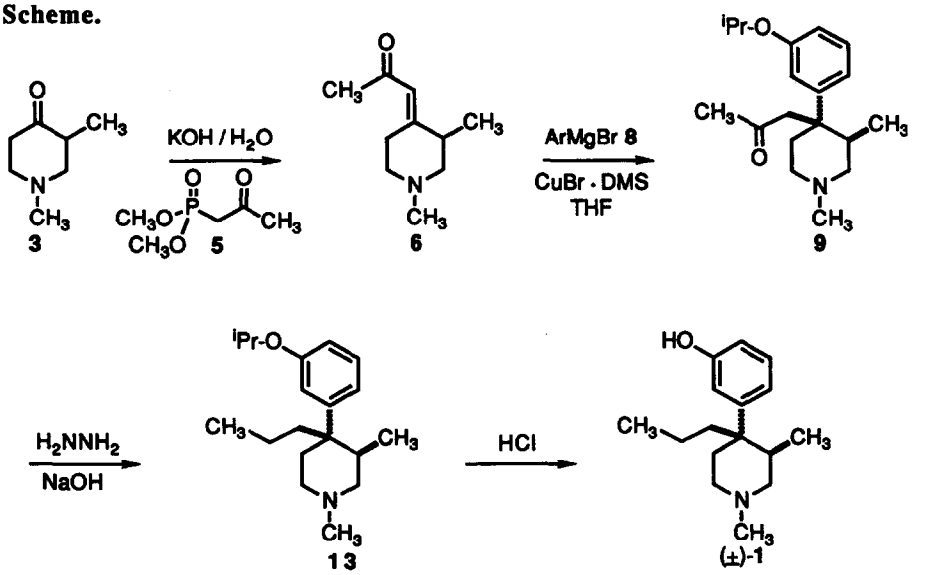
The reluctance of the 4-piperidone carbonyl moiety to undergo Wittig olefination was established in 1960 by direct comparison with the cyclohexanone series.[4] The Horner-Wadsworth-Emmons modification has also been reported for the reaction of 1-alkyl 4-piperidones with phosphonoacetate esters, although yields were moderate and exocyclic to endocyclic isomerization was significant (cf, **4** R'=H, above).[5] Only limited examples of reaction with the ketophosphonate **5** have appeared,[3b] presumably due to facile product isomerization under the reaction conditions.[6] We observed substantial quantities (>20%) of **7** using the classic reaction conditions, such

as NaH in ether solvents or dipolar aprotic media, or alkoxide in alcohol. In addition, a competing self-condensation of the ketophosphonate **5** was also found to occur.

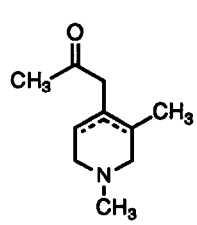
Bosch and co-workers obtained a 1:1 to 4:1 mixture of double bond isomers from the reaction of 1-benzyl-4-piperidone or 1-methyl-4-piperidone with ketophosphonate **5** (NaOH / EtOH / 5 °C to room temp),[7] but found the N-benzyl substrate gave less isomerization. In order to minimize any protecting group manipulation, the N-methyl substituted derivative **3** was viewed as the only option. We noticed a subtle difference in the product profile between reactions using hydrated base, MOH (M = Li, Na, K), and the anhydrous form in alcohol solution. Interestingly, we added water to the reaction mixture[8] in order to obtain a completely homogeneous reaction medium, and found that the olefination proceeded, but observed a decrease in double bond migration concomitant with a decrease in reagent self-condensation. It was eventually determined that the olefination was optimal in H_2O solution (Scheme): The ketophosphonate **5** (2 equiv)[9] was added dropwise to a solution of KOH (1.95 equiv) in H_2O at -5 °C (±3 °C), followed by 1,3-dimethylpiperidone (syringe pump) with continued stirring at -5 °C for 40 h. After extractive workup,[10] the enone **6** was isolated as a 9 : 1 mixture of **6** : **3**, and <3% total endocyclic compounds **7**, with nearly quantitative recovery. Extended reaction times were not detrimental to the double bond integrity, and the reaction could almost be driven to completion. The enone **6** was stable under neutral conditions and could be stored at -15 °C for month periods, but the temperature appeared to be critical during the reaction. The isolated enone **6** when subjected to thermodynamic equilibration (under basic conditions) resulted in formation of the tetrasubstituted olefin (i.e., **7**, Δ^3 isomer).

Scheme.



