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SYNTHESIS OF HEXACYCLIC INDOLE ALKALOIDS RELATED TO VINDOLININE BY SONOCHEMICAL CYCLIZATION[1]

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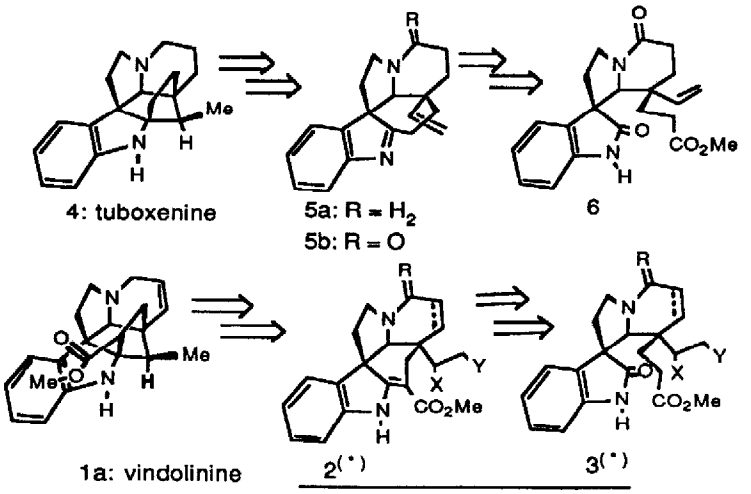
Summary: *Upon treatment with sodium in THF under sonication, 19-iodotabersonine underwent cyclization to the vindolinine ring system. The yields and ratio of the diastereomers thus obtained depended on the sonication parameters.*

Due to their corner-stone position in the biosynthesis of indole alkaloids, pentacyclic representatives of the *aspidosperma* series are ideal relay compounds for synthetic purposes. In earlier work from this laboratory, such *aspidosperma* precursors have been transformed into various naturally occurring molecular frameworks by rearrangement, fragmentation or cyclization processes. Using this strategy, we recently achieved an efficient entry to the highly congested hexacyclic tuboxenine **4** ring system (Scheme 1) by radical cyclization of the hemisynthetic pentacyclic precursor **5a**[2a]. Later, the indolenine **5b** was prepared from the tetracyclic oxindole **6** by a variation of our versatile synthesis of the *aspidosperma* skeleton and its further radical cyclization led to the completion of the first total synthesis of (±)-tuboxenine **4**[2b].

The present work opens a route to vindolinine **1a**[3] and its epimers **1b-d**[4] (Table), which differs from **4** by the presence of a double bond and, more importantly, the methoxycarbonyl group attached to C-16[13]. It deals with the 2-19 cyclization of pentacyclic *aspidosperma* precursors with structure **2**, a reaction required for a planned total synthesis of **1** from a related tetracyclic oxindole (viz **3**). The starting materials in this study were compounds **7-11** (Scheme 2). Derivatives **10a** and **7** were prepared from natural vindolinine following the procedure of Langlois *et al*[5].The 14,15-dihydro analogue **10b** similarly resulted from oxidation of 14,15-dihydrovindolinine with iodine. Next, 19-iodotabersonine **10a** was acylated (TFAA 2.2 eq, pyridine, 0°C, 10 min, 30%) to

the N-trifluoroacetamide **11** (mp 150°C, dec; ms, m/z 558.0539 (M.+, calc, 558.0628), 431(100 %); ^{1}H nmr, ∂ ppm 1.65 (d,1H,J=7Hz,H-19), 3.80(s,3H,COOMe); uv, nm, 210, 227(sh), 235(sh), 290). Lactam **8** (racemic) was obtained by total synthesis and further transformed by action of lead tetraacetate into the acetoxyindolenine **9**[14].

Scheme 1



Initiation of the cyclization could be envisaged by generating a radical, either on C-2, or on C-19, or even by generating a bi-radical which would readily collapse to a C-C bond. Compounds **7** and **9** were used to check the first proposal, while the 19-iodo derivatives **10a**, **10b** and **11** were candidates for the second and/or for the third possible pathway:

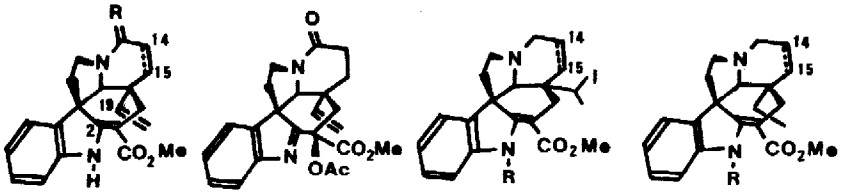
When reacted with sodium in THF, 18,19-dehydrotabersonine **7** gave only reduction products, and sonication failed to improve the reaction. Under similar conditions, the acetoxyindolenine **9** regenerated the anilinoacrylic ester **8**: overcrowding around C-16 disfavored cyclization to the benefit of a reduction process. An attempt of photochemical cyclization (MeOH, AcOH, 254 nm, 1h) of compound **7** was unsuccessful.

