Tetrahedron Letters Vol. 21, pp 3651 - 3654 0040-4039/80/0915-3651$02.00/0

IMPROVED FORMAL TOTAL SYNTHESIS OF TETRAHYDROMETINOXOCRININE[1]

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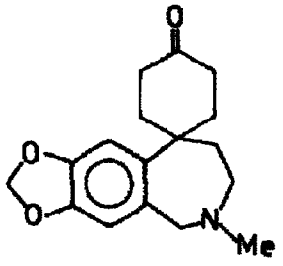
Abstract. An improved, isomer-free synthesis of Tetrahydrometinoxocrinine (1) is described.

Tetrahydrometinoxocrinine (1), an important degradation product of crinine (2), was initially prepared by Wildman[2] in 1959. Later on, Uyeo and coworkers[3] developed a total synthesis of 1 based on the construction of the 7-membered nitrogenous ring via a non-selective Schmidt reaction[4] on tetralone 3, and further extended their synthetic work to encompass dihydrocrinine (4) itself[5].



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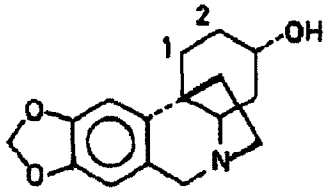

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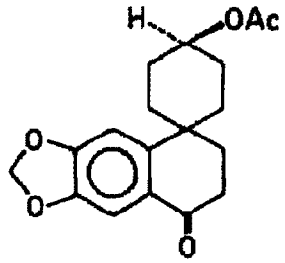

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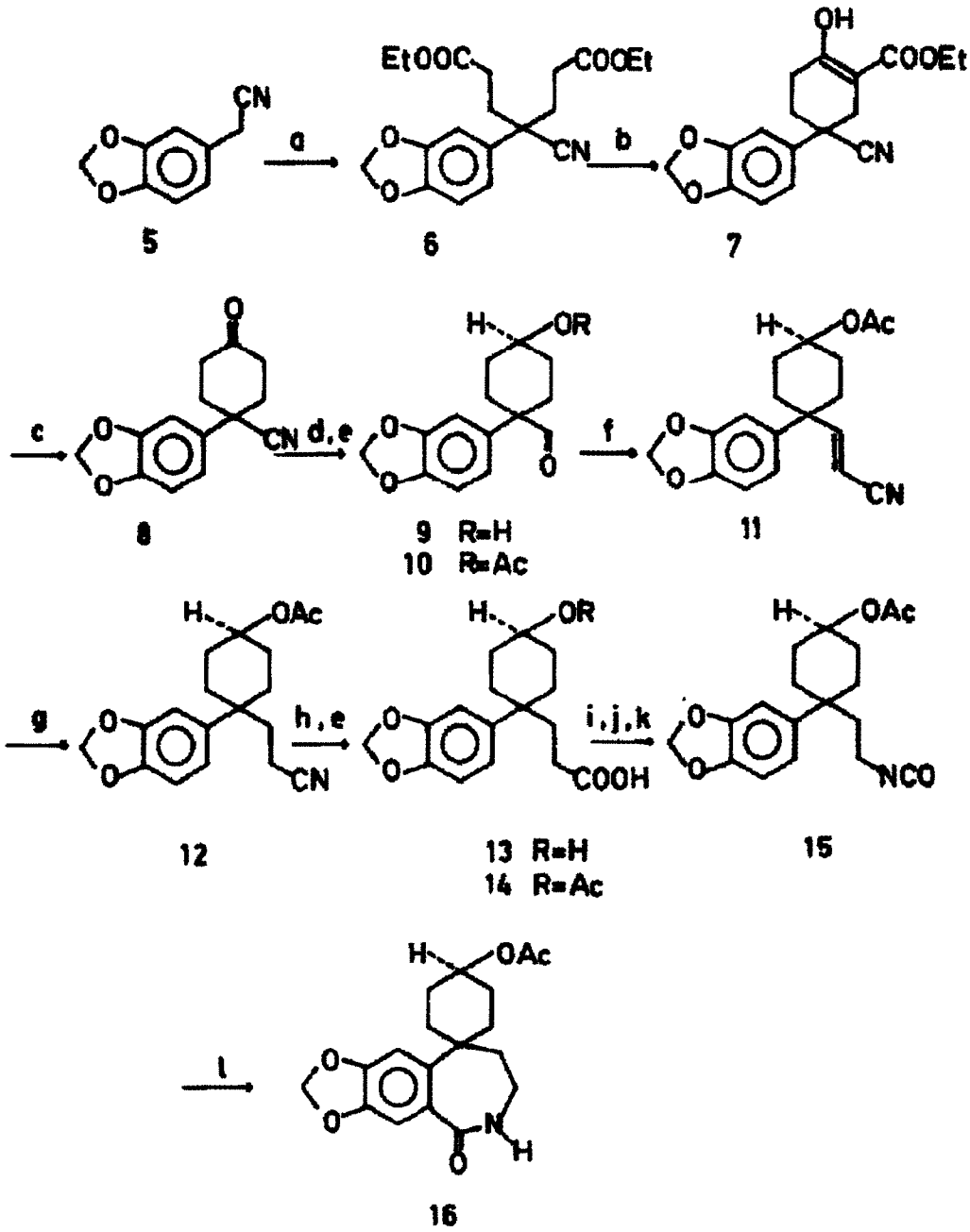
We have thus developed a new specific entry into the heterocyclic ring system[6] of 1, a 1,2,4,5-tetrahydrobenzo-2(3H)-azepin, by performing an acid-catalyzed intramolecular aromatic acylation with a substituted isocyanate[7].

