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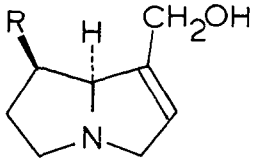
A NITRONE-BASED SYNTHESIS OF THE PYRROLIZIDINE ALKALOID CROALBINECINE

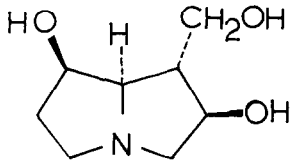
Joseph J. Tufariello and Kevin Winzenberg
Department of Chemistry, State University of New York at Buffalo
Buffalo, New York 14214

Summary: A highly stereoselective and efficient nitrone-based synthesis of dl-croabinecine is recorded herein.

We have previously explored the use of nitrone cycloaddition chemistry in the synthesis of the unsaturated pyrrolizidine alkaloids dl-supinidine (1a) and dl-retronecine (1b).[1,2] The success of these successful synthetic endeavors relied heavily on a firm understanding of the regiochemical features of nitrone-crotonate cycloaddition reactions (vide infra).[1,2] We describe herein the synthesis of dl-croalbinecine (2b); a functionally and stereochemically more complex



1a, R= H
b, R= OH



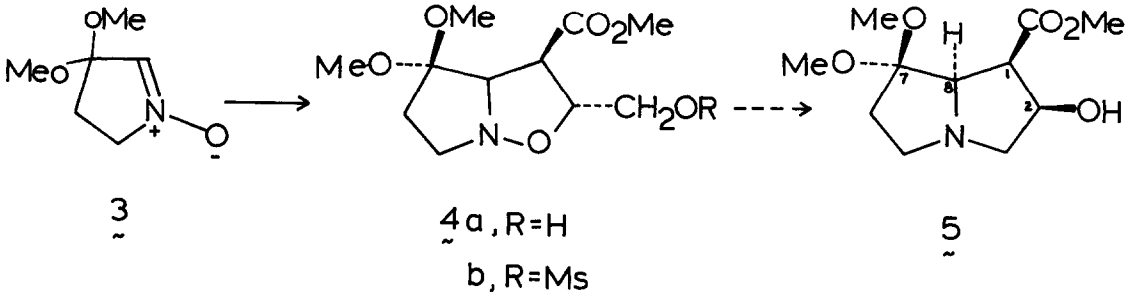
2b

pyrrolizidine alkaloid, the construction of which depends heavily on an understanding of the stereochemical features of the same cycloaddition processes.

Croalbidine, isolated from Crotalaria albida, Heyne ex Roth (Crotalaria montana), is a macrocyclic pyrrolizidine alkaloid which affords the necine base croalbinecine (2b) upon acid hydrolysis.[3] Croalbinecine is one of two naturally occurring pyrrolizidine triols, the other being rosmarinecine.[4,5]

In general, a useful synthetic methodology must either introduce the desired stereochemistry of the target molecule directly or, alternatively, provide a predictable stereochemical outcome alterable to the desired result without undue complication. We have employed the latter strategy to introduce the four continguous chiral centers of croalbinecine with the proper relative stereochemistry.

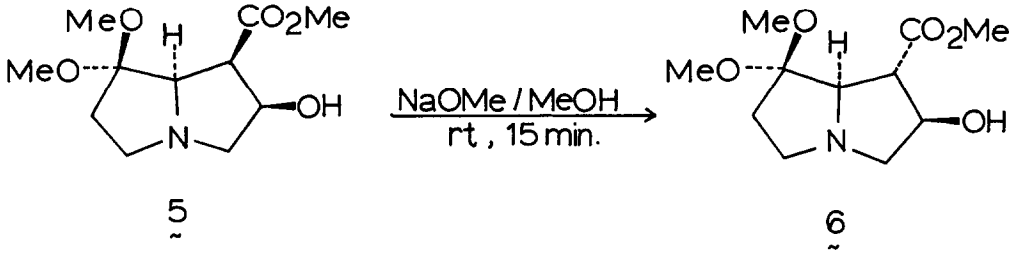
We have previously shown that the addition of pyrroline nitrone 3 to methyl 3-hydroxy-crotonate affords 4a with very high stereoselectivity.[2,6] This isoxazolidine, after routine



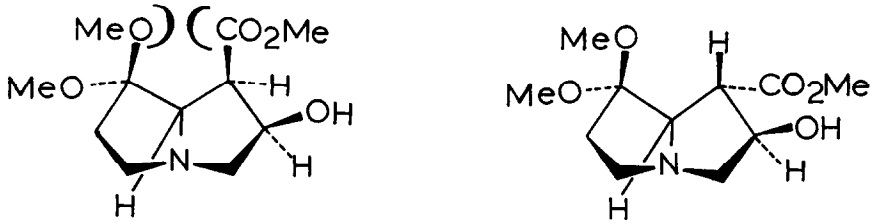
3 4a, R=H b, R=Ms 5

mesylation (i.e. to give 4b) and hydrogenolytic cleavage of the nitrogen-oxygen bond was shown to give pyrrolizidine 5, a key intermediate in the synthesis of dl-retronecine (1b).[2]

