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REGIOSPECIFIC SYNTHESIS OF 1,4,5-TRIOXYGENATED ANTHRAQUINONES. A TOTAL SYNTHESIS OF ISLANDICIN

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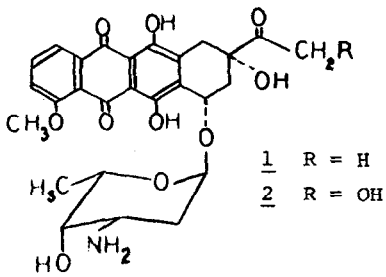
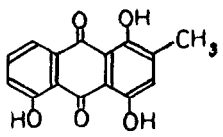
This communication describes a solution to the general problem of the regiospecific synthesis of an unsymmetrically substituted anthraquinone system. Acetogenins containing this moiety are frequently encountered as antibiotics,[1] and the system is characteristic of the clinically important anthracyclines daunomycin 1 and adriamycin 2,[2] as well as of the fungal metabolite islandicin 3 isolated by Raistrick from Penicillium islandicum.[3]



1 R = H
2 R = OH



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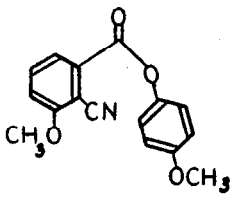
Most anthraquinone syntheses have relied upon the Friedel-Crafts condensation of a phthalic anhydride with a suitable phenol derivative.[4] With two unsymmetrical reactants, however, the orientation of the initial step may be ambiguous or may require the difficult separation of a mixture of structural isomers. Thus the reported synthesis of islandicin in 4.5% overall yield from

3-methoxyphthalic anhydride and m-cresol[5] is uncertain as a structure proof and unsuitable as a general synthetic method for such molecules. We have sought to circumvent this ambiguity by employing the photo-Fries rearrangement[6] as a mild and regiospecific route to o-hydroxybenzophenones suitable for cyclization to the requisite anthraquinones. This type of photochemically directed sequence has led to an unambiguous total synthesis of islandicin as well as to the construction of an olefinic anthraquinone precursor to daunomycinone, the aglycone of daunomycin.

Conversion of 3-methoxy-2-cyanobenzoic acid[7,8] to ester 4[9] (85%; mp 148-149°; λ4.52,5.80μ; δ3.73(s,3H),3.93(s,3H))[10] and subsequent photoisomerization[11] in AR dioxane gave the yellow, crystalline benzophenone 5 (43%; mp 169-170°; λ4.52, 6.15μ; δ3.59(s,3H),3.93(s,3H),11.08(s,1H)). Claisen rearrangement (refluxing o-$Cl_2C_6H_4$, under N_2, 18 hrs.) of the corresponding allyl ether 6 (mp 102-103°; λ4.51,6.01μ; δ3.73(s,3H),3.90(s,3H)), methylation[12], and base hydrolysis (50% aqueous KOH) yielded the side chain isomerized pseudo-acid 7 (mp 144-145°; λ3.00. 5.71μ; δ1.89(d,3H,J=10Hz) 3.61(s,3H),3.66(s,3H),3.91(s,3H)). Cyclization at room temperature using anhydrous HF gave the desired anthraquinone 8 (38% from 5; mp 191-192°; λ5.99μ; δ1.98(d,3H,J=10Hz),3.88(s,3H),3.99(s,6H)).



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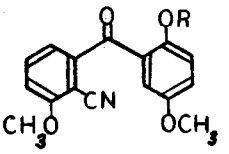
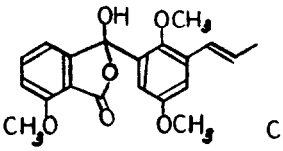


5 R = H
6 R = $CH_2CH{=}CH_2$



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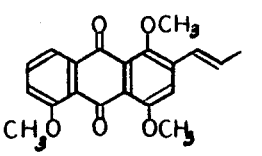

