Tetrahedron Letters,Vol.27,No.17,pp 1873-1876,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A FORMAL TOTAL SYNTHESIS OF AKLAVINONE VIA A BLOCKED ANTHRAQUINONE TAUTOMER

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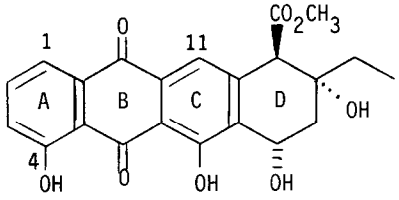
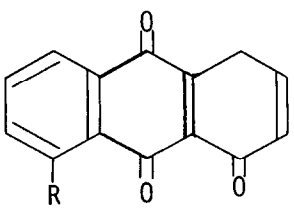
Abstract. An advanced intermediate in the Kishi synthesis of aklavinone was prepared. Juglone was converted into enone 4. Quinone 6 was then prepared from 4 by Michael addition and elimination of PhSOH and HCN.

The anthracyclines comprise a family of quinone-based natural products of diverse structure and activity. The 11-deoxyanthracyclines are of interest because of the clinical utility of compounds such as aklavinone.[1] This valuable biological activity has prompted many efforts to synthesize aklavinone and analogs of aklavinone. Successful strategies for the synthesis of aklavinone have been based on Friedel-Crafts chemistry, metallation of aromatic rings and also the Diels-Alder reaction.[2] In the successful syntheses, the latter

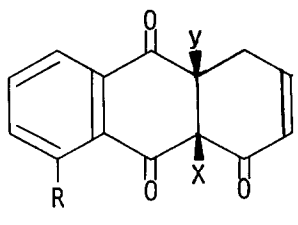


AKLAVINONE

strategy has been used most often. Particularly notable examples of this strategy are the syntheses of both Kishi and Rapoport. Both are extremely convergent and appear suited for the preparation of quantities of aklavinone. The two syntheses are of the AB + D -> ABCD category. A more flexible synthetic route might be derived from a synthesis of the AB -> ABC -> ABCD category, especially if the units for constructing the C and D rings were readily available. The attractive ABC unit I is shown below. Unfortunately, even if it could be prepared, it would rapidly tautomerize.



I

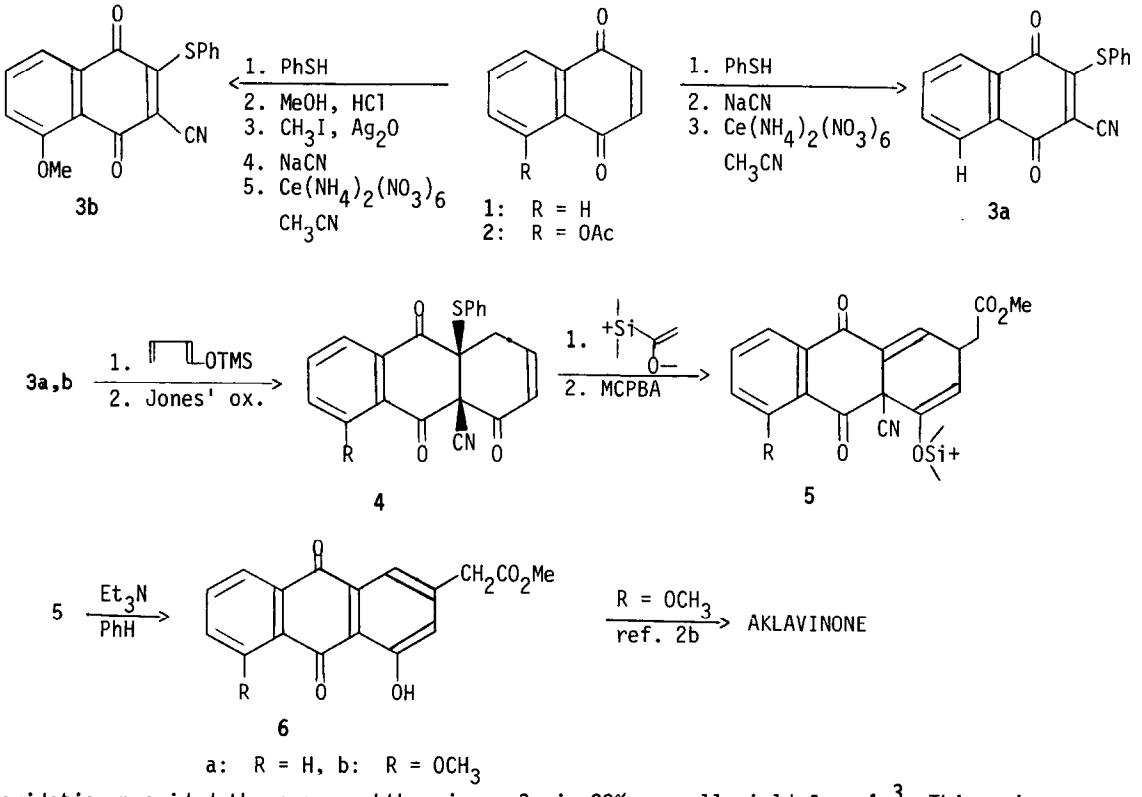


II

An equivalent II in which either X or Y blocks aromatization to the anthraquinone represents an interesting possibility. We have been investigating this possibility and now report the direct synthesis of an advanced intermediate in the Kishi synthesis of aklavinone.