With the enone **6** in hand, we next investigated the conjugate addition. The Grignard reagent **8** was prepared by reaction of *m*-bromo-*iso*-propoxybenzene with magnesium turnings in THF at reflux for 1.5 h. Purified

CuBr-SMe_2 compex[11] (15 wt %) was then added at room temperature, and the mixture cooled to 0 °C after 3 min. The enone was added as a THF solution at 0 °C, and the reaction was complete within 30 min. The major product was the desired 1,4-adduct **9**, which contained <6% of the 1,2-adduct **11**. We have not been able to isolate and characterize any of the the undesired epimer **10** (below), however. As expected,[3] the conjugate addition gave a high degree of selectivity favoring the cis product (relationship of the 3-methyl and 4-(2-propionyl) moieties). Although the conjugate addition could be conducted at a range of temperatures[12] from -30 °C to 0 °C, it was convenient to operate at 0 °C. Furthermore, added TMSCl / HMPA,[13] BF_3·Et_2O,[14] or the use of a variety of other organocopper reagents[15] proved less satisfactory, often resulting in dismal yields (5-20%) and / or poor 1,4 : 1,2 ratios. The reaction of aryl magnesium bromide **8** with enone **6** in the absence of any copper species underwent only 1,2-addition to form **11**. Furthermore, the best chemical yields of adduct **9** were obtained by using the crude enone **6**: 81% chromatographed yield of **9**[16] (two steps, 30 g scale).



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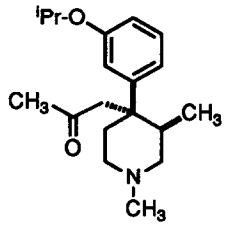

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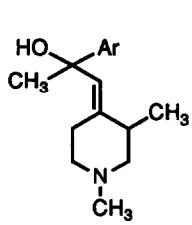

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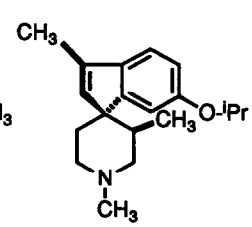

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Clemmenson reduction[17] of **9** with Zn powder in HCl solution resulted in severe degradation of the piperidine ring. Although adduct **9** was acid stable at ambient temperatures, it was acid sensitive at higher temperatures. The disposition between the carbonyl and the amine could allow for a degradative fragmentation, resulting in a variety of olefinic products (NMR). Attempted deprotection of the phenolic oxygen of **9** by reaction with BCl_3[18] caused Friedel-Crafts cyclization to afford **12** in good yield. Likewise, attempted thioketalization of **9** with BF_3·Et_2O and $HSCH_2CH_2SH$ also formed **12**. Wolff-Kishner reduction[19] proceeded smoothly, however, to afford **13** in 93% yield (Scheme). Deprotection of **13** with conc HCl[20] at reflux then provided picenadol (**1**), isolated at the HCl salt (86% yield). The material obtained by this route was identical with an authentic sample in every respect.[21]

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(8) For a discussion of the use of water in the Horner-Wadsworth-Emmons reaction, see: Mouloungui, Z.; Delmas, M.; Gaset, A. *J. Org. Chem.* **1989**, *54*, 3936.

(9) We have not determined the actual reacting phosphorous species, since hydrolysis of at least one phosphonate ester was possible: Westheimer, F.H.; Huang, S.; Covitz, F. *J. Am. Chem. Soc.* **1988**, *110*, 181.

(10) The aqueous solution was acidified and washed with ether to remove reagent by-products. The enone **6** was extracted into methylene chloride after the pH was made basic. The excess reagent **5** remained in the aqueous layer at basic pH. Purification could be accomplished by flash chromatography or vacuum distillation (58-70 °C / 0.7 mm Hg). 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).

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(16) The reaction was quenched with NH_4Cl/NH_4OH and isolated by extraction into organic solvent. The basic product was extracted into acid to remove excess reagents. Final purification was by column chromatography over SiO_2 with 20% CH_3OH / CH_2Cl_2. 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=6.1Hz), 1.83 (br s, 3H), 2.23 (s, 3H), 2.23-2.43 (m, 7H), 2.68 (d, 1H, J=15.8Hz), 2.85 (d, 1H, J=15.7 Hz), 4.51 (sept, 1H, J=6.1Hz), 6.73 (dd, 1H, J=1.7, 8.0Hz), 6.88-6.91 (m, 2H), 7.21 (t, 1H, J=7.9Hz); (^{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).

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(20) Dr. Mary Peters, Eli Lilly & Company, private communication.

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