Starting from the 19-iodo compound **10b**, photochemical (MeOH, Na_2CO_3, 254 nm, 1h) or chemical generation of the 19-radical (AIBN, PhH , reflux with addition of Bu_3SnH, progressive or not[6,7]) only resulted in reduction to vincadifformine **12b**. It was hoped that radical cyclization would be favored by the reduced electronic density of the enaminic 2,16 double bond[8] of the trifluoroacetamide **11**. However, reaction of **11** with Bu_3SnH and AIBN in refluxing benzene gave 1-trifluoroacetyltabersonine **13** as the major product, and treatment of the crude reaction mixture with $NaBH_4$/MeOH mainly gave tabersonine**12a**. Nevertheless, the presence of traces of vindolinine diastereomers **1a-d** (Table), as indicated by ^{1}H nmr, was encouraging.

Reaction of **11** with sodium in refluxing THF (30 min) was still more promising, as it gave a *ca* 5% yield of vindolinines **1a-d**, along with 19-iodotabersonine **10a**. In the event, the reagent had

reductively cleaved the trifluorocetamido group in **11**, and this led to a study of the reaction of 19-iodotabersonine **10a** itself: after refluxing for 5 min a *ca* 8% yield of vindolinines **1a-d** was obtained, in which 19-epi-vindolinine **1c** was largely predominant. However the major product was an unstable indolinic alcohol resulting from overreduction of the ester group, and whose structure was not elucidated.

Scheme 2

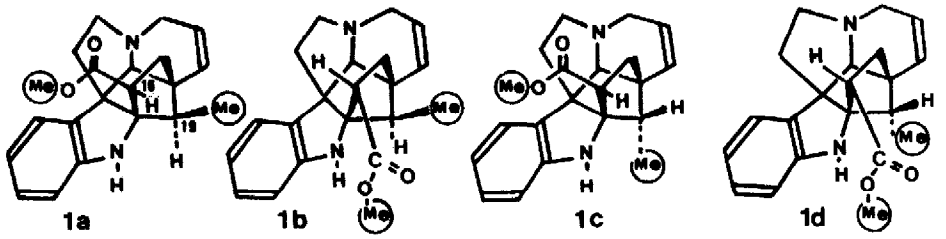


	R	14,15
7	H_2	Δ
8	O	H_2

	R	14,15
10a	H	Δ
10b	H	H_2
11	$COCF_3$	Δ

	R	14,15
12a	H	Δ
12b	H	H_2
13	$COCF_3$	

Table



1a **1b** **1c** **1d**

∂ ppm	vindolinine[3] 16R,19R	16-epi[4a] 16S,19R	19-epi[4b] 16R,19S	16-epi, 19-epi[4c] 16S,19S
19-Me	0.95	0.81	0.51	0.62
COOMe	3.68	3.76	3.60	3.72

The above radical reaction was markedly improved by ultrasonic activation[9,10]. Two sonicators were available: one (A)[11] with variable intensity, but with a disfavorable geometry (500W, 20KHz) and a laboratory cleaner (60W,45KHz) (B)[12]. All experiments were conducted under an argon atmosphere. The composition of the reaction mixtures was evaluated by ^1H nmr, on the basis of the chemical shifts listes in Table , and after separation by tlc.

With apparatus A, a solution of **10a** in dry THF was admixed with an excess of sodium in a small vessel which was externally cooled by an ice-water bath, in which the ultrasonic horn was

immersed. For reaction times ranging from 15 to 90 minutes the yield of cyclization reached 10%, while the unstable overreduced alcohol already mentioned was always present (5-15%). With lower ultra-sonic intensities, vindolinine **1a** and 16-epi-vindolinine **1b** were formed in a 1:2 ratio. With higher intensities, all four diastereomers **1a**, **1b**, **1c** and **1d** were formed in the ratio 14:50:35:1.

With apparatus B, after sonication for 10 to 30 minutes, the reaction mixture was much cleaner : extraction and separation led to the recovery of some starting material (35 %), and to the isolation of 16-epi-vindolinine **1b** (34%, 52% conversion), which was identified (R_F, ir, uv, ms, ^1H nmr) by comparison with a reference sample prepared[4a] from natural vindolinine.

The importance of physical and geometrical parameters on sonochemical reactions is well known, and the above results are likely to be improved by using a more adequate apparatus. Although the reaction is complicated by the eventual formation of all four stereomers, and by competitive reduction processes, it now offers a solution to the yet unsolved problem of the synthesis of the vindolinine skeleton.

Acknowledgement : Thanks are due to Dr D.Royer for measuring some nmr spectra.

Notes and References

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