Tetrahedron Letters, Vol 32, No 32, pp 3981-3984, 1991
Printed in Great Britain

0040-4039/91 $3 00 + .
Pergamon Press plc

Enantioselective Synthesis of Indoloquinolizidines

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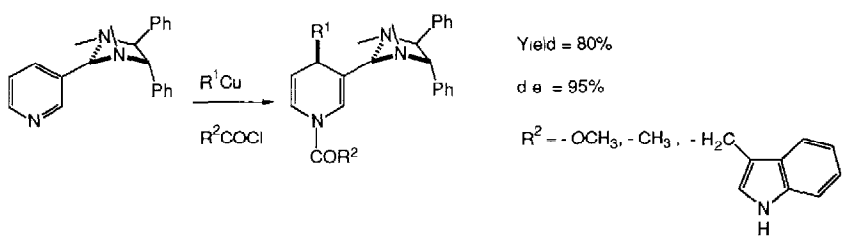
Key Words : Chiral 1,4-dihydropyridines - chiral symmetrical diamines- chiral indoloquinolizidines

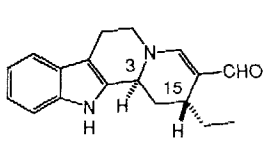
Abstract *Asymmetric synthesis of indoloquinolizidine has been accomplished by using acyl pyridinium salt bearing in 3 position a chiral aminal*

We have recently described the regio and diastereoselective addition of organocopper reagents on 1-acyl pyridinium salts, bearing in 3 position a chiral aminal obtained from an asymmetric chiral diamine [1]. Furthermore, we have shown that it was possible to use, as activating reagent, functionalized acyl chlorides such as β-indolylacetyl chloride [1] (Scheme 1) :

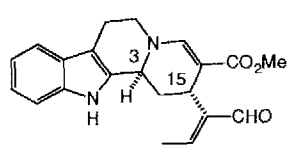


Scheme 1

In the present communication, we describe, using this methodology, a short enantioselective synthesis of indoloquinolizidine **1** as a model of indole alkaloids of the vallesiachotamine type **2** (trans relationship between 3-H and 15-H) [2]



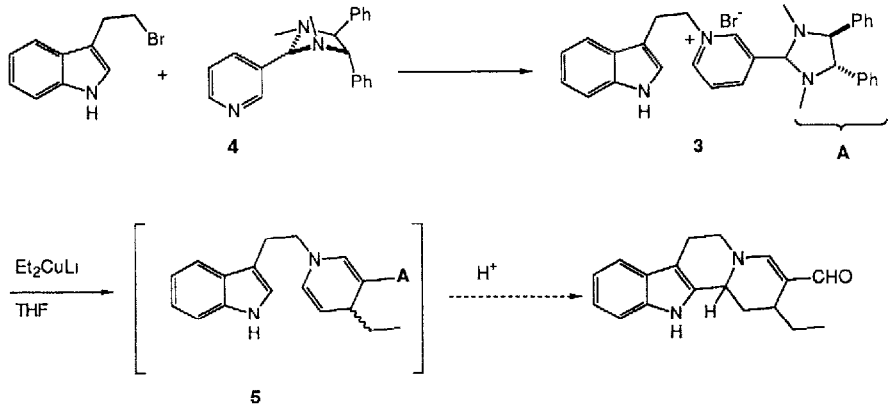
1



2

The preparation of such trans H-3, H-15 indolo [2,3-a] quinolizidine derivatives has been already published [2-7]. Noteworthy, (in racemic series) are the reduction of the appropriate pyridinium bromide[2] by sodium dithionite and the addition of stabilized carbon nucleophiles to N- alkyl pyridinium salts [2,5].

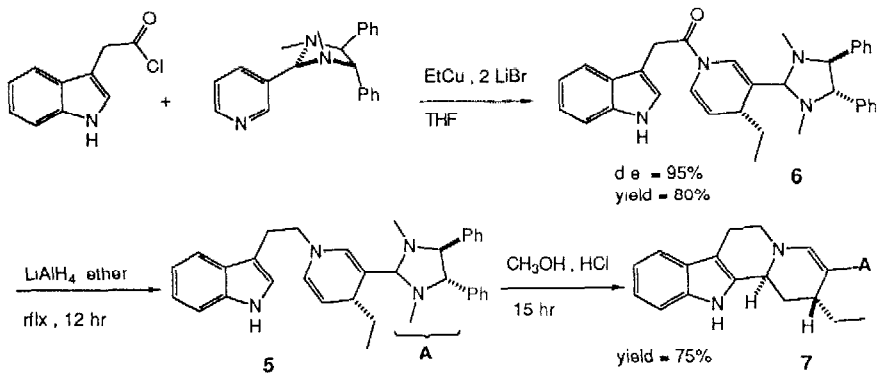
In a preliminary study, in order to effect a very short synthesis (an asymmetric version of the Wenkert[7] procedure) of this type of compound, we decided to use as activated pyridinium salt the compound **3** easily obtained by action of tryptophyl bromide on the pyridine -3-aminal **4** [6] (Scheme 2) :



