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Stereoselective Radical Addition of Tertiary Amines to (5*R*)-5-Menthyloxy-2[5*H*]-furanone: Application to the Enantioselective Synthesis of (-)-Isoretronecanol and (+)-Laburnine

Samuel Bertrand, Norbert Hoffmann* and Jean-Pierre Pete

Laboratoire de Réactions Sélectives et Applications, UMR CNRS et
Université de Reims Champagne-Ardenne, UFR Sciences, B.P. 1039
F-51687 REIMS Cedex 2, France.

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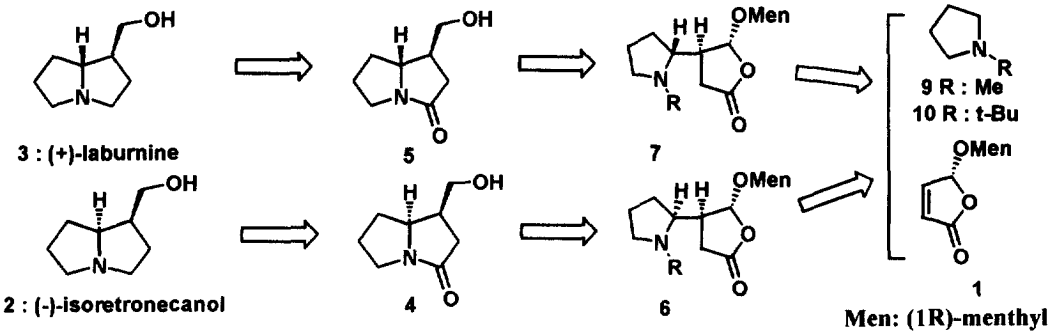
Abstract: The adducts of a stereoselective radical addition of tertiary amines with (5*R*)-5-menthyloxy-2[5*H*]-furanone were transformed very efficiently into enantiomerically pure pyrrolizidine and indolizidine alkaloids, through a three steps sequence.

We recently found that α-aminyl radicals derived from tertiary amines could be added very efficiently to electron deficient alkenes, when these radicals were generated by a Photo-Electron-Transfer (PET) process, induced by 4,4'-dimethoxybenzophenone as photosensitizer.[1] With (5*R*)-5-menthyloxy-2[5*H*]-furanone **1** as electron deficient alkene and N-alkylpyrrolidines, a complete facial stereoselectivity was observed. However, the absolute configuration of the asymmetric center on the pyrrolidine ring of **6** and **7** has to be confirmed. The easily available starting materials, the high chemical and quantum yields observed for the adducts, and the high stereoselectivity of the reaction, led us to apply it in an enantioselective synthesis of some necine bases.[2] These alkaloids have frequently been isolated from plant sources and in some cases also from animals. Due to their toxic properties, they have received extensive chemical and biological study. Recently, some of these structures have been studied for their pharmaceutical activity (eg. antitumor activity, effects on cardiovascular tissues and on neuromuscular tissues).[3] Although numerous strategies have already been described for the synthesis of pyrrolizidines alkaloids such as (-)-isoretronecanol **2** [4] and (+)-laburnine **3** [5], either the described processes needed very elaborated starting materials or quite long sequences of reactions. This report describes a very short, efficient and versatile method for preparing these alkaloids.



As illustrated in the retrosynthetic scheme, the alkaloids **2** and **3** might be obtained from the furanone **1** and pyrrolidine derivatives through a succession of three simple reactions involving a radical addition as the key step. Furthermore, this approach might be extended to prepare indolizidine derivatives such as **16**, possessing the skeleton of stellettamide A[6] if N-alkylpiperidines were used in place of **9** and **10**.

