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A SYNTHETIC APPROACH TO ACTINOBOLIN. TOTAL SYNTHESIS OF (±)-RAMULOSIN

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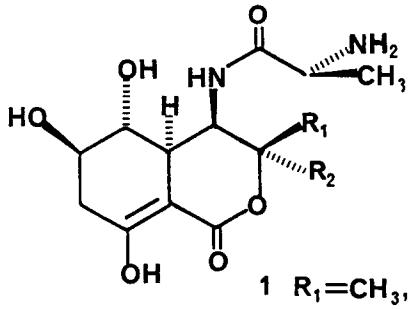
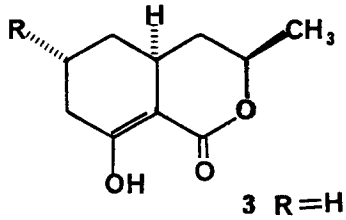
Abstract: A biomimetic type synthesis of (±)-ramulosin from the acyclic precursor 9 is described. Mercury mediated oxidative cyclization and bromolactonization are shown to be useful for the construction of the actinobolin skeleton.

The antibiotic actinobolin (1) was isolated from a Streptomyces culture 25 years ago.[2] Its structure was established in 1967 by Munk, Haskell and coworkers[3] and confirmed in 1975 by x-ray crystallography.[4] The closely related antibiotic bactobolin (2) was recently isolated from a Pseudomonas species.[5] The potent antitumor activity of bactobolin and the novel structures of these antibiotics make them important synthetic targets.[6] Two much simpler but biogenetically related compounds, ramulosin (3)[7,8] and hydroxyramulosin (4)[9] have been isolated from the fungus Pestalotra ramulosa.



1 R_1=CH_3, R_2=H
2 R_1=$CHCl_2$, R_2=CH_3

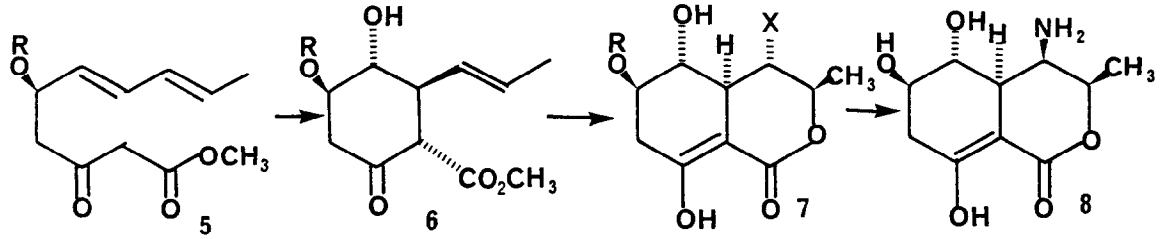


3 R=H
4 R=OH

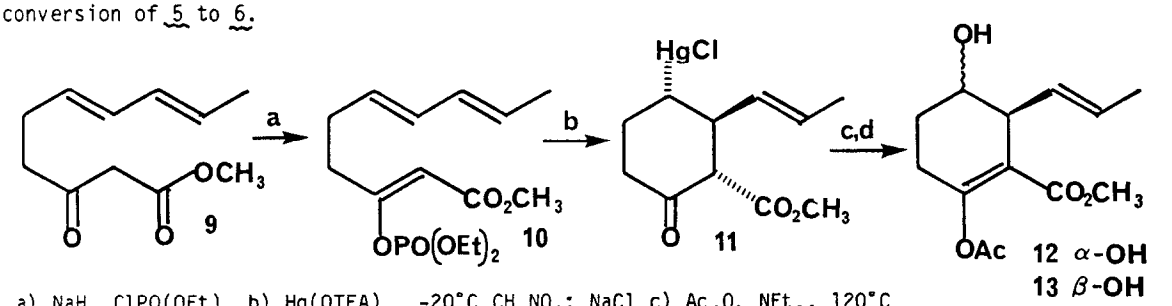
Our approach to the synthesis of actinobolin is based on an analysis of the likely biogenetic pathway. An acyclic pentaketide precursor 5 will be cyclized to the cyclohexanonecarboxylate 6. Halolactonization of 6 will give 7. The amine will then be introduced to give desalanylactinobolin 8 which can be easily converted to actinobolin (1).

Our initial studies, making use of the model compound 9, were designed to demonstrate the feasibility of the oxidative cyclization of 5 to give 6. The obvious approach, formation of the 6,7-epoxide of 9 and cyclization was not examined since ring closure of similar systems occurs on oxygen rather than carbon.[10] Mercuric trifluoroacetate cyclization appears to suffer from similar problems,[11] although these can be solved by the

use of the enol phosphate ester.[12] Methyl acetoacetate was converted to the dianion (NaH, BuLi)[13] and treated with E,E-2,4-hexadienyl bromide[14] to give 9[15] in 79% yield.



