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# A NEW SYNTHESIS OF A STEMMADENINE MODEL

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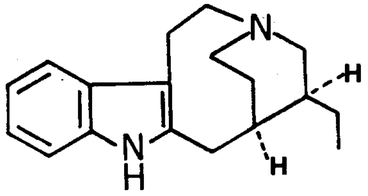
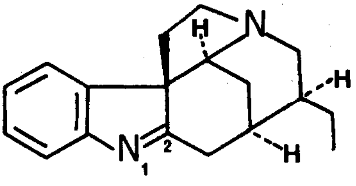
The tetracyclic indole derivative 1 occupies a key position in degradation studies of a number of alkaloids of the Strychnos[1] and aspidospermatine[2] types and has served for the partial synthesis of the known pentacyclic alkaloids tubifoline (2a), condyfoline (3), and tubifolidine (2b).[2,3] Moreover, the skeletal structure of 1 is manifest in the unique and biosynthetically important complex indole alkaloid, stemmadenine.[4] Recently, an ingenious total synthesis of (±)-1 has been effected.[3] We report a new stereoselective synthesis of 1 which embodies two features of general interest: a) a new regioselective $\gamma$-alkylation of an $\alpha$, $\beta$-unsaturated amide via a dianion reaction, 8 → 7; and b) nine-membered lactam formation by Witkop photocyclization, 11 → 12.

Recognition of steric hindrence as the probable cause of the failure to prepare the 2-(4-piperidylidene) indole 4 by our general Wittig synthesis,[5] led us to consider a Wittig (5 + 6a → 7) cum Madelung (7 → 9 → 10) approach in order to achieve the synthesis of the desired key intermediate 10 (SCHEME). To this end, the phosphonate ester 5[6], readily obtained in 60% yield by successive chloroacetylation and Arbusov reaction[7] of o-toluidine, was subjected to Wittig synthesis (Wadsworth-Emmons modification)[8,9] with 1-methyl-3-ethyl-

