FURO[2,3-*c*]-, PYRROLO[2,3-*c*]- AND PYRIDAZINO[4,5-*c*]-QUINOLINES

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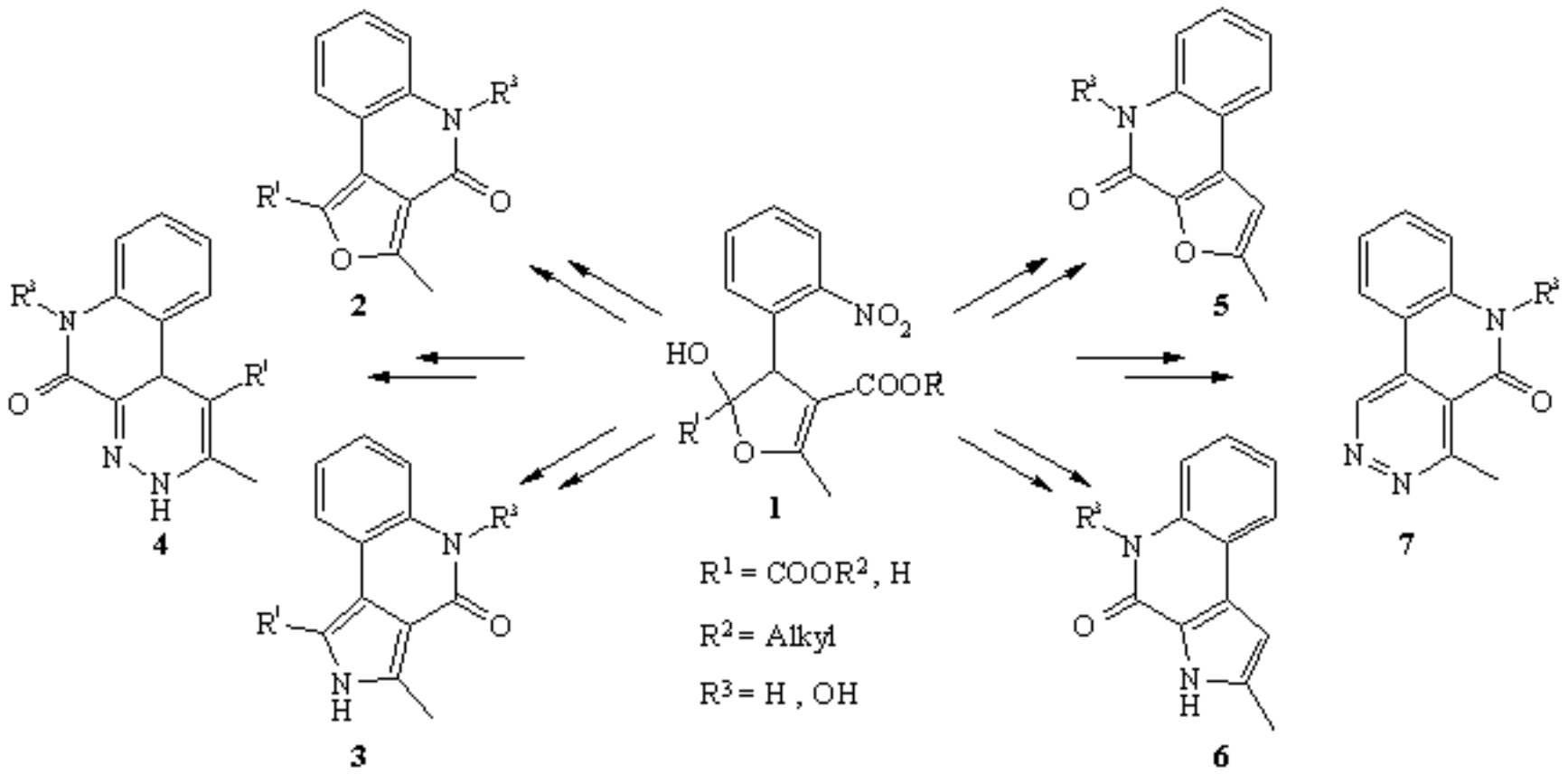
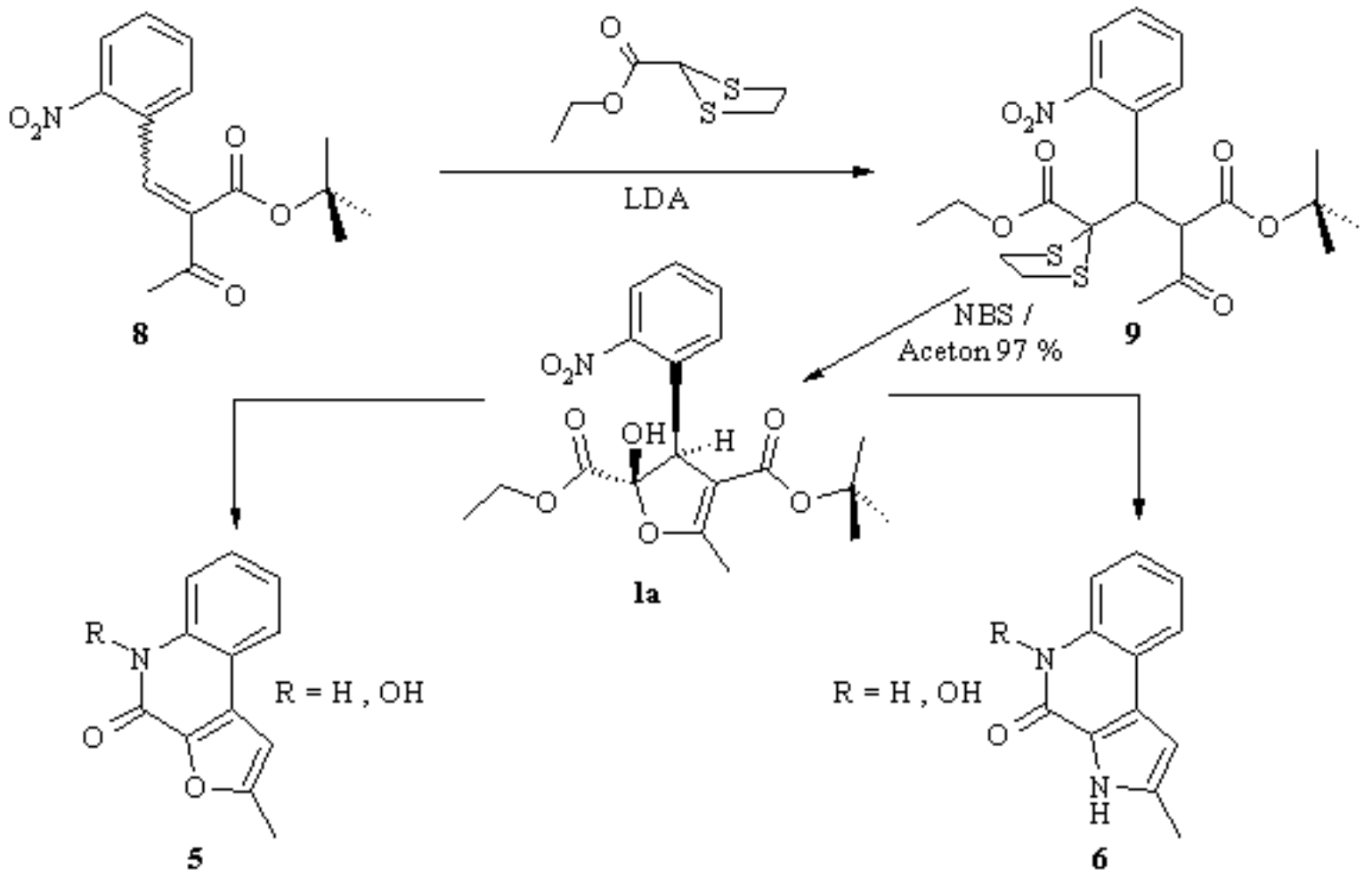
Introduction

