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Total Synthesis of Diazaquinomycin A

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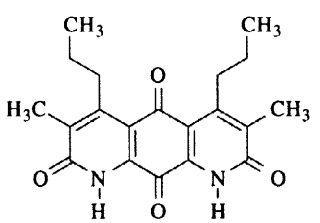
Abstract. Two concise total syntheses of the diazaanthraquinone antibiotic diazaquinomycin A are reported. The first route features a double hetero Diels-Alder reaction between 2,6-dibromobenzoquinone and 2-methyl-2-hexenal dimethylhydrazone, aromatization by a novel, one-pot *N*-oxidation/elimination procedure with percarbamide in trifluoroacetic acid, and double *N*-oxidation followed by rearrangement to a double lactam system. The key step of the second route is a hetero Diels-Alder reaction between 2-methyl-2-hexenal dimethylhydrazone and 3-methyl-4-propyl-1*H*-quinoline-2,5,8-trione.

Diazaquinomycin A (**1**) is a natural antibacterial agent, which was isolated by Omura's group[1] from a *Streptomyces* strain. Further research by the same group[2] suggested that its antibiotic activity was due to inhibition of thymidilate syntase. This mechanism, and its azaanthraquinone structure,[3] hinted at a potential antitumour activity. Unfortunately, this expectation was not fulfilled because of the very poor absorption of diazaquinomycin. Initial attempts to overcome this problem involved the preparation of semisynthetic derivatives,[4] and were followed by extensive research on the synthesis of diazaquinomycin analogues from our group.[5] To date, there is only one total synthesis of diazaquinomycin, with a double Knorr cyclization as the key step.[6]



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Due to the symmetry of the target ring system, we envisaged that a double hetero Diels-Alder approach from 1-dimethylamino-1-azadienes[7] and a benzoquinone derivative would provide a concise approach to a 1,8-diaza-anthraquinone system, which would then be elaborated to give the double lactam. Accordingly, treatment of 2-metyl-2-hexenal dimethylhydrazone[8] with 2,6-dibromobenzoquinone[9] in the presence of triethylamine to trap the liberated hydrobromic acid afforded compound **4**. All attempts to aromatize compound **4** with concomitant double elimination of dimethylamine under literature conditions[10] were unsuccessful. We found, however, that

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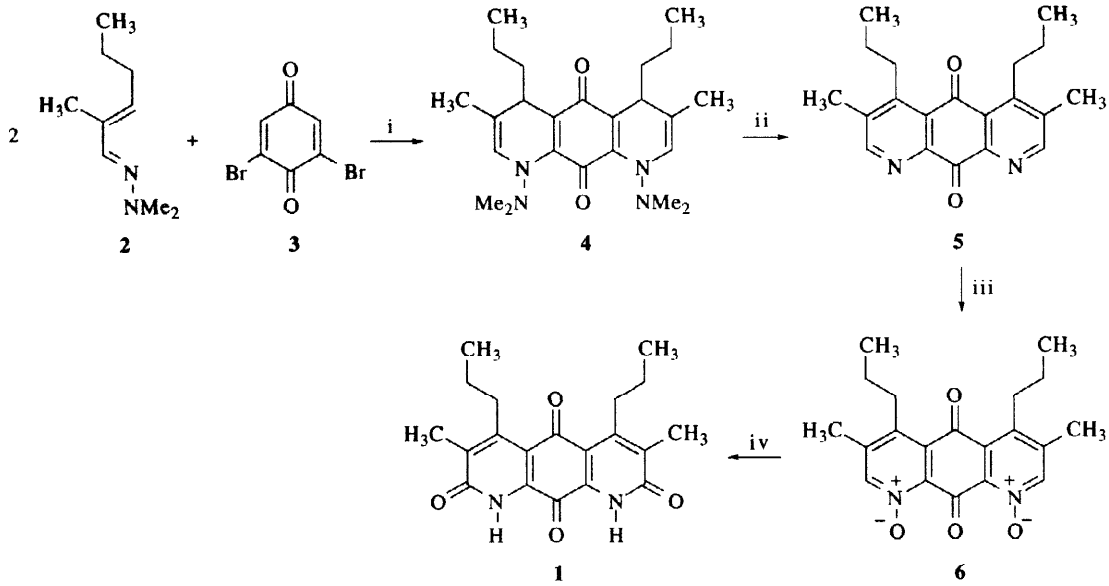
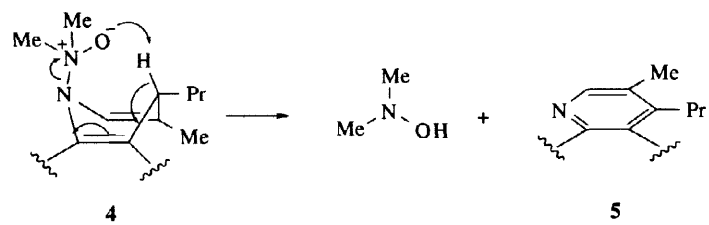
brief exposure to the hydrogen peroxide-urea adduct (percarbamide[11]) in trifluoroacetic acid afforded the 1,8-diazaanthraquinone **5** in 73 % yield (overall from **2**). Finally, compound **5** was transformed into the double *N*-oxide **6** with percarbamide in trifluoroacetic acid; rearrangement to the double lactam by treatment with tosyl chloride in acetonitrile-water afforded 30 % (overall from **5**) of diazaquinomycin A, which was identical to the natural product in all respects (Scheme 1).