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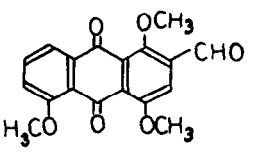
Ozonolysis of the side chain in quinone 8 gave the aldehyde 9 (mp 244-245°; λ5.99; δ3.96(s,6H),4.00(s,3H),10.27(s,1H)) which was converted to its ethylene thioketal (mp 178-181°, dec.; λ5.98μ; δ3.46(s,4H),3.97(s,3H),4.00(s,6H), 6.10(s,1H)) and carefully reduced with Raney nickel to yield 18% of trimethyl-islandicin 10 (mp 161-161.5°; lit.[3] mp 161°; λ5.97μ; δ2.42(s,3H),3.91(s,3H),

4.00(s,6H); λ(EtOH)254,395nm). Further confirmation of identity with the substance obtained by Raistrick came via BBr_3 demethylation of synthetic 10, followed by sublimation and recrystallization to yield pure islandicin 3 as red plates (mp 216°; lit.[3,5] mp 216-218°; λ6.24μ; lit.[4] 6.24μ; λ(EtOH)231.5,252, 288,460(sh),478(sh),490,512,525nm; lit.[4] 231.5,251.5,289,460(sh),479.5(sh),491, 513,527 nm) and conversion to the known triacetate (mp 205°; lit.[3] mp 208°).



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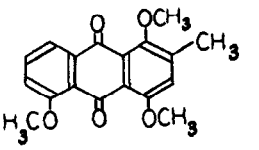
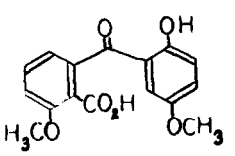
1.) $(CH_2SH)_2$
2.) RaNi



10

When benzophenone 5 was directly hydrolyzed there was obtained acid 11 (mp 160-161°; λ5.85,6.20μ) which could be cyclized with HF to the phenolic anthraquinone 12 (mp 173-174°; λ6.01,6.11μ; δ4.00(s,3H),4.04(s,3H),12.76(s,1H)). Allylation gave triether 13(mp 173-174°; λ6.01μ; δ3.97(s,3H),4.00(s,3H)) and thermal rearrangement produced the allylanthraquinone 14(mp 91-92°; λ6.01,6.13; δ3.53(d,3H,J=10Hz)3.97(s,3H),4.03(s,3H),13.27(s,1H)). Methylation of 14[12] afforded the trimethyl ether 15 (40% from 5; mp 127-128°; λ5.98μ; δ3.41(d,3H, J=10Hz) 3.76(s,3H),3.83(s,3H),3.87(s,3H)).



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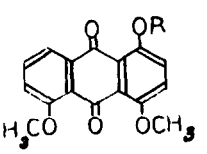
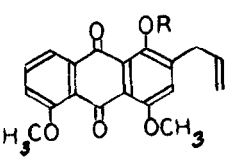


12 R = H
13 R=$CH_2CH=CH_2$



14 R = H
15 R = CH_3

Introduction of the functionality required for the synthesis of daunomycinone from 15, as for example by double carboxylation[13] or equivalent routes, is currently under investigation.[14]

References and Footnotes

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10. All compounds gave satisfactory elemental analyses or mass spectral data. Yields represent values after complete purification. Melting points are uncorrected. Infrared data are for KBr disc spectra. Nmr results refer to solutions in $CDCl_3$ and are ppm values downfield from TMS. Only characteristic signals are given for ir and nmr spectra.

11. Using a 450 watt Hanovia medium pressure lamp and a quartz well. Irradiation of ca. 0.01M solutions for 11-12 hrs. was followed by chromatography.

12. M. Gates, J. Amer. Chem. Soc., 72, 228 (1950).

13. R. F. Heck, ibid, 94, 2712 (1972).

14. We are indebted for partial support of this work to the National Institutes of Health (Grants 1F02GM51050 and CA11326), to the American Cancer Society for an institutional grant to the University of Rochester, and to the Sigma Xi Society for an award to E. L. H.