The Furo-, pyrrolo- and pyridazino[3,4-*c*]quinolines **2**, **3** and **4** can be synthesized from ethyl methyl 2,3-dihydro-2-hydroxy-5-methyl-3-(2-nitrophenyl)furan-2,4-dicarboxylate (**1**; R^1 = COOEt, R^2 = Me) [1,2]. Cyclic hydroxamic acids with these framework are of pharmaceutical interest with regard to lipoxygenase inhibitors, while lactams are suitable educts for aza analogues of the antimalarial drug halofantrine.
Now we report the synthesis of the isomeric furo[2,3-*c*]- and pyrrolo[2,3-*c*]quinolines **5** [3] and **6** from the 4-*t*-butylester **1a** as well as the isomeric pyridazino[4,5-*c*]quinolines 7 from the 4-mono-ethyl ester **1b**.



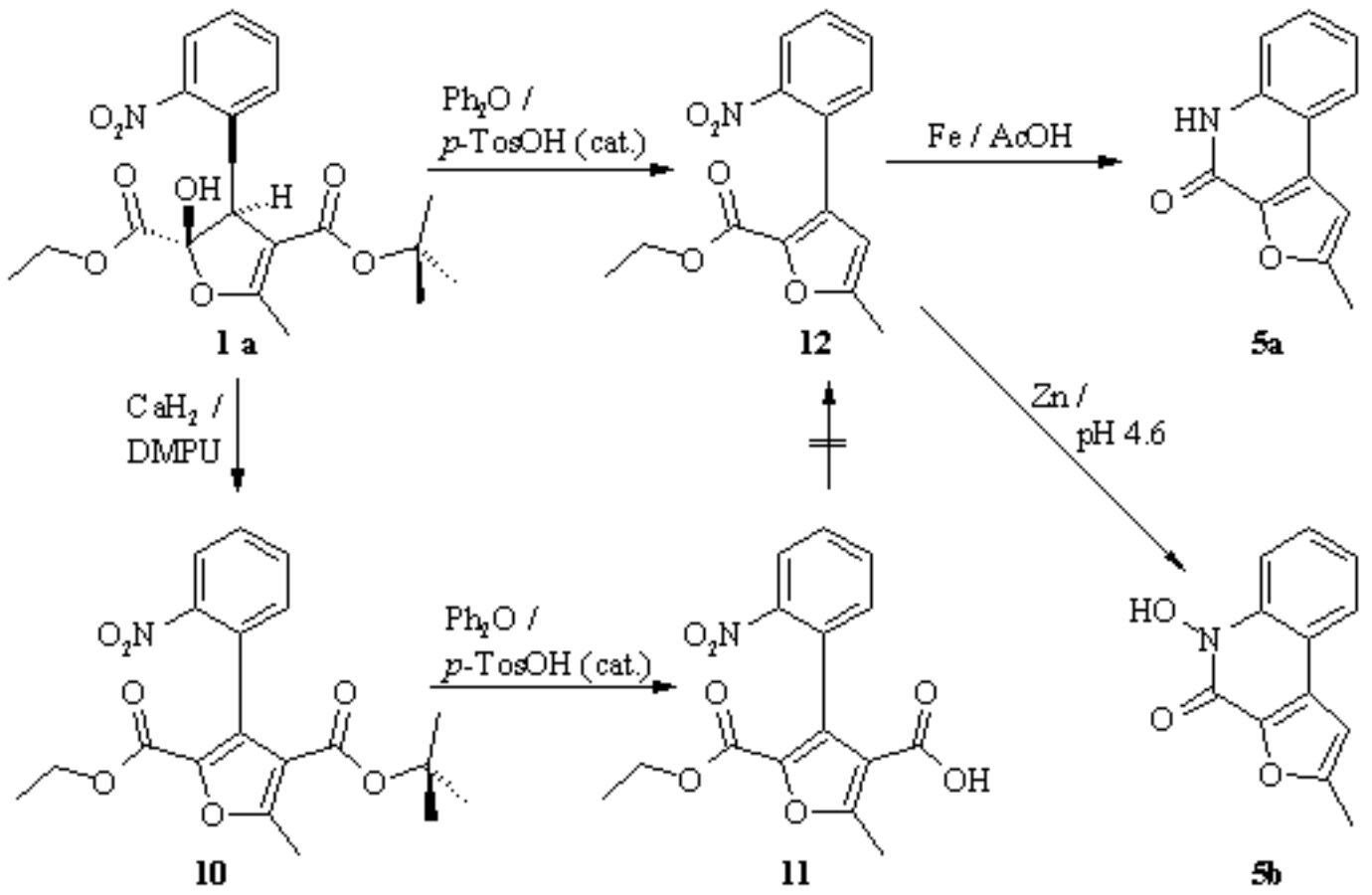
2-Hydroxy-2,3-dihydro-2,4-furandicarboxylates

