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TOTAL SYNTHESIS OF (±)-XANTHOCIDIN AND (±)-DESDIHYDROXY-4,5-DIHYDROXANTHOCIDIN

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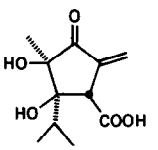
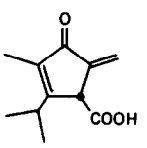
Summary: *The first total synthesis of both (±)-xanthocidin (1), a novel α-methylene cyclopentanoid antibiotic, and (±)-desdihydroxy-4,5-dihydroxanthocidin (2), the likely penultimate biosynthetic precursor is reported.*

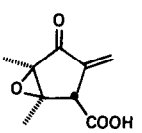
During the past several years a major focus of this laboratory has been the construction, in stereocontrolled fashion, of a small but rapidly growing class of antibiotics termed the cyclopentanoid group. This effort has resulted in the total synthesis of (±)-methylenomycin A (3),[2] (±)-epimethylenomycin A,[2] (±)-desepoxy-4,5-dihydromethylenomycin A (4),[3] (±)-sarkomycin,[4] (±)-pentenomycins (I-III),[5,6] their epimers[5] and dehydropentenomycin.[5] Continuing with our interest in this area, we now wish to announce the *first* total synthesis of the *highly unstable* antibiotic (±)-xanthocidin (1), isolated in 1966 by Asahi et al.[7], as well as the synthesis of desdihydroxy-4,5-dihydroxanthocidin (2), a possible (probable) biosynthetic precursor of xanthocidin.



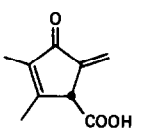
1
Xanthocidin



2
Desdihydroxy-4,5-dihydroxanthocidin



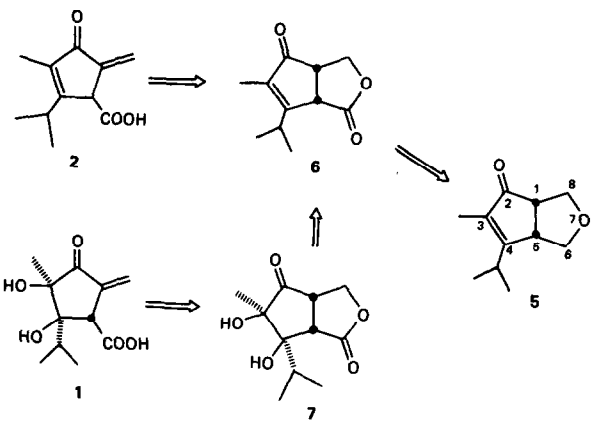
3
Methylenomycin A



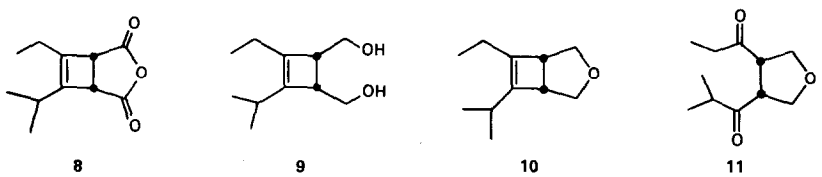
4
Desepoxy-4,5-dihydromethylenomycin A

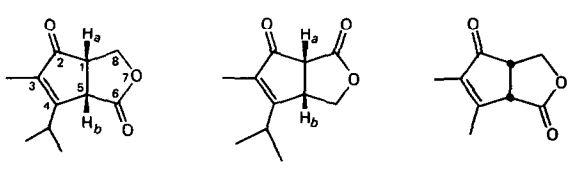
At the outset of this venture only the carbon skeleton of xanthocidin was secure.[7] We conjectured, however, that of the four possible diastereomers for xanthocidin, structure 1 was in fact correct. Our reasoning follows. As in the case of methylenomycin A (3), where in the desepoxy derivative (4) is known[8] to serve as the penultimate precursor, desdihydroxy-4,5-dihydroxanthocidin (2) would be a likely precursor to xanthocidin; enzymatic hydroxylation[9] trans to the carboxyl group would then afford 1. That the above conjecture concerning the stereochemistry of xanthocidin proved correct was recently demonstrated by appearance of a single crystal X-ray analysis of (±)-xanthocidin.[10]

With diastereomer 1 established as our principle synthetic goal, the retrolactonization strategy exploited to great advantage in the methylenomycin area[2,3] appeared directly adaptable to both xanthocidin (1) and the postulated biosynthetic precursor (2).[11] Such a strategy in this case calls initially for construction of bicyclic ketone (5). Subsequent oxidation of the tetrahydrofuran ring at C(6) followed by retrolactonization leads to desdihydroxy-4,5-dihydroxanthocidin, while cis-hydroxylation on the less hindered convex surface affords diol 7, termed cycloxanthocidin. Retrolactonization of the latter would then afford xanthocidin (1).



