Tetrahedron Letters No. 11, pp 979 - 982, 1977. Pergamon Press. Printed in Great Britain.

GENERAL METHODS OF ALKALOID SYNTHESIS. XIII. THE TOTAL SYNTHESIS OF (±)-IPALBIDINE AND (±)-SEPTICINE

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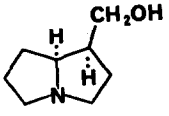
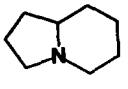
(Received in USA 24 November 1976; received in UK for publication 3 February 1977)

Recently, we reported[1] the total synthesis of (±)-isoretronecanol (1) and (±)-δ-coniceine (2). A key step in each of these syntheses utilized the acid-catalyzed rearrangement of a cyclopropylimine to generate the 3-phenylthio-2-pyrroline synthon (3). The latter intermediate serves as a relatively stable equivalent synthon for the corresponding unstable unsubstituted endocyclic enamine 4. We now report the application of this methodology to the synthesis of the more complex indolizidine alkaloids (±)-ipalbidine (5b)[2] and (±)-septicine (6).[3]



1



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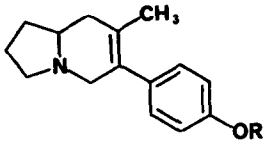
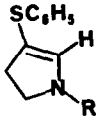


5a R=H
b R=CH₃



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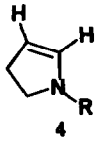

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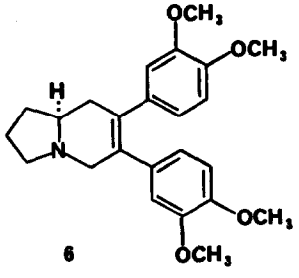
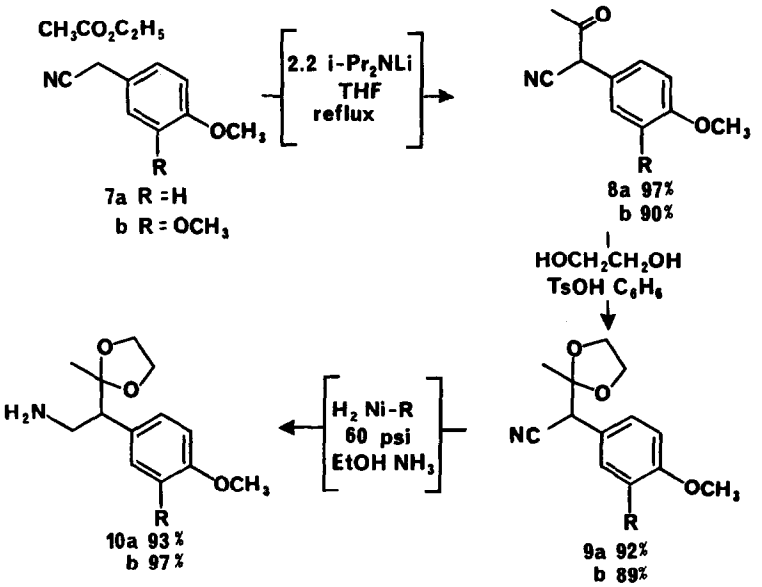
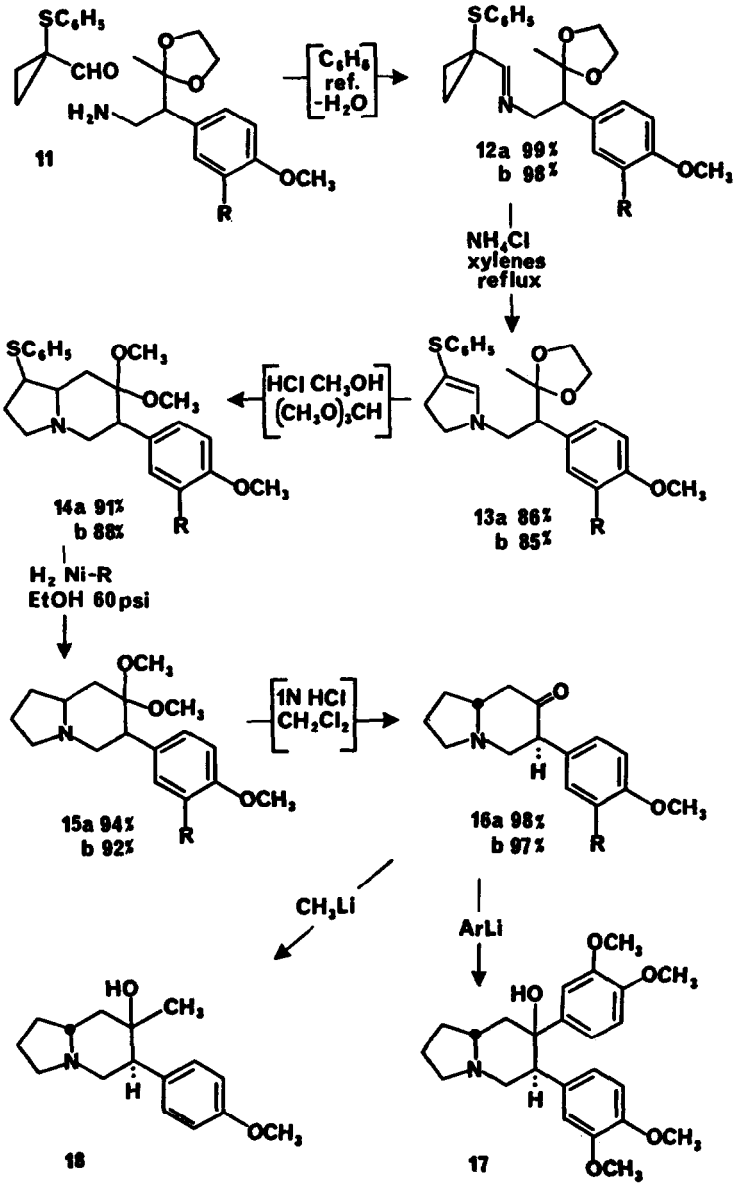