Therefore, piperonyl nitrile[8] (5) was first treated with ethyl acrylate and Triton B in dry acetonitrile[9] to give a nearly quantitative yield of pimelate 6, which suffered a smooth Dieckman condensation (NaH/DME) to afford the enolic carbetoxicyclohexanone 7, mp 114-116°, in 90% yield. Compound 7 was then decarboxylated with sodium chloride in wet DMSO[10] to give cyclohexanone 8 in 95% yield, and further reduced with diisobutylaluminum hydride[11] (DIBAL-H) in refluxing benzene to



[a] CH_2=CH-COOEt/Triton B/CH_3CN; [b] NaH/DME; [c] NaCl/DMSO-H_2O; [d] DIBAL-H/C_6H_6; [e] Ac_2O/Py; [f] $(EtO)_2POCH_2CN$/NaH; [g] Pd/EtOH; [h] KOH/DEG; [i] $(COCl)_2$; [j] NaN_3/Me_2CO-H_2O; [k] $C_6H_5CH_3$/heat; [l] PPA.

furnish in a stereospecific manner the syn-hydroxyaldehyde 9, mp 124-125°, in 90% yield; tosylhydrazone mp 204-206°[12]. Acetylation of 9 under the standard conditions produced acetate 10, mp 103-105° (δ 2.03 ppm, -OAc), in 91% yield; tosylhydrazone mp 183-185°.

Although the reduction of 8 requires careful control of the experimental parameters to avoid the presence of the epimeric alcohol, the present reaction conditions, which allow the isolation of acetate 10 in an overall yield of 69% from 1 represent a considerable improvement upon the reported ones[3].

Futhermore, compound 10 reacted easily with diethyl cyanomethylphosphonate[13] and sodium hydride in dry DME to afford the oily E-acrylonitrile 11, as shown by the observed coupling constant (J=16 Hz) for the olefinic protons (δ 6.72 and 5.10 ppm), in 98% yield. Next, hydrogenation over a borohydride-reduced palladium catalyst[14] afforded an 85% of the saturated nitrile 12, mp 83-85°, which upon base treatment (40% aqueous KOH/diethylene glycol) produced hydroxyacid 13, mp 134-136°, in 97% yield.

Acetylation of 13 gave a quantitative yield of the expected acetoxypropionic acid 14, which was next submitted to the conditions of the Curtius rearrangement[15] to give isocyanate 15, ν max 2260 cm^{-1}. Treatment of 15 (crude) with excess polyphosphoric acid (PPA) at room temperature furnished, in 49% overall yield from 14, the pure acetoxylactam 16, mp 103-105° (Lit.[3] mp 104-105°) This latter compound proved spectroscopically identical with the sample prepared earlier on by Professor Uyeo and coworkers[3].

Since the final trivial transformations of acetoxylactam 16 into the tetrahydrometinoxocrinine (1) have already been performed by Uyeo[3], our present synthesis of 16 constitutes an improved isomer-free synthesis of 1 as well as of dihydrocrinine[5] (2) itself.

Obviously, the chemistry and synthetic strategy involved in these reaction sequences may be conveniently applied to the synthesis of a number of Amaryllidaceae alkaloids possessing the 5,10b-ethanophenanthridine skeleton, and these results will be reported independently.

Acknowledgments. We thank Professors S. Uyeo and H. Irie of the Faculty of Pharmaceutical Sciences of the University of Kyoto for kindly providing us with the original spectroscopic data of acetoxylactam 16.

Financial support by Consejo Nacional de Ciencia y Tecnología, México, PCNB Grant No. 1612/79, is greatly appreciated.

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(Received in USA 28 April 1980)