Construction of bicyclic ketone 5, our initial synthetic target, begins with cyclobutene 8. Towards this end, irradiation[12] of a mixture of 2-methyl-3-hexyne (0.2M) and maleic anhydride (0.15M) in acetonitrile utilizing benzophenone (0.015M) as sensitizer afforded 8[13] in 58% yield after distillation as a pale yellow solid (mp 60-61°C). Reduction of the latter with LAH (3 eq, THF, 45 h at reflux) led to a 94% yield of diol 9[13] which in turn was converted to tetrahydrofuran 10[13] [b.p. 105°C/33 torr, 93%] via treatment with 1.1 eq of tosyl chloride in pyridine at 0°C for 18 h followed by heating at reflux for 2 h.[14] Ozonolysis of 10 in methanol at -78°C followed by reductive work-up with triphenyl phosphine afforded diketone 11[13] [73%, bp 93° (0.5 torr)] which upon cyclization employing the aldol conditions of McCurry and Singh[15] (i.e. 2% NaOH/MeOH at reflux) led to a single cyclopentenone (5)[13] in 74% yield after chromatography.

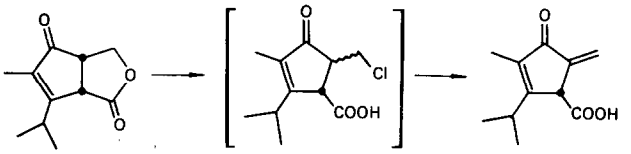




Turning next to the required introduction of a carbonyl at C(6) in tetrahydrofuran 5, oxidation with CrO_3[16] (2.5 eq; Ac_2O, 90% AcOH, 1:2) at 100° for 1/2 h afforded a 1:1 mixture of two lactones 6 and 12 in modest but useful yield (ca. 30-40% based on recovered tetrahydrofuran 5); separation was effected via combined TLC and flash chromatographic techniques (silica gel, ether). This result was in marked contrast to that observed in the methylenomycin A area[2,3] wherein only one isomer (i.e. 13) was isolated.

Lactones 6[13] and 12[13] were differentiated on the basis of the high field ^1H and ^{13}C NMR data. That is, it was a relatively easy matter to demonstrate the allylic disposition of H_b in 6, H_b in 12 and the respective C(3) methyl substituents via double resonance NMR techniques.[17] Furthermore the chemical shifts for carbon resonances C(1) and C(5) (46.1 and 45.5, repsectively) in 6 were found to be quite similar to the values observed for the corresponding carbons in 13 (45.2 and 48.9, respectively), especially when compared to C(1) and C(5) in 12 (i.e. 50.8 and 41.0, respectively).

Having differentiated lactones 6 and 12, we turned to the elaboration of desdihydroxy-4,5-dihydroxanthocidin (2). Employing the retrolactonization protocol developed previously,[3] a 0.3 mole solution of 6 in 2-trimethylsilyl ethanol was treated with 7.5 eq of acetyl chloride (rt, 6 days). Removal of the solvent *in vacuo* followed by addition of 5% aq Na_2CO_3 and immediate acidification to pH 1 gave after extractive (ether) work-up chloroacid 14;[13a] alternatively, prolonged treatment with 5% Na_2CO_3 (ca. 1.5 h) converted the intermediate chloride to desdihydroxy-4,5-dihydroxanthocidin (2),[13] the yield after purification via TLC (ether) being 23%.[18]



6 14 2

Preparation of xanthocidin on the other hand required first the introduction of vicinal hydroxy substituents on the less hindered, convex surface of enone 6. Towards this end, enone 6 was added to 1.1 eq of OsO_4 in pyridine at 0°; hydrolysis of the resultant osmate ester (aq $NaHSO_3$, 18 h, rt) afforded a single crystalline diol 7 (mp 134-135° C) in 65% after flash chromatography (ether). With ample quantities of diol 7 available, retrolactonization employing the conditions outlined above for 2 afforded pure (±)-xanthocidin in 20-25% yield.[18] That indeed racemic xanthocidin was in hand was confirmed by direct comparison of the 60 MHz NMR spectrum to that of the actual published spectrum of natural (±)-xanthocidin.[7]

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References and Notes

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11. Indeed, the retrolactonization strategy appears sufficiently adaptable to permit construction of all of the diastereomers having the xanthocidin carbon skeleton. Work towards this end is currently ongoing in our laboratory; unpublished results of Ms. D. Boschelli.
12. The [2 + 2] photochemical cycloaddition was conveniently carried out on a 20 g scale employing the standard Hanovia 450-W mercury arc fitted with a corex filter.
13. a) The structure assigned to each new compound was in accord with its infrared (CCl_4 or $CHCl_3$) and 250 MHz NMR spectra ($CDCl_3$); b) Analytical samples of all new compounds, obtained by recrystallization or chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high resolution mass spectroscopy.
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17. More specifically, in both 6 and 12 the angular protons (H_a and H_b) display in the 250 MHz NMR spectra as either a doublet of doublets (J = 7 and 1.5 Hz) or as a broad multiplet. The observed collapse of the doublet of doublets at δ 3.76 (H_b) upon irradiation of the C(3) methyl resonance of 6 requires that H_b is coupled to only one vicinal proton and thereby must have the structure assigned. Conversely, the observed sharpening of the broad multiplet at γ 3.39 in 12 upon irradiation of the C(3) methyl resonance confirms that structure.
18. The modest yields realized in the retrolactonization protocols are due to the highly unstable nature of both desdihydroxy-4,5-dihydroxanthocidin and xanthocidin.

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