The *t*-butyl ethyl 1,3-dithiolandicarboxylate **9** is formed by *Michael* addition of *t*-butyl (2-nitrobenzylidene)acetoacetate **8** to lithium 2-carbethoxy-1,3-dithiolan. Cleavage of the dithioacetale with NBS leads to the 4-*t*-butyl 2-ethyl 2-hydroxy-2,3-dihydro-2,4-furandicarboxylate **1a**, whose structure is confirmed by X-ray crystal structure analysis. Compound **1a** represents the educt for the synthesis of the furo[2,3-*c*]- and pyrrolo[2,3-*c*]quinolines **5** and **6**.



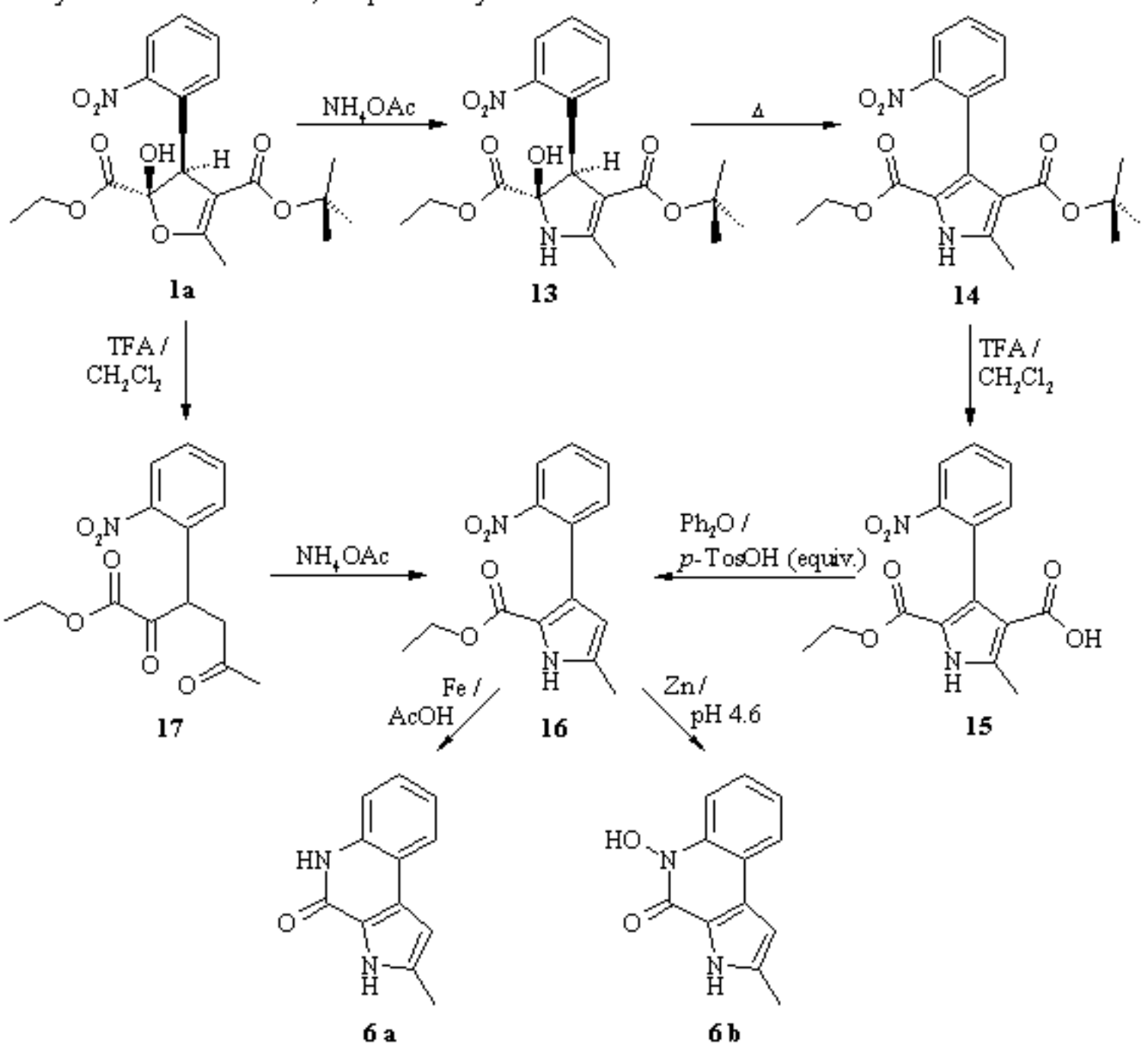
Furo[2,3-*c*]quinolines

Dehydration of the 2-hydroxy-2,3-dihydrofuran **1a** with CaH_2 / DMPU yields the 4-*t*-butyl 2-ethyl 2,4-furandicarboxylate **10.** Compound **10** is converted selectively into the ethoxycarbonyl-furancarboxylic acid **11** by heating in diphenylether / p-TosOH. The *t*-butylester is completely eliminated to yield **12** by using **1a** under the same conditions. Reduction of the nitro group of **12** with Fe / AcOH, followed by ring closure of the obtained amine with the ester function forms the lactam **5a** [3]. Treating **12** with Zn / AcOH (pH = 4.6) forms the hydroxamic acid **5b** by intramolecular cyclization of the intermediate hydroxylamine.



