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CYCLIZATION OF OXINDOLIC METHYLKETONES WITH ACID : A RAPID SYNTHESIS OF (±)-ASPIDOFRACTININE

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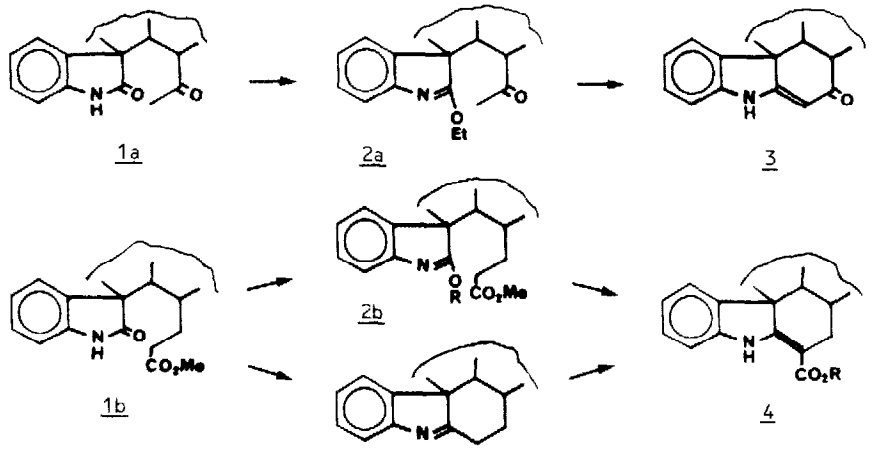
Summary *: The oxindolic methylketone 7 was cyclized in one step to the hexacyclic ketolactam 9 with acid. (±)-Aspidofractinine 23 was prepared by sequential reduction of 9. The model oxindolic methylketone 11, when reacted with acid, gave compounds 12 and 17a,b.*

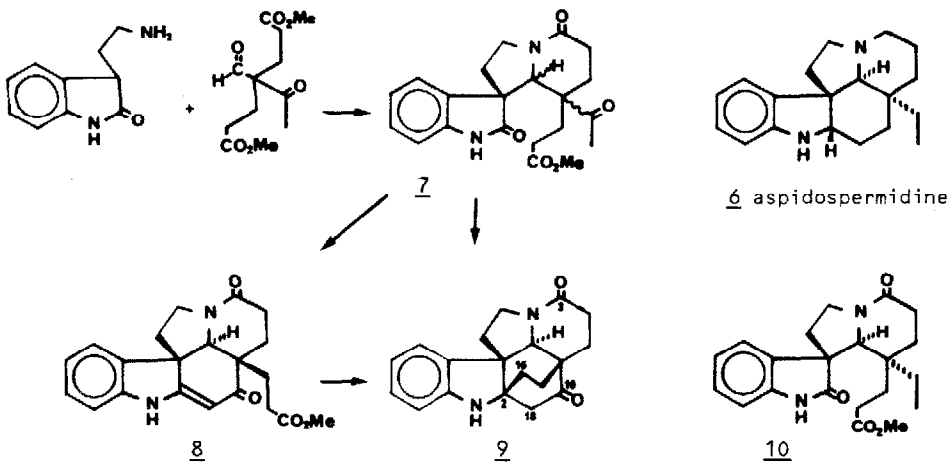
The intra-molecular cyclization of a methylketone onto the oxindolic lactam group (scheme 1) has been first developed by Ban[1] : he converted 1a to an iminoether (2a), which proved suitable for a base-catalyzed (NaH/DMSO) cyclization to 3. Later on, we were able to extend the process to some oxindolic methyl esters 1b, which were derived to iminoethers 2b (R=Me,Et) and further cyclized to anilinoacrylic esters 4 (R=Me,Et)[2]. The observed transesterification and a side-reaction of the dimsyl anion as well had led us to modify Ban's conditions by using a methyl iminoether and NaH/DMF as a basic medium. While the mechanism of this cyclization is not yet fully understood[3], it allowed completion of short total syntheses in the indole alkaloid field[2,4a-c].