The overall route is depicted in Scheme 1. In the case where R=H, naphthoquinone 1 was reacted with benzenethiol. Oxidation, followed by the addition of sodium cyanide and

Scheme 1



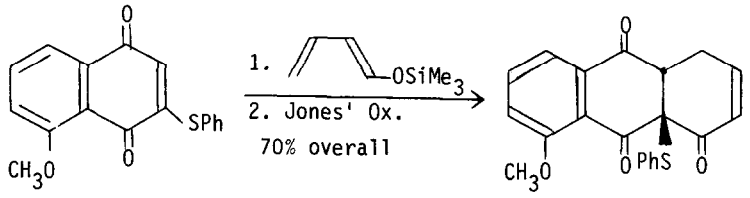
a: R = H, b: R = OCH_3

reoxidation provided the cyanonaphthoquinone 3a in 80% overall yield from 1.[3] This quinone was reacted with commercially available 1-trimethylsilyloxybutadiene at ambient temperature to afford the adduct in 75% yield. This adduct was at least 97% one isomer as evidenced by both 300 MHz proton NMR and 75 MHz carbon NMR. The proton NMR spectrum exhibited one doublet at δ 4.68 (J = 4.5 Hz) for the allylic methine proton and one singlet at -0.35 for the TMS-group. The strong shielding observed here is consistent with the formation of an endo adduct in which the quinone carbonyl groups exert the directing effect. After several experiments with this adduct, it became clear that even traces of base caused decomposition to a purple solution, the NMR of which supported our suspicion that a retro-aldol reaction had occurred. A variety of acid-mediated silyl ether cleavage reactions also resulted in the decomposition of the adduct. However, the adduct reacted readily with Jones' reagent to produce enone 4a in 90% yield.[4] This enone is crystalline and is surprisingly stable.

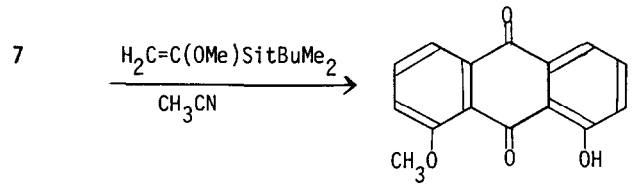
Conjugate addition of the ketene acetal (derived from the reaction of t-butyldimethylchlorosilane and the enolate of methyl acetate) using the method of Tamura[5] followed by oxidation of the sulfide with MCPBA and elimination provided nitrile 5a in 72% yield. This result was unexpected, since the elimination of HCN to afford the anthraquinone should be rapid. Nitrile 5a is stable in crystalline form for days but can be converted into the anthraquinone 6a with triethylamine in benzene at ambient temperature. In practice, 6a was obtained directly by sulfoxide elimination in benzene followed by the addition of triethylamine to the benzene solution. The synthesis of the compound containing the 4-methoxyl group paralleled that of the deoxy-compound. The addition of benzenethiol to **2** was highly regioselective, providing two adducts in a 97:3 ratio.[6] The minor, undesired regioisomer could be easily removed by one recrystallization. Acetate hydrolysis, methylation of the phenol, cyanide addition and oxidation afforded quinone **3b**. The accelerating effect of the methoxyl group in the Diels-Alder reaction resulted in an 85% yield of the desired adduct. Again, the adduct was greater than 97% one isomer by NMR. Jones' oxidation, ketene acetal addition and elimination of PhSOH and HCN generated **6b**. Anthraquinone 6b was prepared in 25% overall yield from 2. Quinone 6b has been used by Kishi in his elegant synthesis of aklavinone.

In principle, only one substituent should be needed to prevent the tautomerization to the hydroxyanthraquinone. We developed a direct synthesis of 7 from the known 3-phenylthio-5-hydroxynaphthoquinone.[3] The key reaction was the facile Jones' oxidation of the silyl ether. However, when enone 7 was reacted with the ketene silyl acetal under conditions which were successful for enone 4, only 1-hydroxy-8-methoxyanthraquinone 8 was produced. Despite several modifications of reaction conditions,[7] only 8 was isolated.

Scheme 2



7



8

Our preparation of 6b constitutes a formal total synthesis of aklavinone. The synthetic route is direct and operationally convenient. We are currently examining other equivalents of I.

Acknowledgement. We thank the National Institutes of Health for generous financial assistance. J.A.W. is the recipient of the 1985 Proctor and Gamble Fellowship at ISU.

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6. The literature report (ref. 3) indicated that this addition was completely regioselective. Our ratio was based on integration of the 300 MHz NMR of the crude product.
7. At room temperature the Tamura reaction afforded only recovered starting material. Lewis acid catalysis afforded several products, of which the major one was quinone 8. A small scale reaction using the ketene acetal as solvent also failed to afford the desired product.

(Received in USA 2 January 1986)