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A REGIOSPECIFIC SYNTHESIS OF ANTHRACYCLINONES

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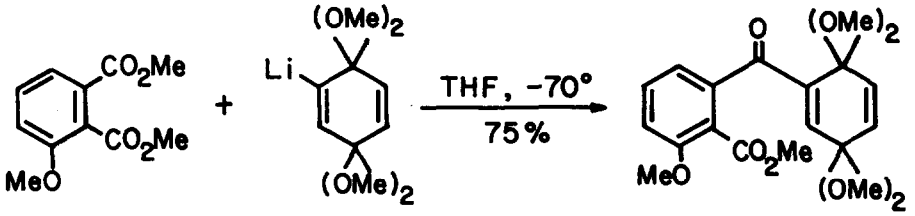
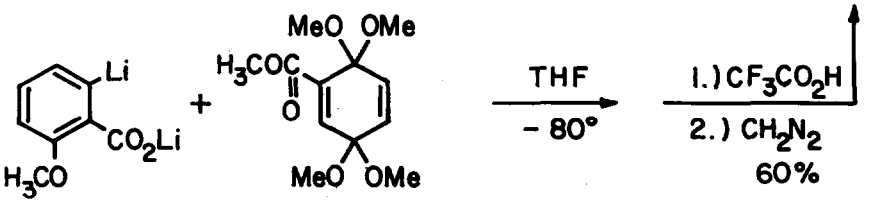
Anthracycline antibiotics in which a Rhodomycinone class of aglycone is bonded to an amino sugar have recently attracted much attention.[1] A major synthetic difficulty associated with the daunomycinone-adriamycinone type of aglycone is the regiospecific construction of the tetracyclic ring system.[2,3] We report here an efficient regiospecific procedure for coupling the AB-ring fragment of the aglycone to dimethyl 3-methoxyphthalate, 1, and the conversion of this material to the tetracyclic ketone 11. Since ketone 11 has been converted to daunomycinone,[2c-e] and the latter to adriamycinone, this route comprises a regiospecific route to these aglycones.

This synthetic approach was founded on the hypothesis that an appropriate organometallic reagent would selectively attack one of the carbonyl groups of 1. Unfortunately, little evidence is available to predict the preferred orientation of such a reaction. Thus