Scheme 1

A striking improvement resulted when we heated esters 1b in PPA, which directly led to indolenines 5 upon cyclization and simultaneous loss of CO_2Me. This last reagent allowed a synthesis of (±)-aspidospermidine 6

in only three steps from 2-hydroxytryptamine[2] and, still more dramatically, a synthesis of the hexacyclic 3,19-dioxoaspidofractinine 9 in two steps from 2-hydroxytryptamine[5] (scheme 2).

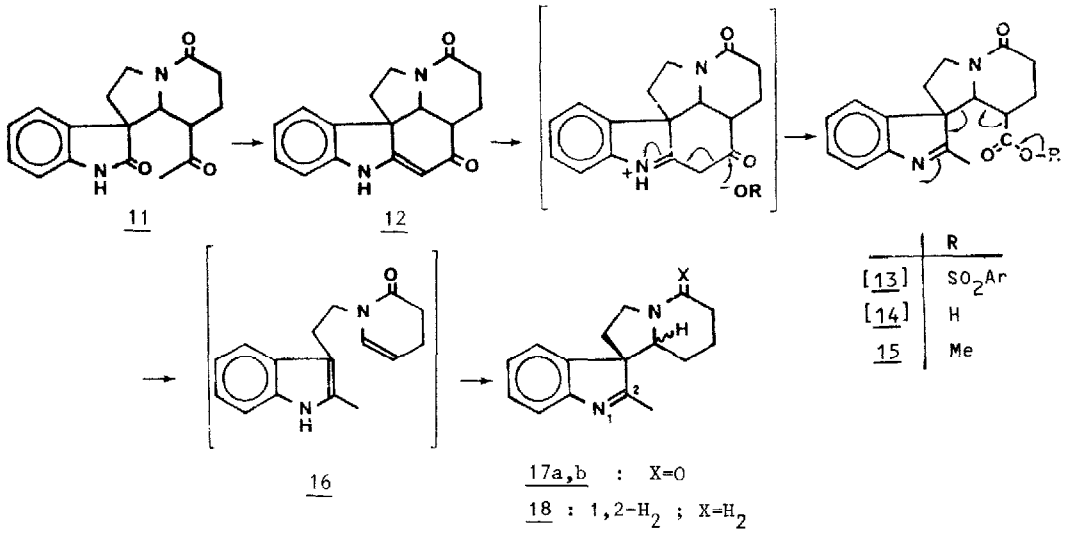


Scheme 2

It remained unclear which of the two carbons C-16 or C-18 had first undergone the cyclization onto C-2. We have now observed that para-toluene-sulfonic acid in boiling toluene (15 h) also performs the transformation of 7 to 9 (Yield : 50% from the more polar isomer or 23% from 2-hydroxytryptamine), while it does not affect the oxindolic ester 10. Moreover, compound 8[10] was prepared from 7 (i/ Me_3OBF_4 ; ii/ NaH, DMF, 48 h, 20°C, 52%) and further heated with TsOH in toluene to yield the hexacyclic ketolactam 9 (c.a. 20%). Thus, the double cyclization of 7 to 9 (TsOH) is thought to proceed through 8, which involves a direct cyclization of an oxindolic methylketone (1a, scheme 1) to an enaminoketone 3.

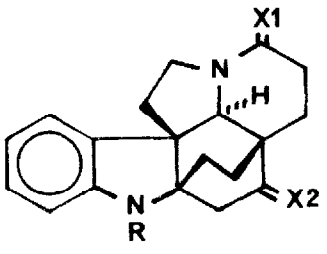
These results prompted to test the reactivity of the model oxindolic methylketone 11[6,7] towards TsOH (scheme 3). Reaction of 11 (major, more polar isomer) with TsOH in boiling toluene yielded three derivatives, which were enaminoketone 12 (traces) and the two epimeric indolenines 17a,b (14% ; 17a, less polar/17b, more polar = 5/7). Reduction of 17a with $LiAlH_4$ in THF gave the methylindoline 18 (methyl doublet at 1.30 ppm, J=7.2 Hz in ^1H NMR). The structure of 12 was supported by its synthesis from 11 using Ban's iminoether procedure (27%). Furthermore, upon heating in toluene plus TsOH, 12 again generated 17a and 17b. Interesting, when MeOH was added to the reaction mixture, the methyl ester 15 resulted (58%). Moreover, 11 was directly transformed into 15 (11%), along with 17a,b (12%) upon treatment with TsOH in toluene, addition of MeOH and reflux for 1 h.

