Pergamon

Tetrahedron Letters, Vol. 38, No. 3, pp. 327-330, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02343-X

Studies Toward Funiculosin. Intramolecular Carbonyl Condensations Using Carboxamidimidazolide Intermediates.

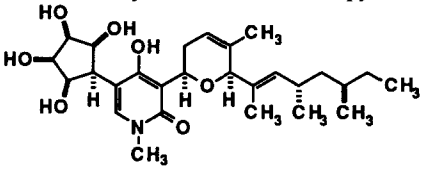
David R. Williams*, Patrick D. Lowder, and Yu-Gui Gu

Department of Chemistry, Indiana University
Bloomington, Indiana 47405 U.S.A.

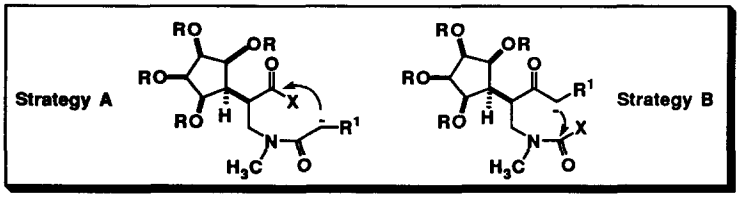
Abstract: *Internal enolate condensations, utilizing carboxamidimidazoles as activated ureas, provide a general synthesis of the 3,5-disubstituted-4-hydroxy-2-pyridinone 2 as found in funiculosin. The novel all-syn-cyclitol, C-linked to the heterocyclic system, is prepared from croconic acid.* Copyright © 1996 Elsevier Science Ltd

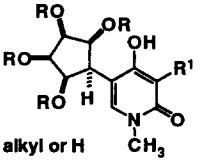
Funiculosin (1) is a member of a small class of natural products featuring the central 4-hydroxy-2-pyridinone heterocycle.[1] This unique secondary metabolite possesses significant antifungal potency as well as antitumor and antiviral effects. The structure exhibits the unusual *syn*-substituted cyclopentanetetrol as a rare example of a substituted cyclitol. The cyclitol is directly bonded to the C_5 carbon of the pyridone ring, providing the perspective of analogy to unnatural nucleosides which are being thematically explored as potential antiviral and antitumor candidates.[2] Herein we will describe two aspects of our studies toward funiculosin (1). Firstly, a pathway for the stereocontrolled synthesis of the all-*syn*-cyclopentane moiety is detailed. Secondly, we will document the utilization of key intermediate carboxamidimidazolides, as unsymmetrical ureas affording a general base-induced cyclization route to the pyridinone nucleus.

1 Funiculosin



Plans for an enantioselective synthesis of 1 require preparation of optically active intermediates for the acyclic component. However, as a matter of stereochemical control, the tetrol portion of 1 possesses a *meso* plane of symmetry, conferring great advantages for a convergent synthesis pathway.[3] Two intramolecular condensation pathways were examined for ring closure of the central 4-hydroxy-2-pyridinone as generalized by strategy A and strategy B below. Our earlier reports of the syntheses of tenellin and illicolin H had utilized strategy A (R = $COOCH_3$).[4,5] However, substrates which lacked the β-keto amide functionality, offering formation of stable enolates in strategy A, gave poor chemical conversions to complex mixtures of products (for example: R^1 = alkyl, X = OCH_3 or X = H or X = imidazole). This has led us to examine the intramolecular condensation, strategy B, for preparation of the substituted 4-hydroxy-2-pyridinone 2 as a precursor to funiculosin.

