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Synthesis of Angularly-Fused Aromatic Antibiotics. Preparation of the ABC Ring System of Aquayamycin

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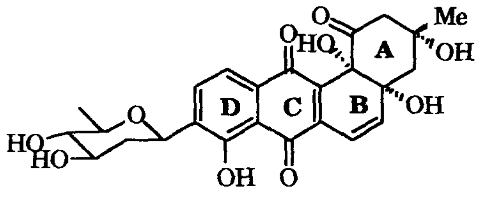
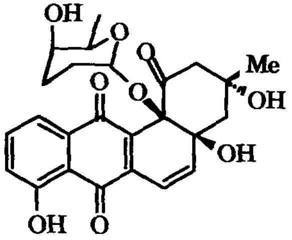
Abstract: An approach to the ABC ring system of aquayamycin which incorporates a selectively protected cis-diol unit is described. The key step is an intramolecular addition of the anion of a protected cyanohydrin to a ketone. © 1997 Elsevier Science Ltd.

The angucycline antibiotics constitute a growing family of naturally-occurring antibiotics.[1] Two biologically active members are aquayamycin (**1**) and sakyomycin A (**2**).[2] Aquayamycin exhibits antitumor activity and also inhibits farnesylprotein transferase and is thought to suppress *ras* functions.[3] The anthraquinones urdamycinone B, vineomycin A and rabelomycin lack the 4a, 12b cis-diol moiety present in **1** and **2**. Syntheses of these structurally simpler members have been reported by a number of researchers.[4,5] Recently, Sulikowski reported an efficient chiral synthesis of urdamycinone B.[6] To the best of our knowledge, only one synthetic approach has addressed the introduction of the 4a, 12b cis diol system.[7] We report herein a synthesis of the ABC ring system of **1** or **2** containing this moiety.

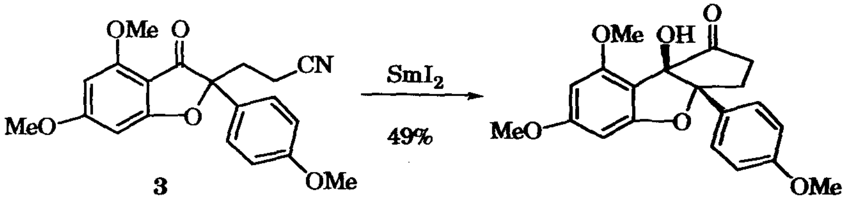


1

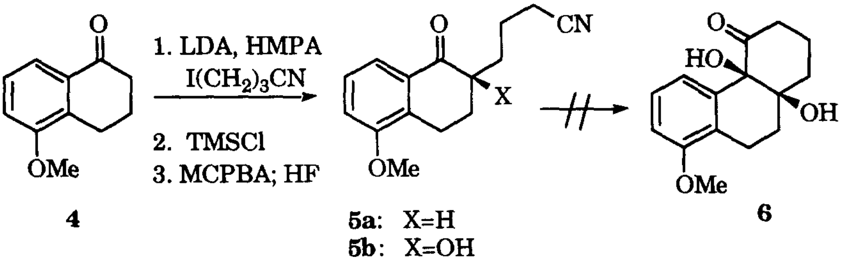


2

We reported that the keto nitrile **3** efficiently cyclized to the α-hydroxy ketone using samarium iodide.[8] Molander has reported that α-hydroxy or alkoxy ketones can be reduced to the corresponding ketones in excellent yield.[9] Although **3** contains an ether linkage alpha to the ketone, no fragmentation was observed. The absence of fragmentation products is likely attributable to stereoelectronic factors.



To extend the scope of this novel samarium-mediated cyclization, we converted commercially available tetralone **4** into keto nitrile **5b** to determine whether reductive cyclization was favored over cleavage of the α-substituent. Alkylation of ketone **4** with lithium diisopropylamide (LDA) and 4-iodobutyronitrile required the addition of hexamethylphosphoric triamide (HMPA) for a reproducible 50% yield of **5a**. Introduction of the α-hydroxyl group via the enol silyl ether produced **5b** in 72% yield. The reaction of **5b** with samarium iodide (2 eq in THF) afforded deoxygenation to **5a**. Corey has used zinc and trimethylchlorosilane to generate ketyl radicals which undergo cyclization with proximate alkenes.[10] The undesired reductive elimination reaction might be prevented by the in situ formation of a five-membered dioxasilane ring, thereby taking advantage of the same factors which stabilized ketone **3**. To test this idea, we treated **5a** with dichlorodimethylsilane and triethylamine in ether at 0 °C and reacted the resulting keto chlorosilane with zinc in THF. Unfortunately, the deoxygenation product **5a** was isolated instead of diol **6**.

