Tetrahedron Letters,Vol.24,No.43,pp 4653-4656,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

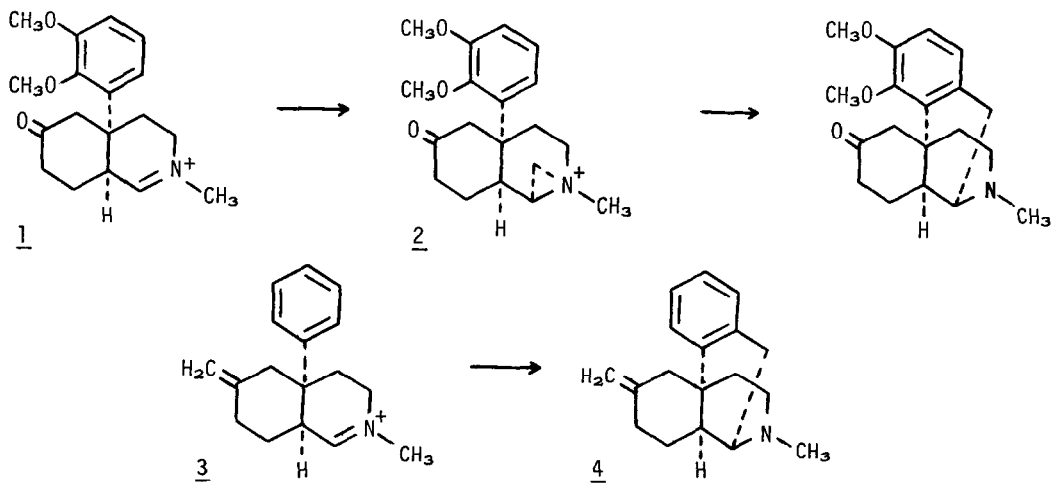
TOTAL SYNTHESIS OF O-METHYLPALLIDININE

by
John E. McMurry* and Vittorio Farina
Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, NY 14853

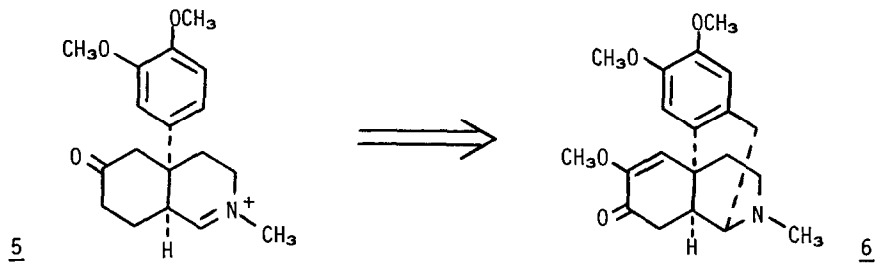
Abstract: O-Methylpallidinine, a recently isolated morphinan alkaloid, has been synthesized in 16 steps from 1,4-cyclohexanedione and 3-bromoveratrole. The synthesis employs a new method for preparing the morphinan skeleton in which diazomethane is added to an aryloctahydroquinolinium salt.

We have been interested for some years in devising general synthetic pathways to the morphine alkaloids. In view of the large amount of work already done in this area[1], we have sought in our own work to explore new chemistry and to create routes fundamentally different from those known.

Our basic idea involved construction of the morphinan nucleus by addition of diazomethane to an iminium ion such as **1**, yielding an aziridinium ion[2] that could undergo intramolecular nucleophilic attack by the appropriately positioned aromatic ring. The product of such a cyclization could be easily transformed into morphine by known chemistry[3,4]. Upon synthesis of **2** by treatment of iminium perchlorate **1** with diazomethane, however, we found that the desired reaction did not occur. Although **2** could be prepared in good yield, we were unable to find conditions that would effect its cyclization[5]. Evans, in independent work on a related system, found similar results[6]. In model work for his morphine synthesis, however, Evans discovered[7] the interesting fact that a morphinan product was formed directly in 30% yield from reaction of diazomethane with the iminium ion **3**, which contains an unsubstituted aromatic ring.



Why does **3**, which contains an unsubstituted aromatic ring, yield morphinan more readily than **1**, which contains a more nucleophilic dimethoxy-substituted ring? After extensive experimentation, we have concluded[8] that it is the C4 (morphine numbering) methoxyl group of **1** that is causing the problems. We believe that the oxygen lone-pair electrons of the C4 methoxyl group of **1** interfere with the desired cyclization by reacting with the intermediate diazonium ion produced by addition of diazomethane. If this C4 methoxy substituent were absent, morphinan formation should ensue. We have now tested this hypothesis in the context of a successful total synthesis of O-methylpallidinine **6**, a B/C-trans morphinan recently isolated[9] by Vecchietti from leaves of the South American plant Ocotea acutangula (Mez). Since O-methylpallidinine is unsubstituted at C4, it should be accessible from iminium ion **5** by reaction with diazomethane if our hypothesis is correct.