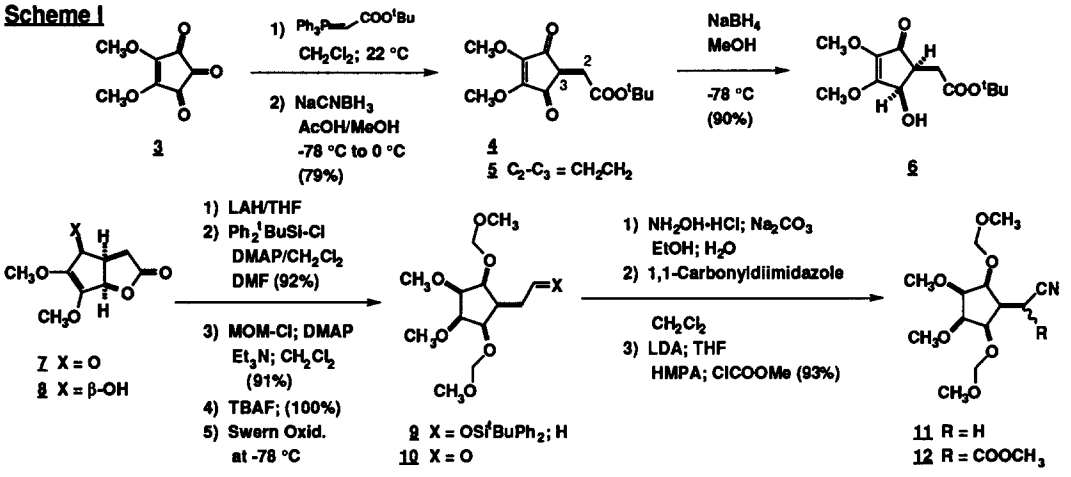




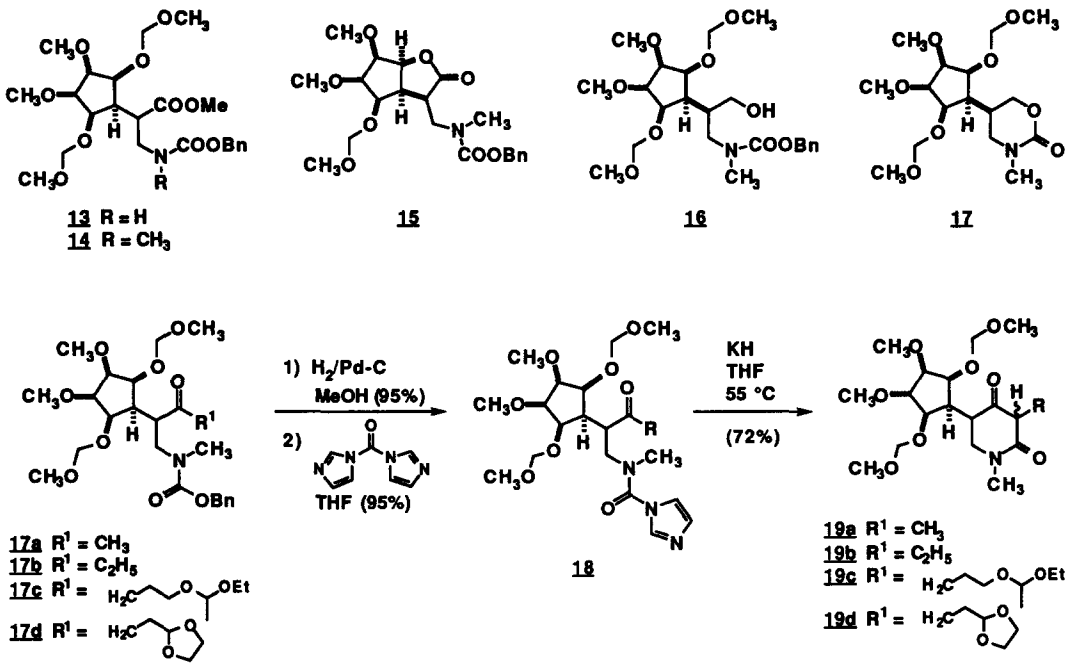
2 R^1 = alkyl or H

Stereocontrolled formation of the novel cyclitol moiety of 2 is illustrated in Scheme 1, beginning with dimethyl croconate (3).[6] Addition of one equivalent of *tert*-butyl(triphenylphosphoranylidene) acetate afforded selective reaction to give the expected α,β-unsaturated ester 4 (93%). Conjugate hydride reduction of the enedione 4 proceeded in excellent conversion (91% yield) at -78 °C with sodium cyanoborohydride in acetic acid (10 equivs) and methanol. When the amount of acetic acid was decreased, substantial quantities of dimer resulting from stepwise hydride-Michael additions of 4 were obtained. The keto carbonyl of 5 was selectively reduced with sodium borohydride (1.0 equiv at -78 °C) giving primarily the *cis*-hydroxyester 6 (*cis*/*trans* ratio 6:1) in 90% yield. Both of these diastereomers were separately converted to lactone 7 upon heating with catalytic amounts of acid.[7] Hydrogenation of 7 in ethyl acetate and acetic acid (0.6 equivs) in a sealed Parr apparatus provided alcohol 8 (mp 84-86 °C).[8] Reduction of 8 with $LiAlH_4$ was followed by immediate conversion of the crude triol to yield the primary *tert*-butyldiphenylsilyl ether (92% overall), and protection of the remaining secondary alcohols gave 9. Standard manipulations of 9 led to the aldehyde 10, which was directly transformed to a 1:1 mixture of *E*/*Z*-oximes under basic conditions.[9] Without purification, this material underwent dehydration with 1,1-carbonyldiimidazole in methylene chloride at reflux (24 hr) producing nitrile 11 in 92% yield from 10. Finally acylation of the enolate of 11 with freshly distilled methyl chloroformate required the presence of excess HMPA leading to methyl ester 12.