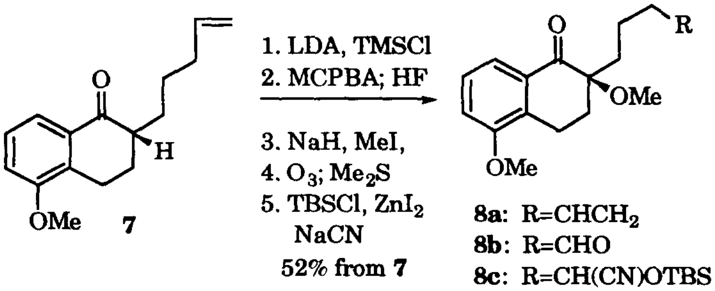


4

5a: X=H
5b: X=OH

6

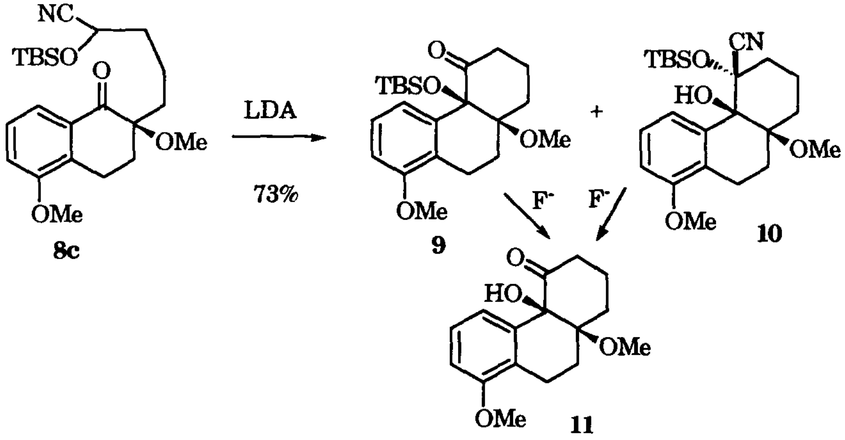
The next strategy we evaluated was an intramolecular cyclization of an acyl carbanion equivalent. Although intramolecular alkylations of acyl carbanion equivalents are well documented, to the best of our knowledge only a few intramolecular reactions with ketones have been reported.[11] We prepared a model system as shown in Scheme 1. The alkylation of ketone **4** with LDA and 5-bromo-1-pentene[12] gave a mixture of mono- and dialkylated products. The reaction of **4** with sodium hexamethyldisilazane and 5-bromo-1-pentene provided a 55% yield of ketone **7**. Installation of the methoxyl group to generate **8a** was accomplished using a three-step sequence involving enol silyl ether formation with LDA and trimethylchlorosilane, oxidation with m-chloroperbenzoic acid followed by HF and methylation with sodium hydride and methyl iodide in DMF.



7

8a: R=$CHCH_2$
8b: R=CHO
8c: R=CH(CN)OTBS

Incorporation of the silyl cyanohydrin was achieved by oxidation of the alkene with ozone to generate aldehyde **8b** followed by treatment of the aldehyde with tert-butyldimethylchlorosilane, zinc iodide and potassium cyanide in dry acetonitrile at 25 °C.[13] Silylated cyanohydrin **8c** was produced in 52% yield from ketone **7**. Treatment of **8c** with LDA in THF at -78 °C for three hours afforded hydroxy ketone **9** and nitrile **10**. The relative stereochemistry of **10** is tentatively assigned based on the fact that the NMR spectrum of **10** contained a methyl resonance at -0.4. This corresponds to a methyl group attached to silicon which has been deshielded by the aromatic ring and would be possible only with the -OTBS group in an endo-configuration. Treatment of the unpurified mixture of **9** and **10** with tetra-n-butylammonium fluoride afforded ketone **11** in 73% overall yield after desilylation. The cis-stereochemistry of the hydroxyl and methoxyl groups was confirmed by x-ray structure determination.[14]



The model chemistry described herein provides a convenient approach to the ABC ring system containing a selectively protected cis- 4a, 12b diol unit. Introduction of the tertiary alcohol at C-3 will be possible via the corresponding enone.

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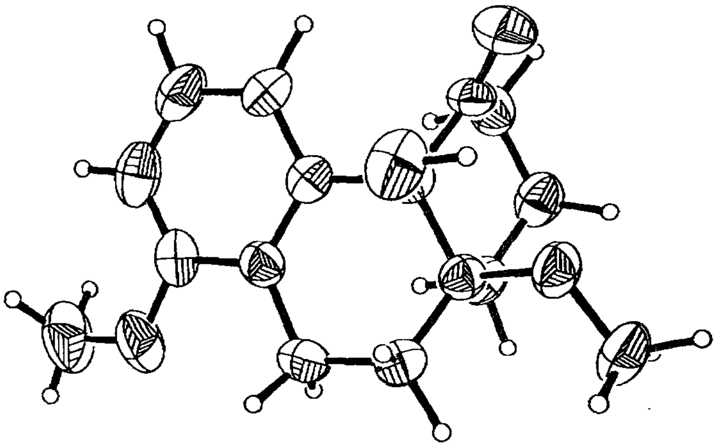
14. X-ray structure of ketone **11**: Siemens P4RA diffractometer with CuKα radiation, 2539 reflections collected. Crystal system: orthorhombic, space group: Fdd2, unit cell dimensions: a = 20.170(4), B = 38.161(8), c = 7.3420(10).



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