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A new efficient synthesis of alkyl substituted Δ^2 -butenolides

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Abstract—A new three-step route to 2-alkyl substituted Δ^2 -butenolides from 3-alkyltetronic acids is described. © 2001 Elsevier Science Ltd. All rights reserved.

 Δ^2 -Butenolides are structural components of numerous natural products such as acetogenins,¹ muconolactones,² leptospharin,³ and strigol.⁴ Most of them have cytotoxic, antitumour, antimalarial, immunosuppressive, and pesticidic activities and other types of biological action.⁵ An interest in α,β -unsaturated lactones had been aroused after their antibiotic properties were discovered. The specific action of these antibiotics is mainly due to the presence of an unsaturated γ -lactone ring. Optically active Δ^2 -butenolides are important and versatile synthons for naturally occurring compounds containing the γ -butyrolactone ring.⁶ Therefore, development of an effective method for the synthesis of Δ^2 -butenolides is of great synthetic and practical value.

This communication describes a new three-step route to 2-alkyl substituted Δ^2 -butenolides from the readily

available 3-alkyltetronic acids.7 The method consists in cvanoborohydride reduction of the enamino derivatives of tetronic acids in acidic medium, followed by retro-Michael elimination of the amine moiety from the aminolactones formed. Thus, boiling of 3-alkyltetronic acids 2a-c with pyrrolidine in toluene results in the formation of the corresponding enaminolactones $3a-c^8$ in 80-90% yields, though the yield of sterically crowded enaminolactone 3d is lower (50-60%) and prolonged heating or addition of *p*-toluenesulfonic acid as a catalyst does not enhance the yield. Reduction of the conjugated double bond in enaminolactones 3a-d with sodium cyanoborohydride in 2N methanolic hydrogen chloride solution proceeds smoothly at room temperature. After removal of the solvent in vacuo and workup of the reaction mixture with an aqueous solution of sodium hydroxide, aminolactones 4a-d were formed as



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a mixture of diastereomers. We have found that aminolactones **4a**–**d**, at reflux in toluene, in the presence of silica gel undergo a retro-Michael elimination of the pyrrolidine moiety to give Δ^2 -butenolides **1a**–**d**⁹ in yields of 55–65% (starting from **3a**–**d**). It should be noted that the use of crude **4a**–**d** in the final step of the scheme does not diminish the yield of the target butenolides.

The 2-alkyl substituted Δ^2 -butenolides **1a–d** thus obtained are excellent precursors for the synthesis of biologically active 10-oxa-PG analogues.¹⁰

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- 8. To a stirred suspension of tetronic acids 2a–d (0.01 mol) in 30 mL of toluene, pyrrolidine 1.0 mL (0.012 mol) was added dropwise. The reaction mixture was refluxed for 5–8 h with azeotropic removal of the water formed. Then the solution obtained was evaporated to dryness and the residue was passed through a silica gel column (CHCl₃) to give the corresponding 4-(1-pyrrolidinyl)furan-2(5H)-ones 3a–d in yields of 50–90%.
- 9. To 1 mmol of 3a-d in 5 mL MeOH was added ca. 0.5 mg of methyl orange followed by several drops of 6N HCl in MeOH to form a deep-red coloured solution. Then 0.15 g (2.4 mmol) of NaBH₃CN was introduced portionwise over 2-3 h with simultaneous addition of 6N HCl at a rate sufficient to maintain the red colour of the indicator. The rate of reaction could be estimated by the acid consumed and by TLC of the mixture. MeOH was removed in vacuo. After dilution of the residue with H₂O (5 mL), Et₂O (15 mL) was introduced and then on stirring a 1N aq. solution of NaOH was added dropwise until the colour of the aqueous phase had turned to yellow. The aqueous phase was extracted with Et₂O (2×10 mL). The organic layers were combined and evaporated to dryness to give a mixture of diastereomeric aminolactones 4a-d. Crude 4a-d were refluxed for 6-12 h in toluene (10 mL) containing silica gel (2 g) until full conversion into butenolides (TLC monitoring). The silica gel was filtered off and washed with toluene (2×10 mL). The combined organic phases were evaporated in vacuo and the residue was purified by column chromatography (Et₂O-hexane) to give pure **1a-d** (55-65% yield). All new compounds reported herein give satisfactory microanalyses and spectral data (IR, ¹H NMR, MS).
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