Tetrahedron Letters No. 44, pp 4229 - 4232.
©Pergamon Press Ltd. 1978. Printed in Great Britain.

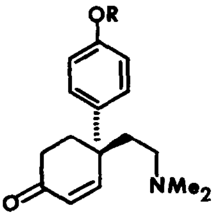
0040-4039/78/1029-4229$02.00/0

A FACILE SYNTHESIS OF RACEMIC O-METHYLJOUBERTIAMINE

Stephen F. Martin* and Thomas A. Puckette

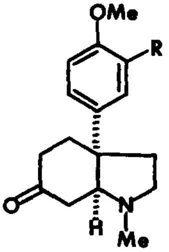
Department of Chemistry, The University of Texas at Austin
Austin, Texas 78712 USA

The recent isolation and characterization of a number of new alkaloids from the various *Sceletium* species of plants[1] has sparked the initiation of synthetic investigations which have culminated in the total syntheses of several of these alkaloids, including joubertiamine (1),[2a] O-methyljoubertiamine (2),[2] and mesembrine (3).[3] The presence of a quaternary carbon atom, the structural feature common to these and most other alkaloids belonging to the *Sceletium* or the closely related *Amaryllidaceae* families, renders the synthesis of these natural products a significant challenge. We have previously designed and developed several new synthetic procedures for the facile creation of quaternary carbon atoms from carbonyl compounds[4] and have also described the successful application of one of these to the total synthesis of the spirosesquiterpene acorone.[5] We now wish to report an important extension of another of these methods to the synthesis of O-methyljoubertiamine (2) and the octahydroindolone 4.



