Tetrahedron Letters,Vol.28,No.5,pp 503-506,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

TOTAL SYNTHESES OF (±)-CRININE AND (±)-BUPHANISINE#

Stephen F. Martin*[1] and Carlton L. Campbell

Department of Chemistry, The University of Texas, Austin, TX 78712

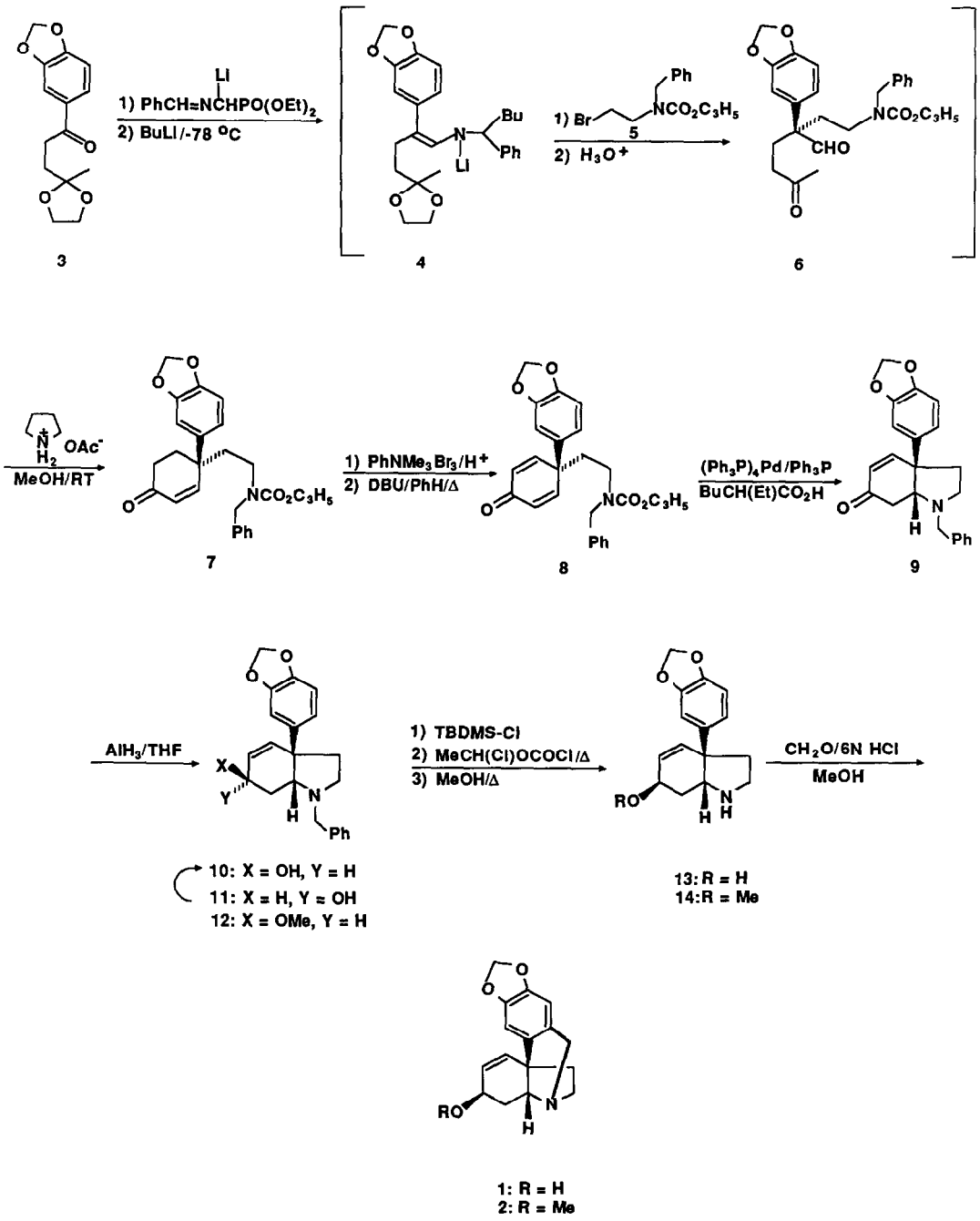
Abstract. The concise total syntheses of the Amaryllidaceae alkaloids (±)-crinine (**1**) and (±)-buphanisine (**2**) have been completed by a strategy that features the application of a general procedure for the elaboration of a quaternary carbon at a carbonyl center for construction of the key intermediate 4,4-disubstituted cyclohexenone **7**.