Treatment of 9 with NaH and diethyl chlorophosphate in ether[12] gave a 94% yield of 10. Treatment of 10 with 1.2 equiv. of mercuric trifluoroacetate in nitromethane at -20°C for 1 hour followed by workup with brine gave a 68% yield of the crystalline chloromercury compound 11, mp 183°C decomp.[16] Oxidative demercuration of 11 was carried out by a two-step procedure. Protection of the ketone as the enol acetate (Ac_2O, Et_3N, 120°C, 30 min) followed by treatment with sodium borohydride in oxygen saturated DMF [12,17] gave a readily separable 3:1 mixture of 12 and 13 in 40% yield. These results indicate that mercury mediated cyclization followed by oxidative demercuration is a viable route for the conversion of 5 to 6.



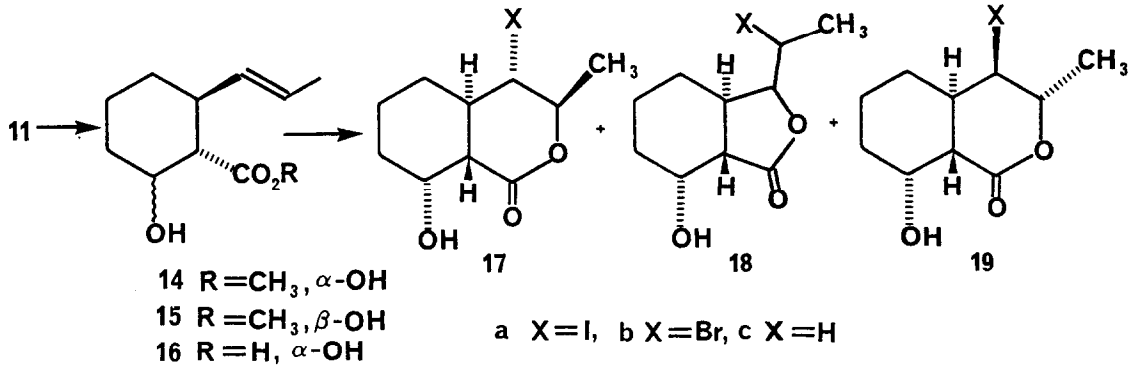
a) NaH, $ClPO(OEt)_2$ b) $Hg(OTFA)_2$, -20°C, CH_3NO_2; NaCl c) Ac_2O, NEt_3, 120°C
d) $NaBH_4$, O_2, DMF

The halolactonization was explored with simpler models lacking the hydroxyl group. Reductive demercuration of 11 with $NaBH_4$ in EtOH gave a 50% yield of 14[16] and a 38% yield of 15, mp 39-40°C.[16] Hydrolysis of the ester of 14 gave 16, mp 86.5-87.5°C[16] in 96% yield. Iodolactonization can give either the γ-lactone or the δ-lactone. In simple systems, the more stable γ-lactone is the major or exclusive product.[18] Iodolactonization of 16 with I_2 and KI in aqueous $NaHCO_3$ solution gave a 91% yield of a 1:4:2 mixture of 17a, 18a (stereochemistry undetermined), and 19a. Iodolactonization with I_2 in ether-THF/aqueous $NaHCO_3$ solution[19] gave an 86% yield of a 3:2 mixture of 18a and 19a. Iodolactonization thus leads primarily to the γ-lactone and in addition produces at best a mixture of diastereomeric δ-lactones favoring the undesired isomer.

We were pleased to find that bromolactonization of 16 with Br_2 in MeOH containing $NaHCO_3$ at -78°C[20] gave a readily separable 3.5:1 mixture of 17b and 18b in 88% yield. The stereochemistry of 17b, mp 136-137°C, was unambiguously determined by analysis of the 500 MHz NMR spectrum.[16] As a further proof of structure, 17b was reduced with tri-n-butyltin

hydride in THF for 26 hr at 25°C[20] to give, after chromatography, a 76% yield of 17c, mp 116-117°C. Oxidation of 17c with $CrO_3 \cdot Pyr_2$ (freshly prepared in situ) in CH_2Cl_2 for 1 hr at 25°C[8,21] gave a 78% yield of (±)-ramulosin (3), mp 115-116°C, which is identical to natural (+)-ramulosin by 500 MHz ^1H NMR, IR and UV spectral, and TLC comparison.[22]

These studies demonstrate an effective approach for forming the skeleton of actinobolin via sequential cyclization initiated by electrophilic attack on alkenes. They have led to the first synthesis of (±)-ramulosin in 7 steps from methyl actoacetate in 11% overall yield. The application of this approach to the synthesis of more highly oxidized members of this family is under investigation.



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