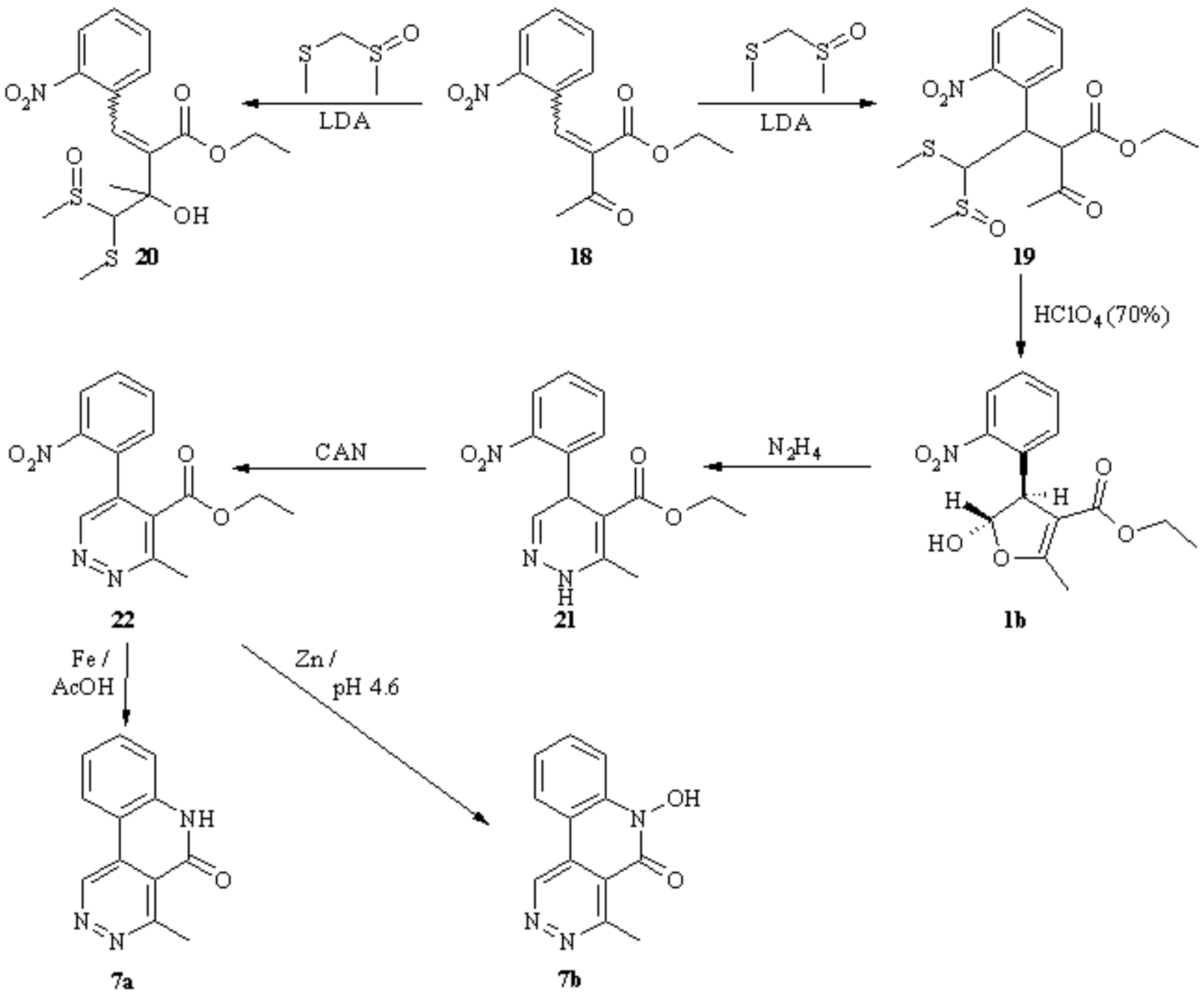
Pyrrolo[2,3-*c*]quinolines

The 4-*t*-butyl 2-ethyl 2,3-dihydro-2,4-pyrroledicarboxylate **13** is obtained from the reaction of the furan **1a** with NH_4OAc. The halfaminale **13** easily looses water to give the pyrrole **14**. The carboxylic acid **15** is received from the selective cleavage of the *t*-butylester by reaction with TFA. The decarboxylation of **15** by heating in diphenylether / p-TosOH gives only low yield of **16**. Much better results are received by an alternative way of reaction. After removing the *t*-butylester of **1a** with TFA the resulting tricarbonyl compound **17** is cyclized with NH_4OAc to yield the pyrrole **16**. Reduction of the nitro group with Fe / AcOH or Zn / AcOH at pH = 4.6 and subsequent ring closure affords the lactam **6a** or the hydroxamic acid **6b**, respectively.



Pyridazino[4,5-*c*]quinolines

Michael addition of the ethyl (2-nitrobenzylidene)acetoacetate **18** with the (methylsulfanyl) (methylsulfinyl)methan leads to the 1,4-adduct **19** as the main product and the 1,2-adduct **20** as the by-product. Cleavage of the dithioacetale **19** with $HClO_4$ yields the ethyl 5-hydroxy-4,5-dihydro-3-furancarboxylate **1b**. The configuration of compound **1b** is elucidated by X-ray crystal structure analysis. Reaction of **1b** with hydrazine forms the 1,4-dihydropyridazine **21**, which can be dehydrogenated by CAN to achieve the pyridazine **22**. Reductive cyclization of **22** under the conditions described previously yields the lactam **7a** or the hydroxamic acid **7b**, respectively.



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References

[1] K. Görlitzer, H. Behrje, *Pharmazie* **1996**, *51*, 523 – 527.
[2] K. Görlitzer, H. Behrje, *Pharmazie* **1996**, *51*, 528 – 534.
[3] T. Usui; Y. Tsubone; A. Tanaka, *J.Heterocycl. Chem.* **1985**, *22*, 849 - 852
[4] Patent; Fujisawa Pharmaceutical Co., *Chem. Abstr.* **1966**, *65*, 13661a