These facts fit with the succession of events depicted on scheme 3, i.e. cyclization of 11 to 12, fragmentation of the protonated 12 to a mixed anhydride 13, which yields either acid 14 (H_2O) or ester 15 (MeOH). Acid 14 itself decarboxylates in acidic medium (arrows) to enamide 16, which finally cyclizes to 17a,b. The poor 14% yield in the reaction probably reflects uncomplete cyclization to 12 and decarboxylation of 14 under the reaction conditions used. The initial "activation" of the lactam carbonyl group by tosylic acid (and by PPA as well) still awaits further experiments to be fully understood[8].



Scheme 3

Finally, the hexacyclic ketolactam 9 was sequentially reduced in order to complete the total synthesis of (±)-aspidofractinine 23 : hydrogenolysis of the thioketal 19 (ethanedithiol, AcOH, BF_3, r.t. 12 h, 70%) with Raney nickel in MeOH exclusively gave the N(1)-methyllactam 20 (98%), which was reduced with $LiAlH_4$ to (±)-N-methyl-aspidofractinine 21 (84%). Replacing MeOH by EtOH in the desulfuration step gave 3-oxoaspidofractinine 22 (87%), which was reduced by $LiAlH_4$ to (±)-aspidofractinine 23 (70%)[9,10].



	X1	X2	R
19	O	$S(CH_2)_2S$	H
20	O	H_2	Me
21	H_2	H_2	Me
22	O	H_2	H
23	H_2	H_2	H

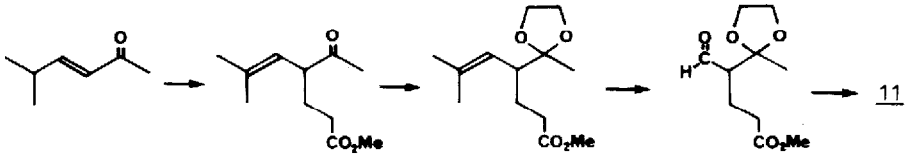
Acknowledgment : M.O. is indebted to the government of Algeria for a research grant.

References and notes :

1. T. Oishi, M. Nagai and Y. Ban, **Tetrahedron Lett.**, 1968, p.491.
2. J.-Y. Laronze, J. Laronze-Fontaine, J. Lévy and J. Le Men, **Tetrahedron Lett.**, 1974, p.491.
3. It probably involves participation of the other functionnal groups present in the molecule.
4. a) J. Lévy, J.-Y. Laronze, J. Laronze and J. Le Men, **Tetrahedron Lett.**, 1978, p.1579.
   b) J.-Y. Laronze, D. Cartier, J. Laronze and J. Lévy, **Tetrahedron Lett.**, 1980, p.4441.
   c) D. Cartier, M. Ouahrani, G. Hugel and J. Lévy, **Heterocycles**, 1988, 27, 657.
5. a) D. Cartier, D. Patigny and J. Lévy, **Tetrahedron Lett.**, 1982, p.1897.
   b) D. Cartier and J. Lévy, in press.

6. Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo and T. Oishi, **Tetrahedron Lett.**, 1982, p.5023.

7. While this compound had been previously synthesised by Ban[6], a more convergent access was devised as follows: 5-methyl-4-hexene-2-one (i) was monoalkylated with methyl acrylate to (ii)[5a,b] and further conducted to dioxolane(iii), which was ozonized to (iv). Condensation of (iv) wich 2-hydroxytryptamine (1/ PhH, reflux wich a Dean-Stark apparatus ; 2/ AcOH, reflux, 20h) yielded 11 (70%) as a mixture of (racemic) isomers, which were separated (tlc) into three compounds in the ratio 15:35:50, in order of increasing polarities.



