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A SHORT TOTAL SYNTHESIS OF (±)-19-HYDROXYASPIDOFRACTININE

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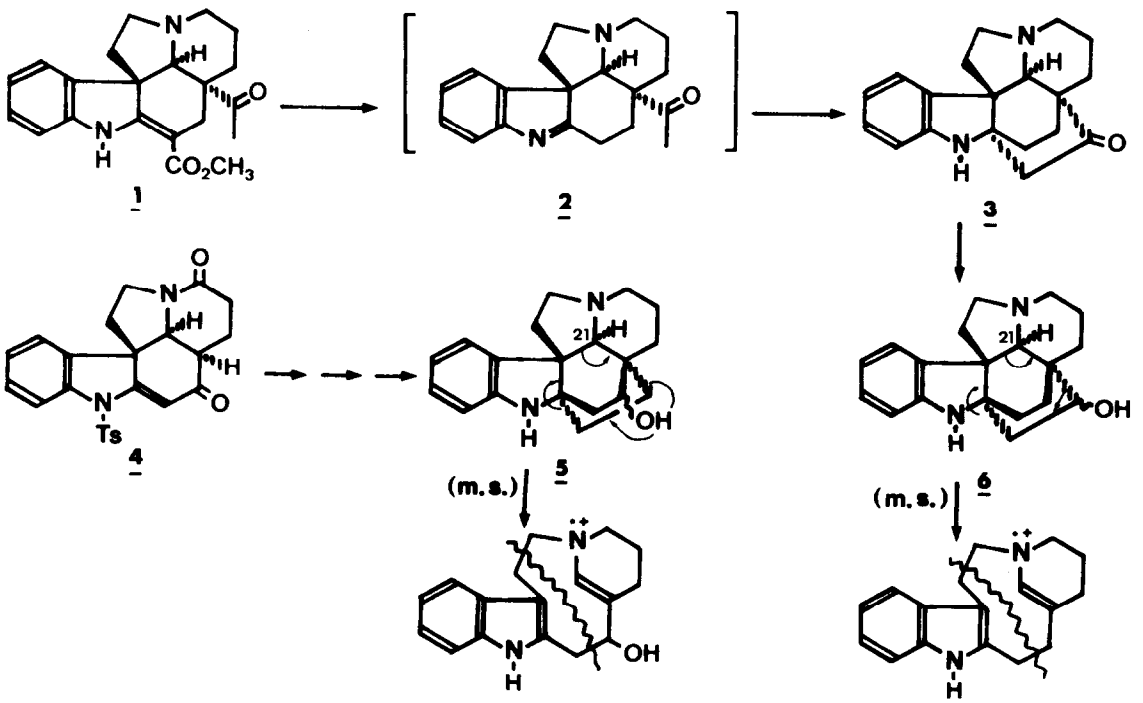
Summary : 3,19-Dioxoaspidofractinine 13 was prepared in two steps from 2-hydroxytryptamine, and further reduced to the title compound 6.