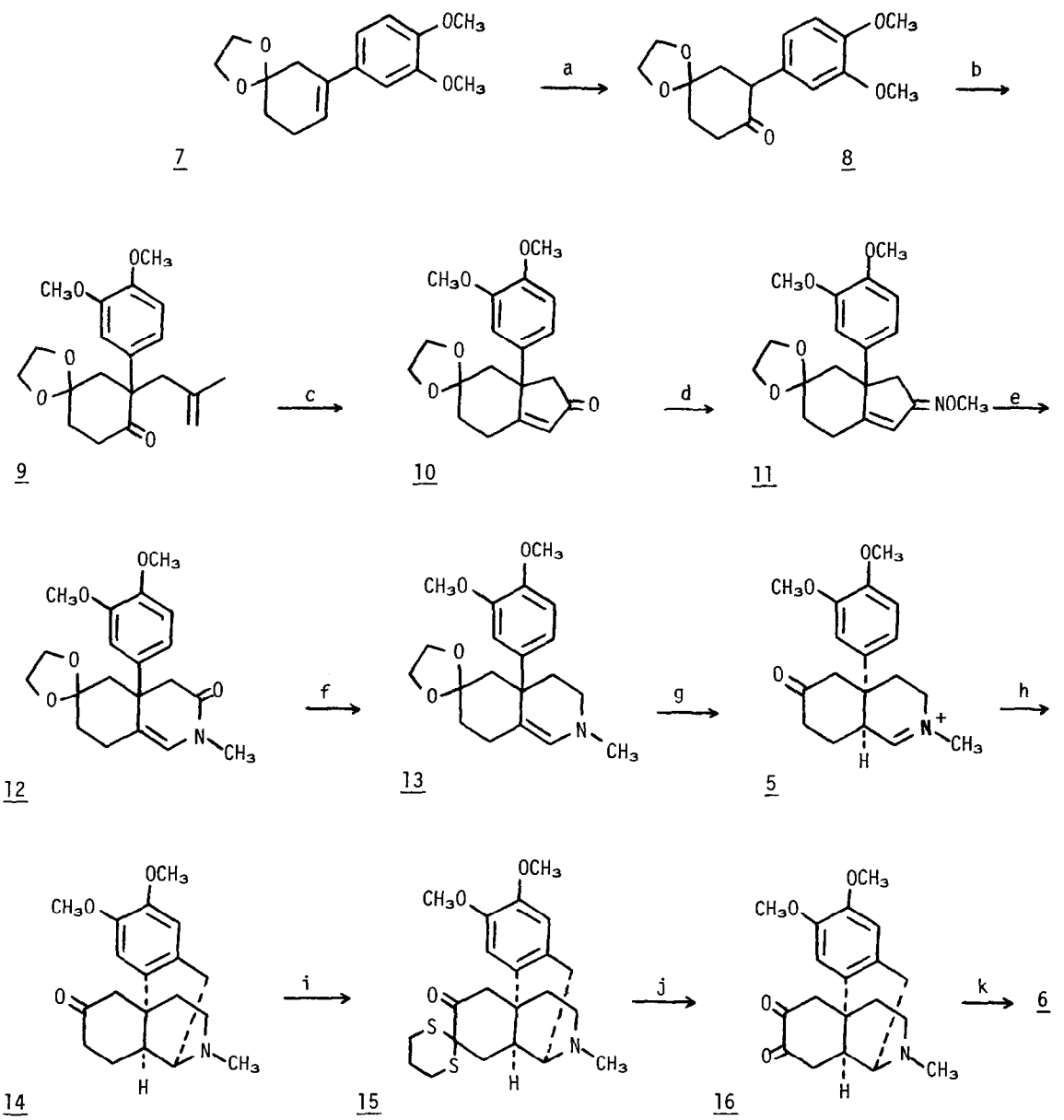


5 **6**

Iminium ion **5** was prepared according to the route shown in the Scheme[10]. Treatment of 3-ethoxy-2-cyclohexenone with 3,4-dimethoxyphenyllithium, followed by acid-catalyzed dehydration and ketalization gave olefin **7**. Hydroboration/oxidation of **7** gave an alcohol, which was further oxidized with pyridinium chlorochromate to yield ketone **8**. Alkylation of the thermodynamic enolate from **8** with methallyl chloride gave the keto olefin **9**, which was oxidized to a diketone and cyclized to yield indenone **10**. Nitrogen was then introduced into the ring by a Beckmann rearrangement[11] of N-methylnitrone **11** to give lactam **12**, which was reduced with $LiAlH_4$ to provide enamine **13**.