The Amaryllidaceae family of alkaloids constitutes an important class of naturally occurring bases, which continues to elicit the interests of synthetic organic chemists.[2] Previous accounts from these laboratories[3] have revealed a general entry to several classes of the alkaloids of the Amaryllidaceae family, and we wish to disclose the extension of this strategy to the facile total syntheses of (±)-crinine (**1**)[4,5] and (±)-buphanisine (**2**). The key tactical element of the approach involves the practical application of a general methodology for the construction of quaternary carbon atoms bearing differentially functionalized alkyl appendages at a carbonyl center.[6]

The opening move in the syntheses of (±)-crinine and (±)-buphanisine required the construction of the 4,4-disubstituted cyclohexenone **7** from the monoprotected 1,4-dione **3**, which was readily available from piperonal.[3c] In the event, reaction of **3** with diethyl N-benzylideneaminolithiomethylphosphonate (1.2 equiv, THF, -78 °C → reflux, 3 h) followed by regioselective addition of n-butyllithium (1.1 equiv, -78 °C, 1 h) to the 2-azadiene thus produced in situ afforded the metalloenamine **4**. Subsequent alkylation of **3** with allyl N-benzyl-N-(2-bromoethyl)carbamate (**5**)[7] followed by treatment with aqueous acid provided the δ-ketoaldehyde **6**. Cycloaldolization and dehydration [pyrrolidine-33% aq. AcOH-MeOH (1:3:30)] of **6** afforded the key intermediate cyclohexenone **7** in 60% overall yield from **3**. The conversion of **7** into the cyclohexadienone **8** was

#This paper is dedicated to Professor Rudolf Gompper on the occasion of his 60th birthday.

Scheme 1


1) PhCH=NCHPO(OEt)2
2) BuLi/-78 °C
1) Br
5
2) H3O+
MeOH/RT
1) PhNMe3Br3/H+
2) DBU/PhH/Δ
(Ph3P)4Pd/Ph3P
BuCH(Et)CO2H
AlH3/THF
1) TBDMS-Cl
2) MeCH(Cl)OCOCl/Δ
3) MeOH/Δ
CH2O/6N HCl
MeOH
10: X = OH, Y = H
11: X = H, Y = OH
12: X = OMe, Y = H
13: R = H
14: R = Me
1: R = H
2: R = Me

then easily achieved in 70-80% overall yield by sequential bromination ($PhNMe_3Br_3$, EtOAc, 25 °C, cat. H_2SO_4, RT, 3 h) and dehydrobromination (DBU, C_6H_6, reflux, 10 h).

The palladium (0)-catalyzed[8] [$Pd(Ph_3P)_4$, Ph_3P, Bu(Et)$CHCO_2H$, CH_2Cl_2, RT, 48 h: 85%] removal of the allyloxycarbonyl function from **8** was accompanied by the spontaneous cyclization of the intermediate secondary amine to deliver the hydroindolenone **9**. Hydride reduction of **9** furnished mixtures of the allylic alcohols **10** and **11** that varied depending upon the hydride reagent employed. Namely, when the enone **9** was treated with DIBAL, a mixture of **10** and **11** (1:10) was obtained, whereas reduction of **9** with alane in THF provided a mixture of **10** and **11** wherein the diastereomer **10**, which has the correct configuration at C(3) of the target alkaloids, was slightly preferred (1.3-1.5:1). Although a number of experimental variants were explored to increase the relative amount of the allylic alcohol **10**, which was required for the synthesis of (±)-crinine (**1**), formed upon reduction of **9**, no significant improvement of the ratio of **10/11** was observed. Nevertheless, the configuration at C(3) of the undesired allylic alcohol **11** could be conveniently inverted in a straightforward fashion to give **10** [(1) Ms_2O, Et_3N, CH_2Cl_2; (2) CsOAc, DMF, RT; (3) MeOH, K_2CO_3, RT: 74%]. On the other hand, the problem of accessing an intermediate for the synthesis of (±)-buphanisine (**2**) was more readily solved since it was discovered that methanolysis (MeOH, RT) of the mixture of mesylates obtained from **10** and **11** led to the formation in 75% overall yield of the single C(3) epimeric allylic ether **12**, bearing the configuration at C(3) corresponding to that present in **2**.