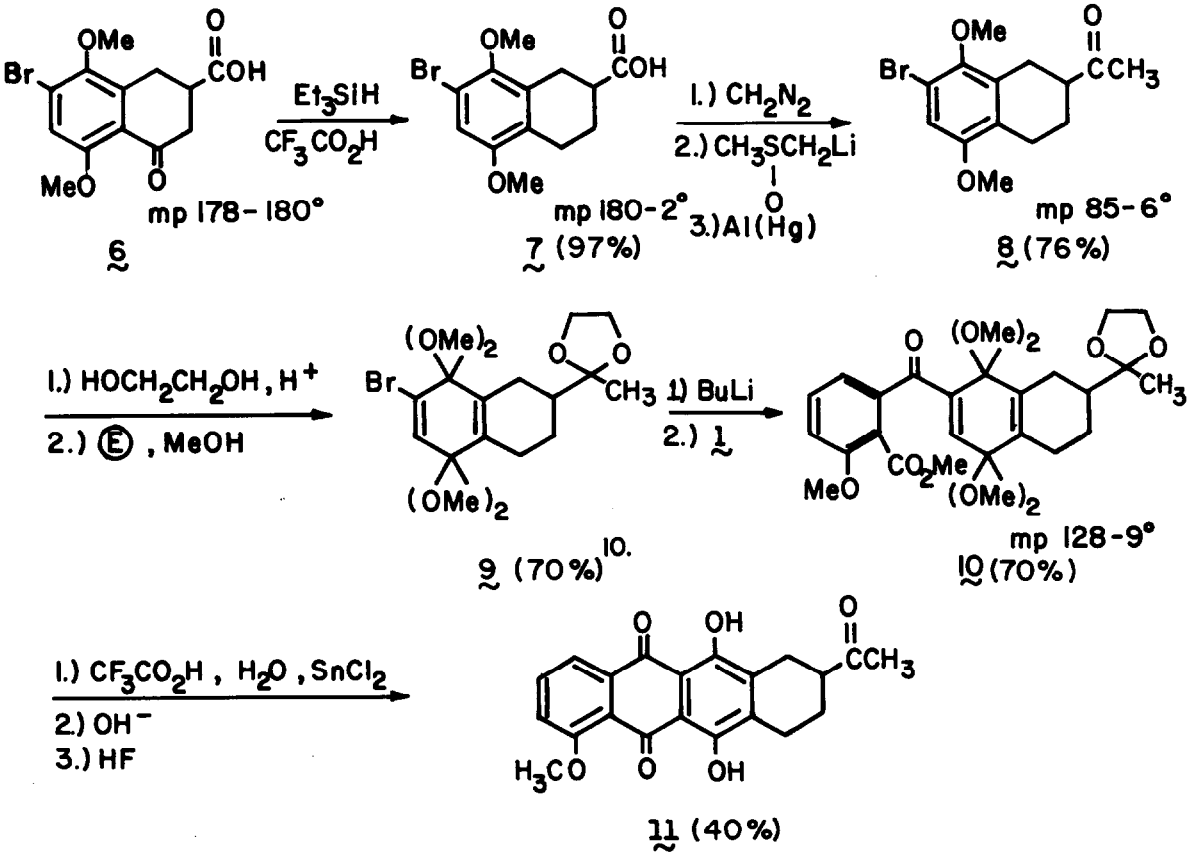


1 2 3



4 5

while Grignards react with 3-methylphthalic anhydride preferentially at the less hindered carbonyl,[4a] the Grignard from 2-bromo-1-methoxynaphthalene preferentially (64:23) reacts with 3-methoxyphthalic anhydride at the more hindered 2-carbonyl.[5] Our recently reported umpolung for quinones seemed an ideal candidate for study since the "neopentyl-like" center of 2 should highly favor attack at the less hindered carbonyl group of 1.[6] Furthermore, the resulting latent quinone afforded considerably more flexibility in effecting subsequent ring closure than a totally aromatic system (i.e., 2-lithio-1,4-dimethoxybenzene[7]. Indeed, condensation of 2 with 1 afforded 3 (75%), mp 153-154°. The CMR spectrum of crude 3 showed only eighteen signals indicative of a highly selective addition. The structure of 3 was confirmed by the alternate route outlined above. Thus, 4, prepared from the bromoacid[8] according to the procedure of Parham,[9] reacted with 5 to give 3 (50%) after careful



acidification and esterification. The bisketal 5 was readily obtained from anodic oxidation of methyl 2, 5-dimethoxybenzoate (90% yield, >90% purity).

For application of this coupling procedure to the anthracyclinone skeleton, 7[6] was converted to 9, and this coupled to 1. The tricyclic system 10 was isolated in 70% yield after silica gel chromatography and showed the expected IR, NMR, and CMR spectra. Conversion of 10 to 11 in 40% yield without isolation of intermediates was effected by reductive hydrolysis to the hydroquinone, saponification, and hydrogen fluoride cyclization. Compound 11, obtained as red needles from glacial acetic acid, showed a mp and IR spectrum identical to authentic 11.[10] There was no evidence for any loss of regioselectivity in these latter three steps.

This sequence starting from the readily available 3-bromo-2, 5-dimethoxybenzaldehyde[12] affords 11 in 8% overall yield in a reaction sequence involving one chromatography and no fractional distillations. Furthermore, this scheme should allow the facile synthesis of side chain analogs via alkylation of the intermediate β-ketosulfoxide. The ready availability of 10 via this regioselective coupling makes it a convenient model for investigating mild procedures for accomplishing the final ring closure. We are presently investigating such ring closure reactions on systems bearing the protected 1, 3-diol group of the anthracyclinone A-ring.[13]

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7. The addition of 2-lithio-1,4-dimethoxybenzene to 1 has been briefly examined and produces a major product tentatively identified as the expected monoadduct. However, considerable amounts of pseudo-ester and other minor products are formed. This reaction, which does not appear to be so clean as the reaction of 2 with 1, will be presented in detail in the full manuscript describing this work. As a reviewer has noted should reaction of the aromatic counterpart of 9 with 1 afford a high-yield regioselective addition this could also have utility in construction of the anthracycline.
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10. We thank Professor Charles Sih for an authentic sample of 11.
11. Although 9 has been characterized as a pure compound by IR and NMR spectroscopy, it is unstable at room temperature. Repeated crystallizations at low temperature from hexane and cyclohexane failed to change the melting point from the initial value of 80-86°.
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