i ii iii iv

8. It may be pointed out that the lactam carbonyl of oxindoles, like that in anilides and in N-acylindoles, partly behave as a ketone towards reducing agents.
9. The synthetic aspidofractinine was compared with an authentic sample kindly provided by Professor Le Men-Olivier.
   Isolation and structure of aspidofractinine :
   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**, 1963, 46, 742.
   B.W. Bycroft, D. Schumann, M.B. Patel and H. Schmid, **Helv. Chim. Acta**, 1964, 47, 1147.
   Previous syntheses of aspidofractinine :
   A. Guggisberg, A.A. Gorman, B.W. Bycroft and H. Schmid, **Helv. Chim. Acta**, 1969, 52, 76.
   Y. Ban, Y. Honma and T. Oishi, **Tetrahedron Lett.**, 1976, p.1111.
10. The structures of the new compounds were fully consistent with their UV, IR, MS, ^1H and ^{13}C NMR spectra. For examples :

	M S M+· (%), **base peak**	^1H N M R (300 MHz) δ (ppm), J (Hz)
15	312(12), **157**	7.58(1H,d, J=7.6) 7.38(1H,dd,J_1=J_2=7.6) 7.20(1H,dd,J_1=J_2=7.6) 7.03(1H,d, J=7.6) 4.25(1H,d,J=9) 4.04(1H,m) 3.86(1H,m) 3.45(3H,s) 2.53-2.38(3H,m) 2.30(3H,s) 1.95-1.85(4H,m)
17a	254(13), **157**	7.55(1H,d, J=7.6) 7.37(1H,m) 7.25(2H,m) 4.08(1H,m) 3.96(1H,dd,J_1=4.5,J_2=11.2) 2.5-2.3(3H,m) 2.25(3H,s) 2.10(1H,m) 1.90(1H,m) 1.63(1H,m) 1.40(1H,m) 1.04(1H,dt,J_1=4.5,J_2=11.2)
17b	254(13), **157**	7.58(1H,d, J=7) 7.36(1H,dd,J_1=J_2=7.6) 7.18(1H,dd,J_1=J_2=7) 7.04(1H,d, J=7.6) 4.09(1H,m) 3.97(1H,dd,J_1=4.5,J_2=11.2) 3.84(1H,m)2.41(2H,m) 2.32(3H,s) 2.26(1H,m) 1.80(1H,m) 1.68(1H,m) 1.37(1H,m) 0.75(1H,dt,J_1=4.5,J_2=11.2)
18	242(7), **97**	7.05(1H,dd,J_1=J_2=8) 7.03(1H,dd,J_1=J_2=7.6) 6.78(1H,d, J=7.6) 6.60(1H,dd,J_1=J_2=8) 3.82(1H,q,J=7.2) ...1.30(3H,d,J=7.2)
19	384(98), **169**	7.08(2H,dd,J_1=J_2=8) 6.77(1H,dd,J_1=J_2=8) 6.66(1H,d, J=8) 4.18(1H,dd,J_1=8.3,J_2=12) 3.92(1H,d,J=1.5) 3.38-3.05(5H,m) 2.66(1H,dd,J_1=3,J_2=14.5) 2.58-1.62(10H,m) 1.48(1H,dd,J_1=6,J_2=14)1.40(1H,m)
20	308(37), **170**	7.14(1H,dd,J_1=J_2=8) 7.07(1H,d,J=8) 6.72(1H,dd,J_1=J_2=8) 6.46(1H,d, J=8) 4.31(1H,dd,J_1=7.5,J_2=12) 3.59(1H,d,J=1) 3.15(1H,ddd,J_1=5.2,J_2=J_3=12) 2.60(3H,s) 2.38(2H,m) 2.10(1H,ddd,J_1=7.5,J_2=J_3=12)-1.95-1.30(12H,m)
21	294(84), **109**	7.36(1H,d,J=8) 7.06(1H,dd,J_1=J_2=8) 6.74(1H,dd,J_1=J_2=8) 6.40(1H,d, J=8) 3.23(1H,dd,J_1=8,J_2=17) 3.15-3.00(3H,m) 2.70(1H,ddd,J_1=3.7,J_2=8,J_3=14) 2.56(3H,s) 2.20-1.20(13H,m)
22	294(72), **169**	7.15(1H,d,J=7.6) 7.08(1H,dd,J_1=J_2=7.6) 6.83(1H,dd,J_1=J_2=7.6) 6.75(1H,d, J=7.6) 4.34(1H,dd,J_1=8,J_2=11) 3.80(1H,s) 3.30(1H,ddd,J_1=5.4,J_2=8,J_3=11) 2.70-1.35 (15H,m)

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