It is critical to the success of the synthesis that enamine **13** be protonated to yield cis-fused iminium ion **5**, a stereochemical outcome we could predict with confidence based both on our own earlier work[12] in the morphine series where we had proved the stereochemistry of an analogous iminium ion by X-ray studies, and on Evans' work[6,7]. In fact, treatment of enamine **13** with dilute $HClO_4$ gave a single crystalline iminium salt that, when treated with diazomethane, gave the anticipated morphinan **14** (30%) along with aziridinium ion.

Conversion of morphinan **14** into O-methylpallidinine was accomplished as indicated in the Scheme. Formylation of **14** occurred exclusively at the less hindered site to give a hydroxymethylene ketone that could be converted into keto thioacetal **15** on treatment with 1,3-propanedithiol ditosylate. Oxidation and subsequent hydrolysis of the thioacetal group then gave diketone **16**, which was identical with an authentic sample prepared by hydrolysis of natural O-methylpallidinine[13]. Although enol methylation of **16** under thermodynamic conditions (HCl/methanol) gave almost exclusively the undesired enol ether, reaction under kinetic conditions (p-TsOH/ methanol) gave largely (±)-O-methylpallidinine along with only a minor



Scheme. Synthesis of O-Methylpallidinine. (a) BH_3, THF; then H_2O_2, NaOH (100%); then pyridinium chlorochromate, NaOAc (84%); (b) NaH, THF; then $CH_2=C(CH_3)CH_2Cl$ (79%); (c) $KMnO_4$ (tr), $NaIO_4$, dioxane (100%); then KOH, EtOH (80%); (d) CH_3NHOH, NaOAc (100%); (e) p-TsCl, pyridine, H_2O (40%); (f) $LiAlH_4$, THF (100%); (g) $HClO_4$, H_2O, EtOH (78%); (h) CH_2N_2, CH_3CN (30%); (i) HCOOEt, NaH, PhH (72%); then $TsS(CH_2)_3STs$, KOAc (70%); (j) MCPBA, then HCl, H_2O (70%); (k) p-TsOH, MeOH (55%).

amount of its isomer (4:1 ratio). Our synthetic material, mp 198-202 °C (hydrochloride), was identical with an authentic sample[12] of the natural product by spectroscopic comparison (300 MHz ^{1}H NMR, ^{13}C NMR, IR, MS).

We conclude that our hypothesis concerning the need for an unsubstituted C4 position appears to be borne out. This limitation clearly precludes the use of the diazomethane-iminium ion route in the synthesis of alkaloids having the morphine oxygenation pattern.

Acknowledgment: We thank the National Institutes of Health for their support of their work through Grant GM 28569.

References

1. For reviews of the chemistry of morphine alkaloids, see: (a) Stork, G. In Manske, R. H. F. (ed.) "The Alkaloids, Vol. VI"; Academic Press: New York, 1960; pp. 219-146. (b) Bentley, K. W. In Manske, R. H. F. (ed.) "The Alkaloids, Vol. XIII"; Academic Press: New York, 1971; pp. 1-164.
2. Crist, D. R.; Leonard, N. J. Angew. Chem. Int. Ed. Engl. **1969**, 8, 962.
3. Gates, M.; Shepard, M. S. J. Am. Chem. Soc. **1962**, 84, 4125.
4. Weiler, D. D.; Rapoport, H. J. Med. Chem. **1976**, 19, 1171.
5. McMurry, J. E.; Davidson, A. H.; Summers, D. R.; Shenvi, A.; Scott, W. J. unpublished results.
6. Evans, D. A.; Mitch, C. H. Tetrahedron Lett., **1982**, 23, 285.
7. Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. J. Am. Chem. Soc. **1980**, 102, 5955.
8. A full paper detailing our results and supporting our conclusions is in preparation.
9. Vecchietti, V.; Casagrande, C.; Ferrari, G. J. Chem. Soc., Perkin I, **1981**, 578.
10. All synthetic intermediates were fully characterized by ^{13}C and ^{1}H NMR, by IR, and by exact mass measurement.
11. Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. J. Chem. Soc., Perkin I **1975**, 1964.
12. McMurry, J. E.; Scott, W. J. unpublished results.
13. We thank Dr. V. Vecchietti, Simes Research Laboratories, Milan, Italy for providing us with an authentic sample of O-methylpallidinine.

(Received in USA 1 August 1983)