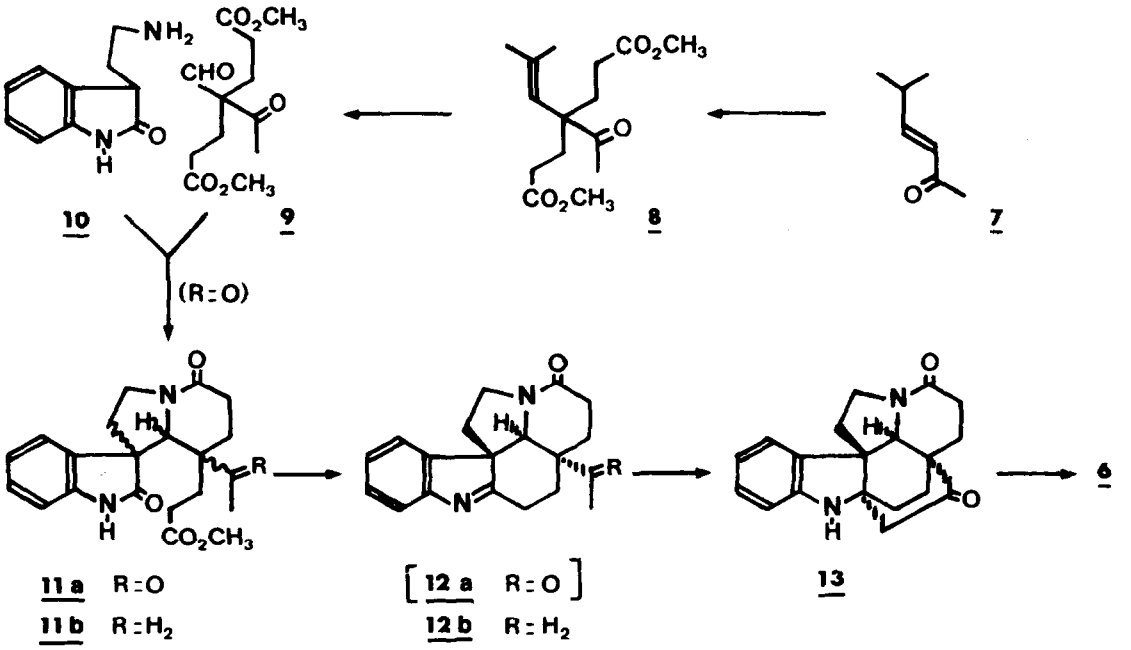
The hexacyclic ring systems of the pleiocarpine-aspidofractinine alkaloids was first built up by Biemann[1], through decarboxylative cyclization of minovincine 1 to 19-oxoaspidofractinine 3 *via* indolenine 2 (scheme 1).



SCHEME 1

The first total synthesis in this series is due to Ban[2], who annelated his precursor (±)-4 to yield (±)-5, a compound epimeric with the alcohol 6 derived from ketone 3. Attachment of the hydroxy group to the two-carbon bridge *cis* or *trans* to the 21-H is best diagnosed by the highly differential M.S. fragmentation of 5 *vs* 6[2,3].

Our expeditious synthesis of (±)-6 (scheme 2) is based on Biemann's cyclization of 1 to 3, and on our previous synthesis[4] of 1-dehydro 3-oxoaspidospermidine 12b through the polyphosphoric acid (PPA) promoted decarboxylative cyclisation of the oxindolic ester(s) 11b. These premises designated the ketooxindolic ester(s) 11a as a synthetic target.

