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A Stereocontrolled Route to a Synthon for the Aglycone of the Aureolic Acids

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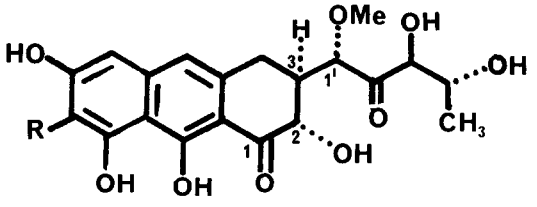
Abstract. Cyclohexenone 3, a synthon for the aureolic acid aglycone, has been prepared using D-fucose and trimethylsilyloxybutadiene as starting materials.

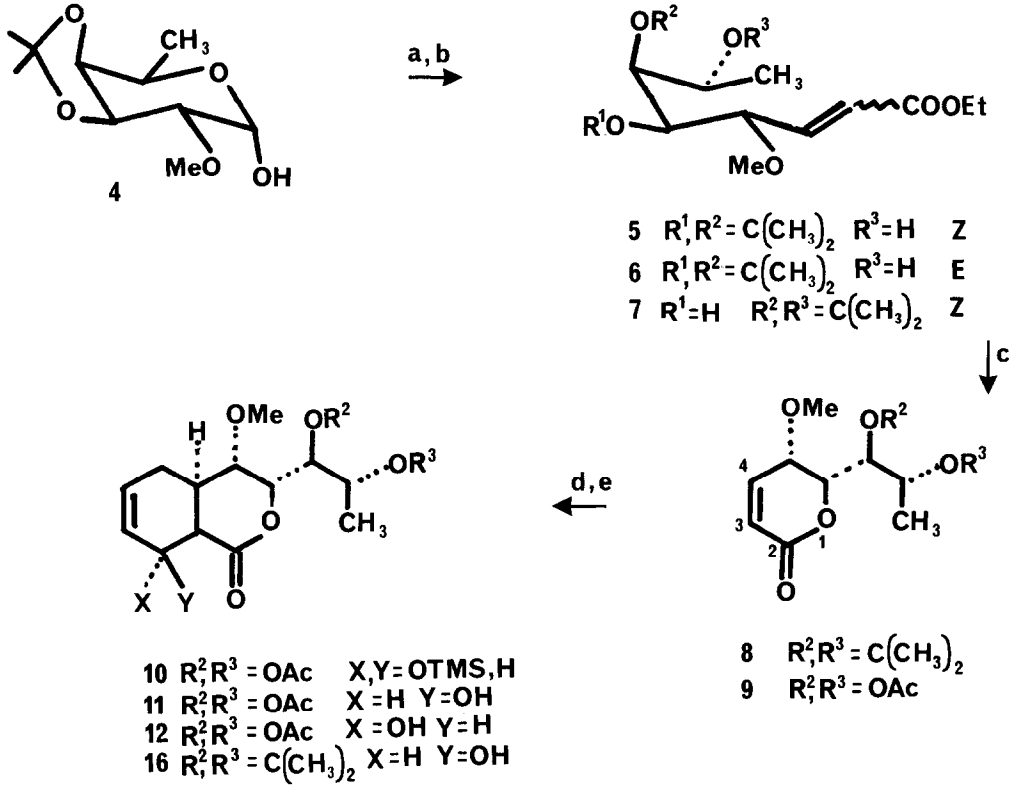
The aureolic acid group of antitumor antibiotics is comprised of mithramycin, the chromomycins, the olivomycins and variamycin.[1] The synthesis of their aglycones olivin (1) and chromomycinone (2) have been the subject of several investigations.[2] In recent work, enones related to 3 have been proposed[3a] and successfully used[3b] as synthons for a synthesis of the aglycones. We wish to report



1 R=H 2 R=CH$_3$

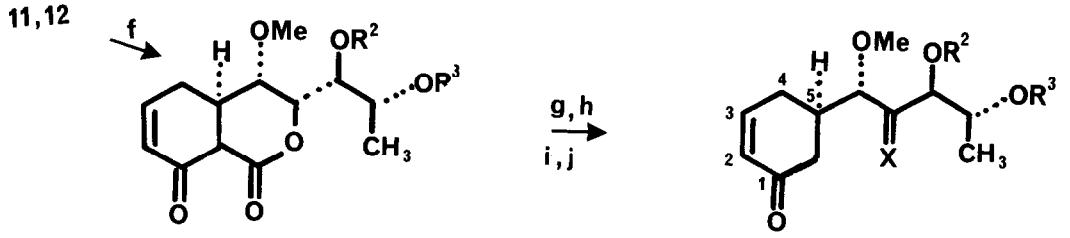
an efficient and stereoselective preparation of enone 3 from D-fucose using a Diels-Alder reaction to establish the chirality at C-5 in the synthon (to become C-3 in the aglycone). D-Fucose was converted to the protected pyranes 4 using known methodologies in 78% overall yield.[4] When 4 was subjected to the Wittig reaction with carboethoxymethylene triphenylphosphorane in refluxing acetonitrile (72 hr), a mixture of E and Z alkenes was obtained. Separation of the mixture by radial chromatography gave the Z isomer 5 in 55% yield and the E isomer 6 in 23% yield.[5] This is a rather unusual outcome for the Wittig reaction where the use of stabilized reagents normally favors the formation of the E product.[6] However, obtention of the Z isomer offered a direct route to the preparation of lactone 8. The conversion was effected by refluxing the Z isomer 6 in acetone containing a catalytic amount of p-TosH. The initial reaction is the migration of the acetonide from the 3 and 4 to the 4 and 5 hydroxyl groups to form 7. It was expected that the desired pair of hydroxyls would be blocked because it is well prece-