Addition of N-alkylpyrrolidines **9** and **10** to **1** led to a mixture of two diastereoisomers (55 : 45) having

E-mail: norbert.hoffmann@univ-reims.fr Fax: + 33 3 26 05 31 66

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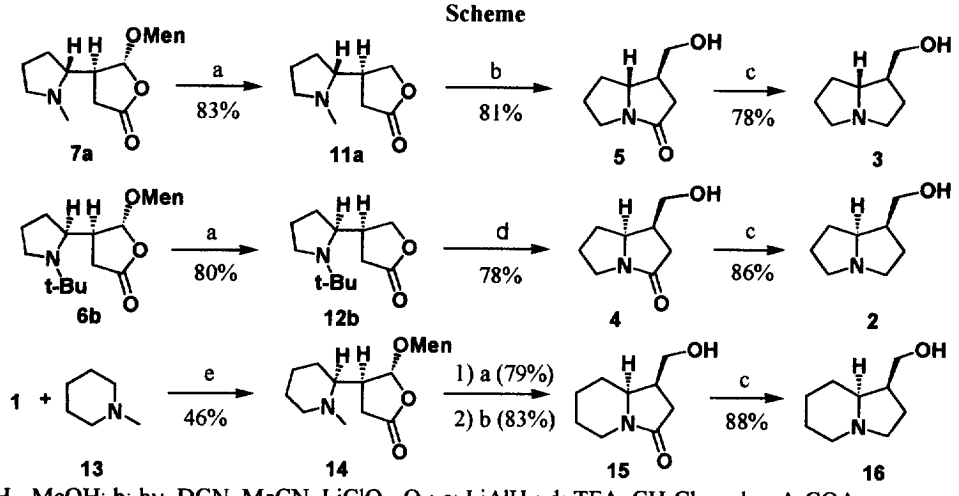
the same (*3S*)-configuration of the furanone ring. The N-methyl stereoisomer **7a** (52%) was selectively transformed into (+)-laburnine **3** by a three steps sequence. Successive reduction of the ketal group of **7a**, photooxidation of the N-methyl group[7] followed by an in situ cyclization, and finally reduction of the lactame **5** led to (+)-laburnine **3** ($[\alpha]_D^{21}$= +14.0 (c=1.20; EtOH)) with an overall yield of 27%.[8] A slightly different scheme was used to prepare (-)- isoretronecanol **2**. The adduct **6b** 44 % of t-butylpyrrolidine and **1** was treated successively by sodiumborohydride, trifluoroacetic acid to promote the formation of lactame **4**, and finally $LiAlH_4$ to give **2** ($[\alpha]_D^{24}$ = -76.4 (c=1.14; EtOH)) from furanone **1**, with a overall yield of 23%.[8]

Scheme



a: $NaBH_4$, MeOH; b: hv, DCN, MeCN, $LiClO_4$, O_2; c: $LiAlH_4$; d: TFA, CH_2Cl_2; e: hv, ArCOAr

In an attempt to extend this strategy to indolizidines, we irradiated **1** in the presence of a large excess of N-methylpiperidine **13** and catalytic amounts of 4,4'dimethoxybenzophenone as sensitizer.[9] Interestingly, **14** could be isolated from the reaction mixture, without any evidence of another diastereoisomer. Transformations similar to those described for the synthesis of pyrrolizidines **2** and **3**, allowed the synthesis of **16** with an overall yield of 27%. If we consider that the two enantiomers of **1** are similarly available in large quantities, this approach can be extended to many other pyrrolizidine and indolizidine alkaloids.

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References and Notes

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8) **2** and **3** were enantiomerically pure (>98% ee, chiral gas chromatography, Chrompack, CP-Cyclodextrin-B-236-M-19).

9) A solution of **1** (240 mg, 1 mmol), **13** (6 g, 60 mmol) and 4,4'-Dimethoxybenzophenone (24 mg, 0.1 mmol) in 50 ml acetonitrile was irradiated at λ=350 nm for 20 min. After evaporation, the residue was chromatographed (silica gel, ethyl acetate/petrolether: 1/2). Starting material **7a** or **6b** was easily separated as a pure diastereomer by chromatography of the reaction mixture of the radical addition of pyrrolidine on **1**.[1]