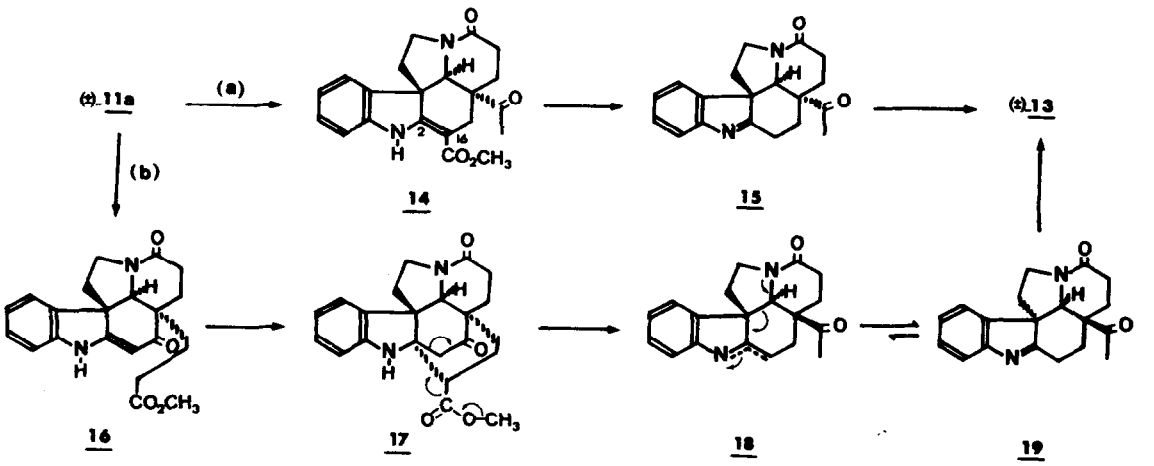


SCHEME 2

Accordingly, the unstable, highly functionalized synthon 9 (ν_{CO}1700,1710,1740cm^{-1} ; δ^{TMS}_{ppm} , 9.72(s,1H), 3.66(s,6H), 2.20(s,3H)) was prepared through ozonolysis[5] of the olefin 8 ($Eb^{0,5mmHg}$148-150°C ; ν_{CO}1710,1740cm^{-1} ; δ^{TMS}_{ppm}, 5.12(m,1H), 3.75(s,6H), 2.08(s,3H), 1.75(d, J=1Hz,3H), 1.5(d,J=1Hz,3H)), resulting from the Michael addition (benzene/Triton-B(cat.)/ K_2CO_3,1eq., reflux 20 hours ; Y=26%[6]) of methyl acrylate on 2-oxo 5-methyl hex-3-ene 7. Upon reaction with 2-hydroxytryptamine 10, (equimol., toluene/reflux, Dean-Stark, 2hrs, then AcOH/reflux, 5hrs) 9 gave a mixture of stereoisomeric oxindoles 11a (40%), of which only three components were distinguishable on t.l.c. The major, more polar oxindole (33,5% from 10 $M^{+\cdot}$,384 ; ν_{CO},1690,1710,1720,1740cm^{-1} ; λ^{nm}_{max}215,255,285 ; δ^{TMS}_{ppm} , 4.42(s,1H), 3.57(s,3H), 1.74(s,3H)), was heated in PPA (120°C,2hrs) to give 3,19-dioxo aspidofractinine 13 (SM,m/z(%) 308,$M^{+\cdot}$(100), 280(10), 265(50), 252(20), 237(20), 169(65), 154(95) ; ν_{CO}1705,1720cm^{-1} ; λ^{nm}_{max}210,243,292) as the sole indolinic derivative (17,3%), along with unidentified polar

material. Heating the mixture of oxindoles 11a in PPA and completion of the isolation through acidic treatment ($MeOH/H_2SO_4$, reflux,3hrs) of the more polar material led to 13 in 8.7% yield from 10.

$LiAlH_4$ reduction of 13 (THF) afforded 19-hydroxyaspidofractinine (65%),the mass spectrum of which : 296, $M^{+\cdot}$(55), 278(15), *252(65)*, 167(20), 158(30), 149(30), 140(25), *109(100)* clearly fitted with structure 6 and not 5 (see scheme 1). Comparison with an authentic sample prepared[1,7] from minovincine 1 showed identical IR,UV and mass spectra, and identical R_F's on t.l.c.



SCHEME 3

The PPA cyclisation of 11a to 13 is depicted on scheme 3 : The simplest pathway (a) involves cyclization (onto a 2-phosphorimidate ?) to 3-oxominovincine 14, followed by hydrolysis, decarboxylation and cyclization to 15 → 13. Path (b) would imply cyclization of the methylketone to 16 (the configuration of which results from the previous synthesis of 12b from 11b). Intermediates 18 and 19 would now account for the decarboxylation, and for the actual relative configuration of 13. However in each case, formation of the 2-16 bond in acidic medium awaits interpretation.

References and Notes

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N. LANGLOIS and R.Z. ANDRIAMIALISOA, *J.Org.Chem.*, 44, 2468 (1979) performed a similar cyclization of minovincine with retention of the methoxycarbonyl group.

2) T. OHNUMA, T. OISHI and Y. BAN, *J.Chem.Soc., Chem.Comm.*, 301 (1973). Lateron, Y. BAN, Y. HONMA and T. OISHI,(*Tetrahedron Lett.*, 1111 (1976)), synthesized (±)-aspidofractinine itself from 4.

3) C. DJERASSI, H. BUDZIKIEWICZ, R.J. OWELLEN, J.M. WILSON, W.G. KUMP, D.J. LE COUNT, A.R. BATTERSBY and H. SCHMID, *Helv.Chim.Acta*, 46, 742 (1963).

4) J.-Y. LARONZE, J. LARONZE-FONTAINE, J.LÉVY and J. LE MEN, *Tetrahedron Lett.*, 491 (1974)

5) The ozonolysis was stopped upon discolouration of Sudan III, after T. VEYSOGLU, L.A. MITSCHER and J.K. SWAYZE, *Synthesis*, 807 (1980).The yield was appr.65%(NMR).

6) The major derivative (56%) was the monoalkylated product.

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