1, R=H

2, R=Me



3, R=OMe

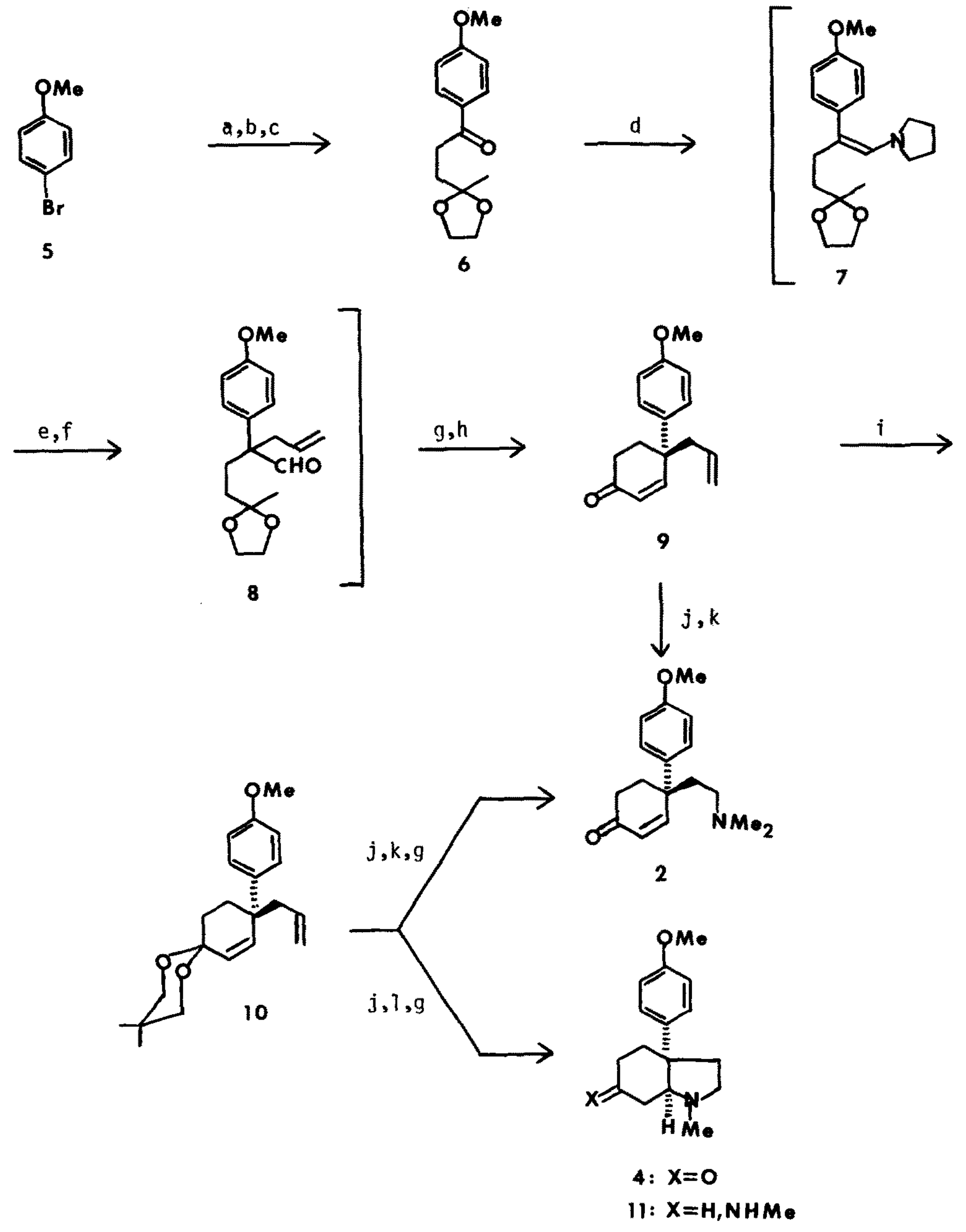
4, R=H

The key step in this new entry to the *Sceletium* and *Amaryllidaceae* alkaloids is the *direct* conversion of a carbonyl group to a nucleophilic, functional derivative of the homologous aldehyde, which may then be alkylated *in situ*, thereby completing the construction of the crucial quaternary carbon center. Since this synthetic strategy mandates the use of a carbonyl compound as the starting material, the mono-protected 1,4-diketone 6 was first prepared in 90% yield by the reaction of the Grignard reagent derived from *p*-bromoanisole (5) with 2-(2-cyanoethyl)-2-methyl-1,3-dioxolane.[6,7] Subsequent treatment of the ketone 6 with lithio diethylpyrrolidinomethylphosphonate and alkylation of the enamine 7 thus generated *in situ* with allyl bromide produced the protected δ-ketoaldehyde 8. After cleavage of the ketal protecting group, base-catalyzed cycloaldolization afforded the key intermediate allyl cyclohexenone 9[7] in 30% overall yield from 6.

At this stage the completion of the synthesis of O-methyljoubertiamine (2) was accomplished in several ways. When the allyl cyclohexenone 9 in methylene chloride was treated with one equivalent of ozone at -78^{o} and the resulting ozonide subjected directly to reductive amination ($NaBH_3CN/(CH_3)_2NH_2Cl/t\text{-}C_4H_9OH$),[8] O-methyljoubertiamine (2) was obtained in 60% overall yield. Alternatively, the ketal 10, generated from 9 by acid-catalyzed transketalization using 2,2,5,5-tetramethyl-1,3-dioxane, also suffered selective ozonolysis of the monosubstituted double bond. Reductive amination of the ozonide thus obtained as before and subsequent ketal hydrolysis produced O-methyljoubertiamine in 46% overall yield from 9. Unfortunately, repeated attempts to prepare the octahydroindolone 4 by ozonolysis of 9 followed by reductive amination using sodium cyanoborohydride[8] and methylamine hydrochloride were frustrated by the concomitant formation of 11 as the major product, regardless of the reaction conditions. This annoying circumstance, however, was easily remedied. In the event, the reductive amination ($NaBH_3CN/CH_3NH_3Cl/CH_3OH$) of the ozonide that was formed upon ozonolysis of the ketal 10 followed by the hydrolytic removal of the ketal moiety and cyclization of the intermediate amino enone gave the desired octahydroindolone 4 in 40% overall yield from 9. Since 4 has been previously converted to O-methyljoubertiamine (2) and joubertiamine (1),[2a] this latter sequence represents new, formal total syntheses of these two alkaloids.

Obviously the chemistry and synthetic strategy involved in these reaction sequences may be conveniently applied to the syntheses of a number of alkaloids possessing the octahydroindolone nucleus including mesembrine and the more complex *Amaryllidaceae* alkaloids, and these results will be reported independently.

Acknowledgment. We wish to thank the Robert A. Welch Foundation for their generous support of this work.



^{a}Mg/Et$_2$O/Δ; ^{b}NC(CH$_2$)$_2$C(OCH$_2$CH$_2$O)CH$_3$; ^{c}NH$_4$Cl/H$_2$O; ^{d}(CH$_2$)$_4$NCHLi$\overset{O}{\overset{\|}{P}}(OEt)_2$/THF/-78°→25°; ^{e}CH$_2$=CHCH$_2$Br/dioxane/Δ; ^{f}H$_2$O; ^{g}H$_3O^+$; ^{h}KOH/H$_2$O/MeOH; ^{i}Me$_2$C(OCH$_2CMe_2CH_2$O)/TsOH/Δ; ^{j}O$_3$/CH$_2Cl_2$/-78°; ^{k}Me$_2NH_2$Cl/NaBH$_3$CN/*t*-BuOH; ^{l}MeNH$_3$Cl/NaBH$_3$CN/MeOH.

References and Notes

1. (a) P. W. Jeffs, T. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, **39**, 2703 (1974); (b) F. O. Snyckers, F. Strelow, and A. Wiechers, *J. Chem. Soc. Chem. Commun.*, 1467 (1971); (c) P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *ibid.*, 1466 (1971); (d) P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970); (e) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970).
2. (a) R. V. Stevens and J. T. Lai, *J. Org. Chem.*, **37**, 2138 (1972); (b) H. F. Strauss and A. Wiechers, personal communication.
3. (a) R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, **40**, 3495 (1975); (b) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Lett.*, 3963 (1975); (c) S. Yamada and G. Otani, *ibid.*, 1133 (1971); (d) S. L. Keely, Jr., and F. C. Tahk, *J. Am. Chem. Soc.*, **90**, 5584 (1968); (e) R. V. Stevens and M. P. Wentland, *ibid.*, **90**, 5580 (1968); (f) T. Ohishi and H. Kugita, *Tetrahedron Lett.*, 5445 (1968); (g) T. J. Curphey and H. L. Kim, *ibid.*, 1441 (1968); (h) M. Shamma and H. R. Rodriguez, *ibid.*, 4847 (1965).
4. (a) S. F. Martin and R. Gompper, *J. Org. Chem.*, **39**, 2814 (1974); (b) S. F. Martin, *ibid.*, **41**, 3337 (1976); (c) S. F. Martin, T. S. Chou, and C. W. Payne, *ibid.*, **42**, 2520 (1977).
5. S. F. Martin and T. S. Chou, *J. Org. Chem.*, **43**, 1027 (1978).
6. E. Brown and R. Dhal, *Bull. Soc. Chim. Fr.*, 4292 (1972).
7. All compounds were adequately characterized by spectral methods (IR, NMR, and MS), and all new compounds have satisfactory high resolution mass spectral and/or combustion analytical data.
8. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

(Received in USA 31 May 1978)