Scheme I



Catalytic reduction of nitrile 12 (5% Rh on alumina at 2100 psi H_2) at 22 °C in a solution of methanol and concentrated ammonium hydroxide (9:1 by volume) gave the corresponding β-aminoester, which was immediately treated with benzyl chloroformate (CH_2Cl_2; $NaHCO_3$; 0 °C) yielding 13 (77%). Subsequent N-alkylation via deprotonation with sodium hydride and addition of methyl iodide in a solution of 5% anhydrous DMF in THF at 0 °C gave 14 (97%) in gram quantities. Hydrolysis of the methyl ester 14 and our subsequent attempts for acyl activation of the resulting carboxylic acid using 1,1-carbonyldiimidazole promoted facile nucleophilic participation of the MOM ether to give lactone 15. However, the $LiAlH_4$ reduction of 14 in THF (-20 °C with warming to 0 °C; aqueous quench at 0 °C; then dropwise addition of 10% HCl at 0 °C) afforded the key primary alcohol 16 in 89% isolated yield. Conventional basic workup on warming to room temperature prior to acidification resulted in formation of the cyclic carbamate 17.



Substrates for the intramolecular condensation strategy B were assembled via the general three step protocol featuring Swern oxidation of 16 to its corresponding aldehyde (83%), addition of various organolithium or Grignard reagents at -78 °C, and further Swern oxidation providing the ketones 17a-d with overall yields ranging from 61% to 77% for the later two steps. Smooth conversion of 17 afforded the N-substituted carboxamidimidazolides 18 as cyclization precursors which were stable to silica gel chromatography. These unsymmetrical ureas are excellent electrophiles for introduction of the amido function.[10] Thus, treatment of 18a-d with potassium hydride in refluxing THF gave the desired 5,6-dihydropyridine-2,4-diones 19 as mixtures of diastereoisomers (~2:1) in 68-74% yields.[11] Finally, oxidations[12] of 19 with $BrCCl_3$ (CH_2Cl_2; DBU at 0 °C) produced the family of 3,5-disubstituted-4-hydroxy-2-pyridinones 2a-d as key intermediates in our efforts for total synthesis of funiculosin (1).[13]

In conclusion, our studies have described a route for preparation of an all-*syn*-cyclopentanetetrol derivative as a unique pseudosugar. Secondly, the utility of carboxamidimidazolides in intramolecular carbonyl condensation processes has been demonstrated for the synthesis of 4-hydroxy-2-pyridinones. Continuing studies will be reported in due course.

Acknowledgements: Generous financial support for this research was provided by an award sponsored by the National Institutes of Health (GM-41560).

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7. Empirically, the *syn*-hydroxyester 6 provided lactone 7 (catalytic TsOH; CH_2Cl_2; reflux for 45 min) at a much faster rate (100% yield) than lactonization of the *anti*-hydroxyester (catalytic TsOH; benzene; reflux; two hrs; 84% yield). The lactone 7 was decomposed by extending reaction times.
8. Reduction with 5% rhodium on alumina (Aldrich) at room temperature with 1900 psi hydrogen (48 hrs) gave 8 in 82% yield. Moderate hydrogen pressures (50-100 psi) were also effective, but less reproducible, and were accompanied by small quantities of elimination side products. Direct hydrogenation of 4, 5 or 6 gave complex mixtures.
9. Oxime formation in the presence of pyridine or triethylamine, in place of Na_2CO_3, permitted competing formation of the five-membered ethyl acetal formed via hydrolysis of one MOM ether.
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11. The pyridin-2,4-diones 19 displayed two distinct carbonyl absorptions at 1725 and 1660 cm^{-1} in their infrared spectra. Proton and carbon NMR data indicated that these β-keto amides exist as their carbonyl tautomers with no evidence for enol isomers. The final pyridinones 2 are characterized solely as C-4 enols.
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13. Isolated yields are reported for purified products which were fully characterized by proton and carbon NMR spectra, infrared, and high-resolution mass spectrometry. Combustion analyses data were used to check one third of the compounds in the synthesis sequence.

(*Received in USA* 8 *August* 1996; *revised* 19 *November* 1996; *accepted* 21 *November* 1996)