dented that parf[7] (threo) glycols form more stable 5-membered cyclic ketals than do pref (erythro) related hydroxyls in acyclic polyols. Intermediate 7 could be isolated and characterized before continuing the lactonization process by further heating in toluene and p-TosH. Hydrolysis of the ketal of 8 followed by acetylation with Ac_2O in pyridine resulted in the isolation of lactone 9 in 90% yield.[5]



a 4→5 $Ph_3P{=}CHCO_2Et$; *b* 5→7 acetone, p-TosH; *c* 7→8 p-TosH, toluene; 8→9 H_3O^+, then Ac_2O, py; *d* *OR, PhCl, 125°, 3 d.*; *e* NH_4Cl, *MeOH*, H_2O.

The unsaturated lactone acetate 9 was subjected to the Diel-Alder reaction with 1-trimethylsilyloxybutadiene in a sealed tube with chlorobenzene as solvent at 125° for 3 days.[3] Isolation of the product was effected by PLC to afford a silyl ether mixture 10 in 83% yield, which could be separated after hydrolysis to the epimeric alcohols 11 and 12 using NH_4Cl:H_2O:MeOH for 2 hr. at 30°. Oxidation of both alcohols with Jones reagent at 0° afforded a single ketone 13 in 80% yield. The Jones oxidation could also be carried out directly on the silyl ether mixture to give ketolactone 13 in comparable yield. Saponification of 13 with aqueous K_2CO_3 in THF followed by acidification and decarboxylation gave the trihydroxyenone 14 in 75% yield. This compound was treated with acetone and p-TosH to give the ketal 15 in essentially quantitative yield; the regioselectivity is rationalized using arguments cited above. Lastly, Swern oxidation of 15 produced the synthon 3 in 80% yield.

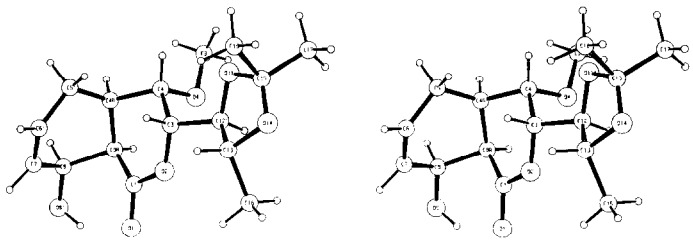


13 R^2,R^3 = OAc

14 R^2,R^3 = H X = H,OH
15 R^2,R^3 = $C(CH_3)_2$ X = H,OH
3 R^2,R^3 = $C(CH_3)_2$ X = O

f Jones rgt., -30°; g K_2CO_3, H_2O, *THF; h* H^+, Δ; *i acetone, p-TosH; j Swern, DMSO-TFAA-*Et_3N.

An examination of models would suggest the stereochemical outcome illustrated in our case, namely diene attack of the lactone double bond in 9 from the face opposite the allylic methyl ether (re face at C-4). But, opposite face selectivities have been observed in Diels-Alder reactions with two similar carbohydrate-derived acyclic dienes.[9,10] Therefore, it was felt that the critical stereochemistry at C-5 of synthon 3 required determination by X-ray crystallography. The experiment was carried out with 16, prepared in a manner similar to 11, using lactone 8 instead of lactone 9 in the sequence.[11,12] The stereochemistry displayed in the figure is in accord with our simple prediction about face selectivity to be expected in the Diels-Alder reaction of lactones 8 and 9; and furthermore, it corresponds to the stereochemistry assigned to the natural aglycones. Therefore, when synthon 3 or another member of this series is incorporated into a total synthesis of olivin, the relative and absolute configuration of the aglycone will have been established unequivocally. Up till now, the assignments at C-3 and C-1' have been based on inference from CD and NMR comparisons with data from model compounds. The merger of synthons prepared in this research with aromatic species to produce the natural aglycone will be the subject of a future communication.



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References and Notes

*Address correspondence to Department of Chemistry, Hunter College, 695 Park Ave., New York, NY 10021; this investigation was supported by PHS grant no. CA-27116 awarded by the National Cancer Institute, DHHS.

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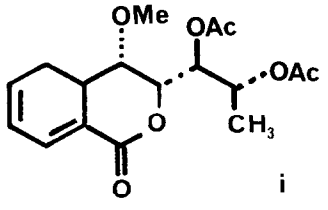
11. The crystals were orthorhombic, space group $P2_12_12_1$, with a= 7.36(2), b= 17.37(3), c= 25.69(4) A, and d_{calcd}= 1.264 g cm^{-3} for Z= 8 $C_{16}H_{24}O_6$, M= 312.36). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination) The size of the crystal used for data collection was approximately 0.15 x 0.15 x 0.75 mm. A total of 2546 independent reflections were measured for θ < 57°, of which 1230 were considered to be observed [I < 2.0σ(I)]. The structure was solved by a multiple-solution procedure [G. Germain, P. Main, and M.M. Woolfson, Acta Cryst. A27, 368 (1971)] and was refined by full-matrix least squares. In the final refinement, the nonhydrogen atoms were refined isotropically and the hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R= 0.124 and wR= 0.103 for the 1230 observed reflections. The final difference map has no peaks greater than ± 0.5 e A^{-3}.

12. Compounds 11 and 16 were interrelated by converting them both to (i), mp 82-83, mmp 82-83. The conversions were accomplished in both cases by dehydration with aqueous HCl, followed by acetylation.



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