The pyrrolizidine 5 requires inversion of the relative stereochemistry at C-1 to conform to that present in croalbinecine. The alteration proceeds with remarkable ease (NaOMe, MeOH, rt, 15 min.; 96% yield) as a consequence of an unfavorable transannular interaction in 5 (cf. 5a)



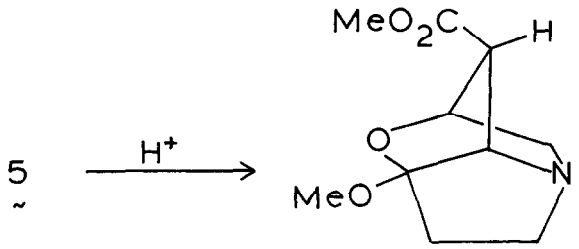
5 6



5a 6a

which is absent in the epimer 6 (cf. 6a). In the pmr spectrum of 6, $H_1\alpha$ appears as a one-proton quartet (J=6 Hz) at δ 4.46 ppm while in that of 5 the $H_1\beta$ proton appears as a multiplet between δ 4.50 and 4.35 ppm.

It was anticipated that the requisite acid hydrolysis of ketal 6 might prove burdensome due to the proximity of the basic nitrogen to C-7, and to the reported[6] propensity of 5 to undergo an



5 ~

7 ~

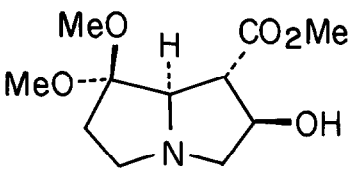
acid catalyzed intramolecular rearrangement (i.e. to give 7). While this observation engendered some caution with regard to the projected synthesis of croalbinecine, it was at the same time encouraging since it could only be accommodated by the relative stereochemical assignments at C-2 and C-8 depicted for 5, and consequently for 6 as well.

In order to prevent the unwanted participation of the C-2 hydroxyl group in the transketalization reaction, it was decided to protect this function as the corresponding acetate. This was accomplished by initial reduction of the ketal 6 with lithium aluminum hydride to give the amino diol 8a in 89% yield (cf. Scheme). The salient features of the pmr spectrum of 8a are a two-proton singlet at δ 3.35 ppm, exchangeable with deuterium oxide, and a two-proton doublet (J=5.3 Hz) at δ 3.65 ppm which can be assigned to the hydroxyl groups and to the methylene protons of the C-1α-hydroxymethyl substituent, respectively. Acetylation of 8a gave the diacetate 8b (85%), thereby providing the required block of the C-2 hydroxyl group. The ketal diacetate 8b proved to be unreactive to the standard conditions (e.g. 90% aq. acetic acid) of ketal hydrolysis which would not concomitantly unmask the hydroxyl group at C-2. Fortunately, treatment of 8b with excess triflouroacetic acid at room temperature, followed by neutralization with sodium bicarbonate solution, afforded the required ketone 9 in 98% yield. The two three-proton singlets at δ 2.08 and δ 2.00 ppm which appear in the nmr spectrum of 9 indicate that the acetate moieties remain intact. We suggest that the progenitor of 9 is the trifluoroacetyl ketal 8c, a precursor which should be readily hydrolyzed upon mild alkaline treatment.

The preferred butterfly shape of the pyrrolizidine nucleus suggests that hydrogenation should occur from the more exposed convex face. Indeed, hydrogenation of 9 using Adams catalyst in glacial acetic acid provided a stereospecific means of generating the alcohol diacetate 2a in 98% yield.

Reaction of alcohol diacetate 2a with alane[6] in THF at 0° gave, in 79% yield, 1α-hydroxymethyl-8α-pyrrolizidin-2β,7β-diol which was spectroscopically identical (pmr, ir, tlc) with authentic croalbinecine (2b) obtained by the hydrolysis of a sample of croalbidine.[7,8]

Acetylation of the synthetic pyrrolizidine triol (2b) produced, in 86% yield, the corresponding triacetate 2c which was similarly identical (pmr, lr, tlc) with the triacetate prepared from authentic croalbinecine.



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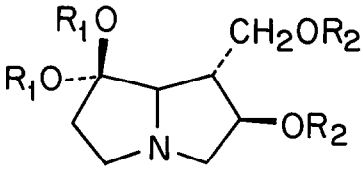
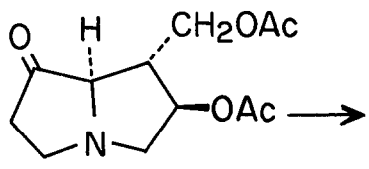


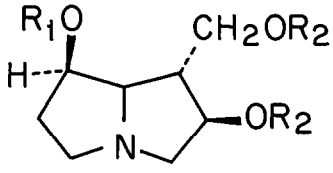
8a, R_1=Me, R_2=H

b, R_1=Me, R_2=Ac

c, R_1=CF_3CO, R_2=Ac



9



2a, R_1=H, R_2=Ac

b, R_1=R_2=H

c, R_1=R_2=Ac

References and Notes

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8. We thank Dr. R. S. Sawhney (University of Tennessee) for a generous gift of authentic croalbidine and Dr. C. C. J. Culvenor (CSIRO, Melbourne, Australia) for the pmr spectrum of natural croalbinecine.

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