

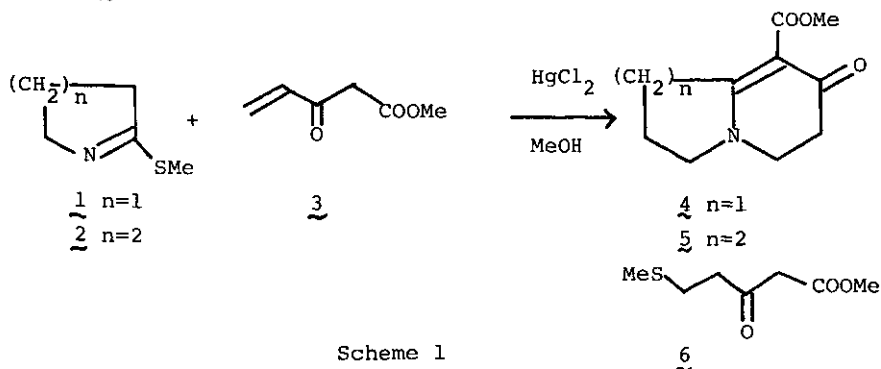
REACTION OF CYCLIC THIOIMIDATES WITH METHYL 3-OXO-4-PENTENOATE
(NAZAROV'S REAGENT). TOTAL SYNTHESIS OF (+)-EPI-LUPININE

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Abstract - Annulation of cyclic thioimidates with Nazarov's reagent in the presence of mercuric chloride gave indolizidine and quinolizidine derivatives. Stereospecific transformation of the quinolizidine to (+)-epi-lupinine is described.

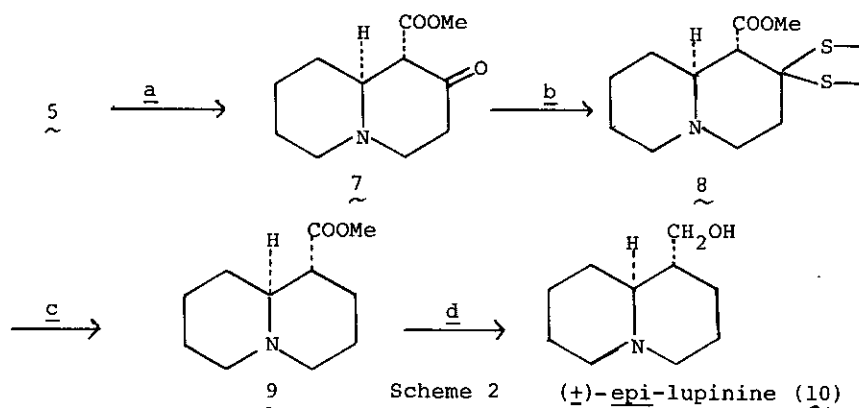
Cyclic thioimidates are important building blocks for synthesis of N-heterocycles such as alkaloids.¹ In connection with our research on the utilization of cyclic thioimidates in a heterocyclic synthesis,² we studied the annulation of cyclic thioimidates with methyl 3-oxo-4-pentenoate (Nazarov's reagent). In this communication, we describe an efficient and stereospecific synthesis of (+)-epi-lupinine³ from the annulated product.

Robinson annulation using Nazarov's reagent is an important route to functionalized 6-membered ring compounds.⁴ Reaction of cyclic thioimidates (1 and 2) with Nazarov's reagent (3)⁵ in the presence of mercuric chloride (HgCl_2)⁶ (1 eq.) in methanol at room temperature gave indolizidine (4)⁷ and quinolizidine (5)⁷ in 59% and 62% yields, respectively, together with methyl 5-methylthio-3-oxo-pentenoate (6).



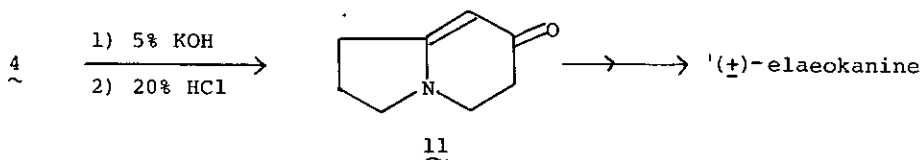
Transformation of 5 into (+)-epi-lupinine is shown in Scheme 2. Reduction of 5 with diisobutylaluminum hydride (DIBAL-H) in the presence of triethylamine (NEt₃) in tetrahydrofuran (THF)⁸ stereospecifically gave β-ketoester quinolizidine (7)^{7,9} in 55% yield. Thioketalization of 7 with 1,2-ethanedithiol in the presence of boron trifluoride etherate (BF₃·OEt₂) in trifluoroacetic acid (CF₃COOH) afforded the corresponding thioketalized compound (8) in 81% yield, which was converted to ester quinolizidine (9)⁷ (51%) by desulfurization with Raney Ni (W-2). Finally, 9 underwent reduction with lithium aluminum hydride (LiAlH₄) to give (+)-epi-lupinine (10) (75%) which had spectra identical to that of authentic material.^{3a}

Next, hydrolysis of 4 with aq. potassium hydroxide solution followed by dicarboxylation with aq. hydrochloric acid gave enaminoketone (11) (85%) which was served as the key intermediate for (+)-elaeokanine synthesis.¹⁰



a: DIBAL-H, NEt₃, THF, -50°C, 5 h. b: HS(CH₂)₂SH, BF₃·OEt₂, CF₃COOH, r. t., 15 h.

c: Raney Ni (W-2), EtOH, reflux, 3 h. d: LiAlH₄, THF, reflux, 1 h.



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