6

Acylation of p-methoxybenzyl cyanide (7a) with ethyl acetate has been reported[4] to proceed in 60% yield with t-BuOK as the base. We have found[5] that by employing i-Pr_2NLi in THF this yield could be improved to 97%. Ketalization of 8a and 8b[6] under standard conditions afforded 9a (mp 65°)[7] and 9b (mp 87-88°). Catalytic reduction of these nitriles to the corresponding amines proceeded smoothly: 10a (bp 120°/0.28 mm); 10b (bp 150°/0.3 mm).



The requisite cyclopropylimines 12a (viscous oil) and 12b (mp 54.5-55.5°) were prepared from 11[1] in the usual fashion. By employing slightly more than one equivalent of NH_4Cl suspended in refluxing xylene, each of these substances rearranged to the corresponding 2-pyrroline: 13a (viscous oil), λ_{max}244nm, ε = 709; 13b (viscous oil), λ_{max}245nm, ε = 703. Attempts to purify these substances by distillation or chromatography resulted in extensive decomposition. Nevertheless, treatment of crude 13a and 13b with methanolic HCl and trimethyl orthoformate afforded indolizidines 14a (mp 112-114°) and 14b (mp 104-105°) in high yield. Although two chiral centers are created in this step, it is clear from their melting points and tlc behavior that only one stereoisomer is produced. Having served its mission to stabilize these endocyclic enamines (13), the sulfur (configuration unknown) was now removed from 14 with hydrogen and Raney nickel: 15a (mp 83-84°), 15b (mp 88-89°). Hydrolysis of these ketals afforded the known ketones 16a: mp 105.5-106°, lit[2] mp 105-106°, ms calcd for 245.1416, found 245.1409; and 16b[3]: viscous oil, ms calcd for 275.1522, found 275.1512.


SC6H5
CHO
H2N
11
C6H6 ref. -H2O
12a 99%
b 98%
NH4Cl xylenes reflux
13a 86%
b 85%
HCl CH3OH (CH3O)3CH
14a 91%
b 88%
H2 Ni-R EtOH 60psi
15a 94%
b 92%
1N HCl CH2Cl2
16a 98%
b 97%
CH3Li
ArLi
18
17

Conversion of these ketones to ipalbidine and septicine was achieved as described previously.[2,3] Thus, treatment of 16a with methyl lithium provided indolizidine 18: mp 133-135°, lit[2] mp 133-135°; ms calcd for 261.1728, found 261.1724. Dehydration of 16a in sulfuric acid yielded O-methyl ipalbidine 5b: mp HCl salt 215-217°, lit[2] mp 215-217°; ms calcd for 243.1623, found 243.1634. Finally, demethylation of 5b afforded racemic ipalbidine 5a: mp 147-148°, lit[2] mp 147-148°; ms calcd for 229.1467, found 229.1464. Similarly, treatment of 16b with 3,4-dimethoxyphenyl lithium gave indolizidine 17: viscous oil, m/e 413, 395, 326, 295, 264, 164, 151. Dehydration of this substance yielded racemic septicine 6: mp 135-136°, lit[3] mp 135-136°; ms calcd for 395.2096, found 395.2102. The success of these experiments coupled with those cited earlier[1] provide a new and apparently quite general method for the synthesis of functionalized indolizidine alkaloids.

Acknowledgments. We are indebted to the National Science Foundation and The Robert A. Welch Foundation for generous financial support.

References and Notes

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(5) R. V. Stevens, P. M. Lesko, and R. Lapalme, J. Org. Chem., 40, 3495 (1975) and references cited therein. Curiously, employment of less than 2.2 equivalents of base resulted in lower yields.

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(7) The structures of all new compounds in this paper are corroborated by IR. ^{1}H NMR, and low resolution mass spectral data and, of course, by the success of the syntheses.

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