Scheme 2

Indeed, the addition of diethyl cuprate (but not ethylcopper) occurs well [7] to afford the relatively stable (several days in refrigerator) dihydropyridine **5** (Scheme 2) as a clean crude product. Attempts to effect a purification of this compound were unsuccessful. The d.e. of this product was measured by ^{1}H NMR[8] and was shown to be low (~ 40%). We have tried to improve this selectivity by changing the reaction parameters (nature of the copper salt, of the organocopper reagent, the solvent etc ..) but without success.

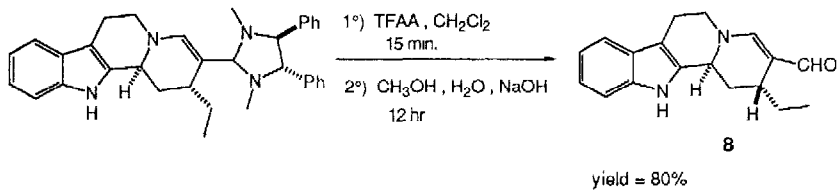
In a parallel effort, we have reduced the amide **6**, prepared as shown in Scheme 3 (d.e = 95%)[1], using $LiAlH_4$ in ether (the use of THF as solvent leads to cleavage of the amide bond[9]) and again we have obtained the dihydropyridine **5** but now with an excellent diastereoisomeric excess (d.e. = 95%). The clean crude product was then treated with anhydrous methanol saturated with HCl to afford the indoloquinolizidine **7** without removal of the aminal (Scheme 3) as a single diastereoisomer (75% yield after chromatography on alumina).



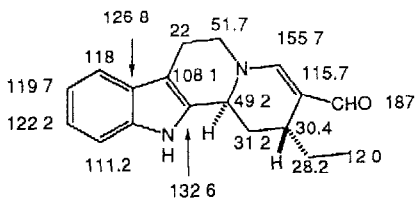
Scheme 3

In fact, the most difficult reaction was the deprotection of the aldehyde function. An aqueous acidic treatment was totally unsuccessful leading, depending on the reaction conditions, to the starting material or to complete degradation, even with a "diamine acceptor" such as formaldehyde.

Finally, the indoloquinolizidine **7** was treated with trifluoroacetic anhydride and the very polar compound thus obtained was treated with a 50% mixture of MeOH and aqueous NaOH (12%) to afford the aldehyde **8** : [10]



The trans relationship between 15-H and 3-H postulated by Lounasmaa and Wenkert for such a cyclization [2,5] was fully confirmed by ^{13}C NMR :



From our previous study[1], we have assigned to the C-15 atom the R configuration (starting from the S,S diamine) and therefore the S configuration to the C-3 atom.

In summary, the addition of an organocopper reagent on an activated N-acyl pyridinium salt having in the 3-position a chiral aminal prepared from a chiral symmetrical diamine appears well suited for an easy asymmetric

synthesis of structures related to the vallesiachotamine family of indoloquinolizidines Efforts to extend this research are now underway.

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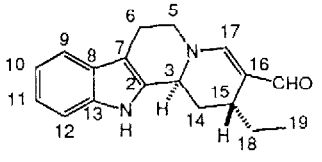
(10) **8** :



m p.= 232 (CH_3OH) , $[\alpha]_D^{20}$ = -110 (c 1,8, CH_2Cl_2) , UV λ_{max} (EtOH) 215, 240, 285 nm;
MS , m/z = 280, 251, 149, 121, 119, 85, 83. IR (film) : 3300, 1600, 1580, 1430 cm^{-1}.
^1H NMR (400 MHz) : 1.03 (t, 3H, J = 7 Hz, H-19), 1 3 (m, 1H, H-18), 1.6 (m, 1H, H-14), 1.75(m, 1H, H-18'), 2.41 (dd, 1H, J = 13 Hz, J_2 = 2 Hz, H-14'), 2.9 (m, 3H, H-15 + H-6), 3.75 (m, 2H, H-5), 4.7 (broad d., 1H, J = 12 Hz, H-3), 7.03 (s, 1H, H-17), 7.12 (t, 1H, J = 7 Hz, H-10), 7 18 (t, 1H, J = 7 Hz, H-11), 7.35 (d, 1H, J = 7 Hz, H-9), 7.49 (d, 1H, J = 7Hz, H-12), 8.8 (s, 1H, N-H), 8.95 (s, 1H, CHO).

(Received in France 24 April 1991)