Removal of the N-benzyl protecting group from **10** to give the secondary amine **13** was smoothly effected through the agency of ACE-Cl[9] according to either of two protocols: (1) [(a) TBDMSOTf, Hunig's base, CH_2Cl_2, 0 °C; (b) ACE-Cl, $ClCH_2CH_2Cl$, reflux, 3 h; (c) MeOH, reflux, 2 h: 93%]; or (2) [(a) ACE-Cl, $ClCH_2CH_2Cl$, Proton Sponge, reflux, 3 h; (b) MeOH, reflux, 2 h: 63%]. N-Debenzylation of **12** was achieved according to Method 2 above to provide **14** (>95%). The crude secondary amines **13** and **14** were then transformed directly into (±)-crinine (1) and (±)-buphanisine (**2**), in 85% and 70% overall yields from **10** and **12**, respectively, by a Pictet-Spengler reaction [40% aq CH_2O, MeOH, RT, 10 min; 6N HCl, RT, 3 h]. The synthetic crinine and buphanisine thus obtained were identical (^1H and ^{13}C NMR, IR, MS, TLC) with authentic samples.[10]

Acknowledgment. We thank the National Institutes of Health (CA21860) and the Robert A. Welch Foundation for their generous support of this research. We also wish to acknowledge NSF (CHE8305785) and NIH (RR01912) for instrumentation grants used for the acquisition of 500 MHz and 360 MHz NMR spectrometers.

REFERENCES AND NOTES

1. Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.
2. For reviews of the chemistry of the Amaryllidaceae alkaloids see (a) Fuganti, C. in "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press, New York, 1975; Vol. 15, p. 83-164. (b) Grundon, M. F. in "Specialist Periodical Reports, The Alkaloids"; The Chemical Society: London, **1983**; Vol. 13, p. 187-195. See also Vols. 1-12. (c) Tsuda, Y., Heterocycles **1978**, 10, 555.
3. (a) Martin, S. F.; Puckette, T.A. and Colapret, J.A. J. Org. Chem. **1979**, 44, 3391. (b) Martin, S. F. and Garrison, P. J. J. Org. Chem. **1982**, 47, 1513. (c) Martin, S. F. and Davidsen, S. K. J. Am. Chem. Soc. **1985**, 107, 6431.
4. For previous syntheses of crinine, see: (a) Muxfeldt, H.; Schneider, R. S. and Mooberry, J. B. J. Am. Chem. Soc. **1966**, 88, 3670. (b) Whitlock, H. W., Jr. and Smith, G. L. ibid. **1967**, 89, 3600. (c) Overman, L. E.; Mandelson, L. T. and Jacobsen, E. J. ibid. **1983**, 105, 6629. (d) Overman, L. E. and Sugai, S. Helv. Chim. Acta **1985**, 68, 745.
5. For representative syntheses of alkaloids and compounds related to crinine, see: (a) Uyeo, S.; Irie, H. and Yoshitake, A. J. Chem. Soc. (C) **1968**, 180, 2. (b) Schwartz, M. A.; Holton, R. A. J. Am. Chem. Soc., Chem. Comm. **1970**, 92, 4. (c) Kametani, T. and Kohno, T. Tetrahedron Lett. **1971**, 3155. (d) Kametani, T.; Kohno, T.; Shibuya, S.; Fukumoto, K. Tetrahedron **1971**, 27, 5441. (e) Stevens, R. V.; Dupre, L. E., Jr. and Loewenstein, P. L. J. Org. Chem. **1972**, 37, 977. (f) Ninomiya, I.; Naito, T. and Kiguchi, T. J. Chem. Soc., Perkin Trans. I **1973**, 2261. (g) Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. J. Am. Chem. Soc. **1973**, 95, 612. (h) Kotani, E.; Takeuchi, N.; Tobinaga, S. J. Chem. Soc., Chem. Comm. **1973**, 551; Tetrahedron Lett. **1973**, 29, 2735. (i) Tomioka, K.; Koga, K.; Yamada, S.-I. Chem. Pharm. Bull. **1977**, 25, 2681. (j) Fushimi, T.; Ikuta, H.; Irie, H.; Nakadachi, K.; Uyeo, S. Heterocycles **1979**, 12, 1311. (k) Keck, G. E. and Webb, R. R., II J. Am. Chem. Soc. **1981**, 103, 3173; J. Org. Chem. **1982**, 7, 1302. (l) Sanchez, I. H.; Lopez, F. J.; Soria, J. J.; Larraza, M. I. and Flores, H. J. J. Am. Chem. Soc. **1983**, 105, 7640.
6. Martin, S. F.; Phillips, G. W.; Puckette, T. A. and Colapret, J. A. J. Am. Chem. Soc. **1980**, 102, 5866.
7. Prepared in 85% overall yield from commercially available N-benzylethanolamine.
8. Jeffrey, P. D. and McCombie, S. W. J. Org. Chem. **1982**, 47, 587.
9. Olofson, R. A., Senet, J.-P., Martz, J. T., Piteau, M., Malfroot, T. J. Org. Chem. **1984**, 49, 2081.

10. We wish to thank Professor L. E. Overman (UC Irvine) and Dr. H. M. Fales (NIH) for providing generous samples of authentic (-)-crinine and (-)-buphanisine.

(Received in USA 11 September 1986)