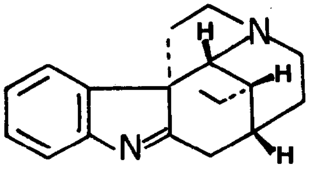


1

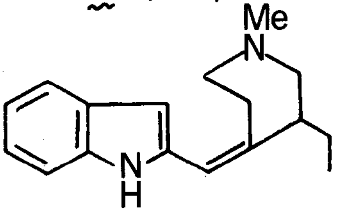


2a

2b: 1,2-dihydro

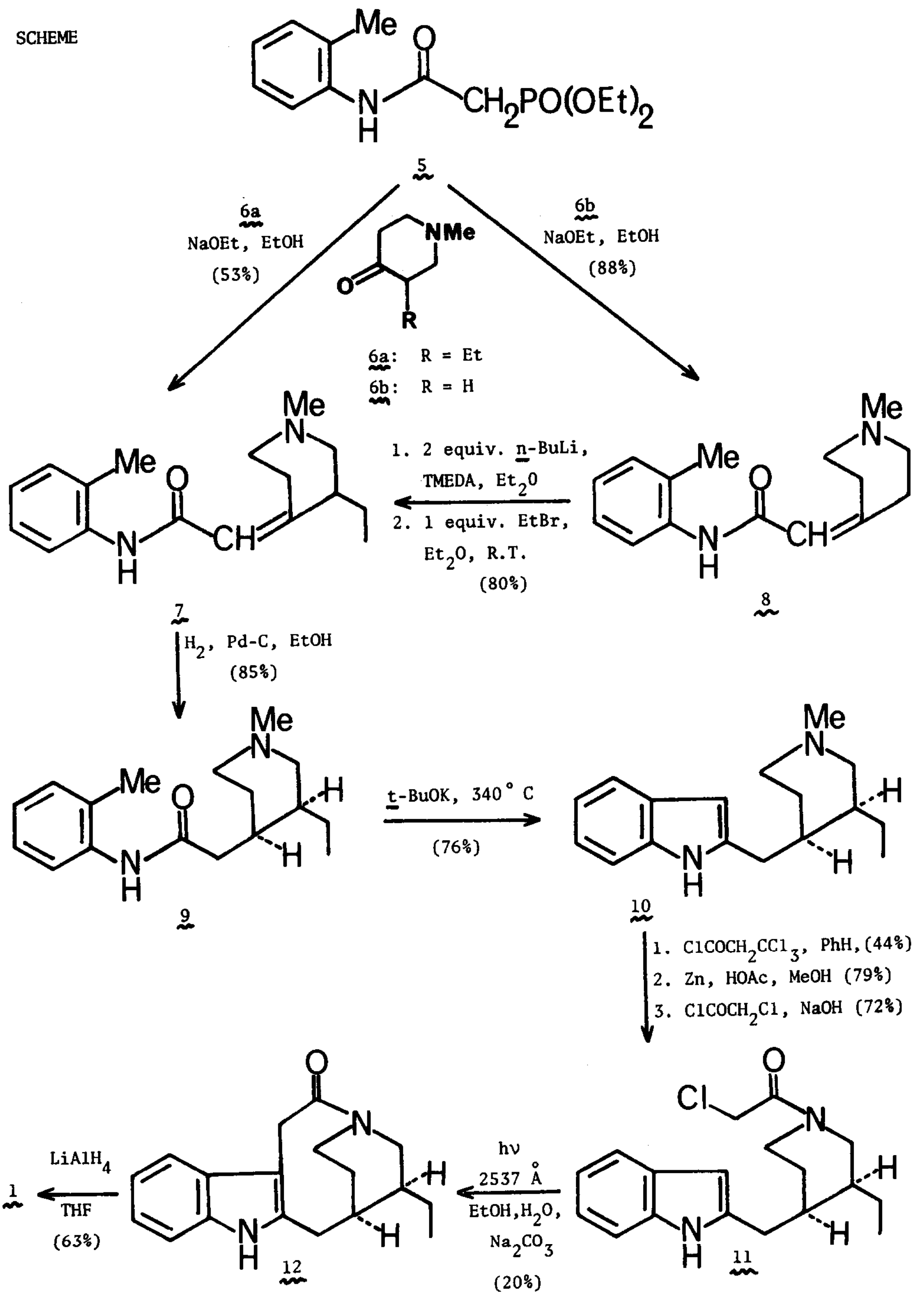


3



4

SCHEME


5
6a
NaOEt, EtOH
(53%)
6b
NaOEt, EtOH
(88%)
6a: R = Et
6b: R = H
7
8
1. 2 equiv. n-BuLi, TMEDA, Et$_2$O
2. 1 equiv. EtBr, Et$_2$O, R.T.
(80%)
H$_2$, Pd-C, EtOH
(85%)
9
t-BuOK, 340° C
(76%)
10
1. ClCOCH$_2$CCl$_3$, PhH, (44%)
2. Zn, HOAc, MeOH (79%)
3. ClCOCH$_2$Cl, NaOH (72%)
11
hν
2537 Å
EtOH, H$_2$O, Na$_2$CO$_3$
(20%)
12
LiAlH$_4$
THF
(63%)
1

4-piperidone (6a) to give the adduct 7: mp 122-123°C; ir (max) 1680 $cm^{-1}$; uv (max) 232 (ε 21,700), 273 sh (ε 9500) nm; nmr τ 4.30 (br s, 1). The tedious, multi-step preparation of 6a[10] led us to seek an alternate synthesis of 7 using dianion alkylation[11] of 8, readily obtained from the Wittig reaction of 5 with commercially available 1-methyl-4-piperidone (6b). In the event, successive treatment of 8 with *n*-BuLi-TMEDA[12] and ethyl bromide gave 7, shown to be identical (mp, mixture mp, ir, nmr) with the product of the direct Wittig reaction. Although several examples of α-C-alkylation of amide dianions have appeared recently,[13] the transformation 8 → 7 represents, to the best of our knowledge, the first case of a regioselective γ-alkylation of an α, β-unsaturated amide *via* a dianion route. Hydrogenation of 7 proceeded with high stereoselectivity[8,16] to give the *cis*-amide 9[17] which upon Madelung reaction[9,18,19] smoothly gave the key intermediate 10: oil, methiodide mp 152-154°C; ir (max) 3420, 2750 $cm^{-1}$; uv (max) 225 (ε 17,400), 282 (ε 7400), 291 (ε 7200) nm; nmr τ 3.70 (s, 1), 7.50 (s, 3), 9.20 (t, 3).

N-Demethylation of 10 was effected according to a modified Hobson-McCluskey procedure.[20] The resulting secondary amine was chloroacetylated under Schotten-Baumann conditions to give the chloroacetamide 11. Witkop photocyclization[21,22] of 11 gave, after preparative tlc, the tetracyclic lactam 13: mp 119-120° C; ir (max) 3500, 1640 $cm^{-1}$. To complete the synthesis, 12 was subjected to hydride reduction. The resulting oily tetracyclic amine 1 was converted into its methiodide, mp 195-197° C which was shown to be identical (mp, mixture mp, mass spectra) with authentic material.[3,23] Since 1 has been transformed into 2a, 3, and 2b, a new formal synthesis of these pentacyclic alkaloids has been achieved by this work.[24]

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14. The general synthetic utility of this reaction and its obvious consequences for the preparation of γ-substituted α,β-unsaturated carboxylic acids is being explored.

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17. The assigned stereochemistry was confirmed by hydrolysis to *cis*-1-methyl-3-ethyl-4-piperidine acetic acid whose methyl ester was shown to be identical (tlc, ir, nmr, mass spectrum) with an authentic sample prepared by Clarke-Eschweiler methylation of 3*S*-ethyl-4*R*-piperidine acetic acid methyl ester hydrochloride very generously provided by Dr. M.R. Uskokovic (Hofmann-La Roche).

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22. For related photocyclizations, see K.S. Bhandari, J.A. Eenkhoorn, A. Wu, and V. Snieckus, Syn. Commun., **3**, 79 (1975).

23. We are deeply indebted to Prof. Harley-Mason for the comparison sample.

24. We are grateful to P. Bernath and J.N. Reed (both Chem 13 News Award recipients) for a model study and synthesis of an intermediate. Support by the National Research Council of Canada is gratefully acknowledged.