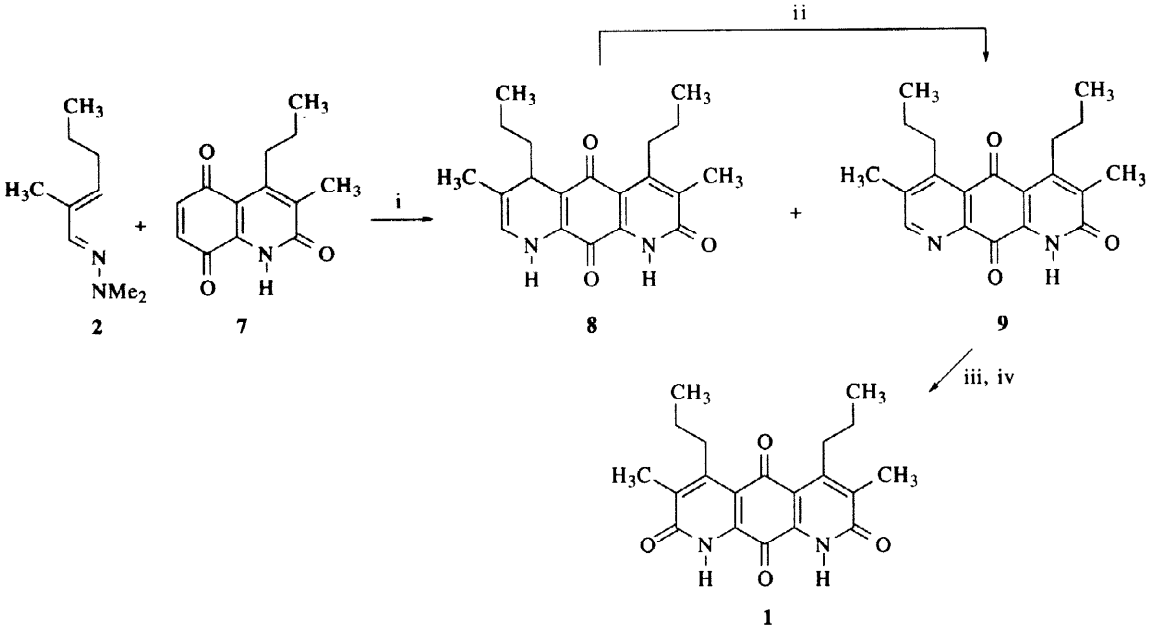
Reagents and conditions: i. CH_2Cl_2, Et_3N, r.t., 15 min. ii. H_2O_2.urea, TFA, r.t., 10 min. iii. H_2O_2.urea, TFA, r.t., 24 h. iv. TsCl, CH_3CN-H_2O, 60 °C, 24 h.

Scheme 1

The novel aromatization of **4** to **5** is of some interest, due to the very mild conditions required and the good yield obtained. It can be rationalized as a double *N*-oxidation of both dimethylamino groups, followed by *in situ* aromatization through a vinylogous Cope mechanism:



An alternative route, also based on hetero Diels-Alder chemistry, is shown in Scheme 2. Quinone **7**, prepared from 2,5-dimethoxyaniline and *S-tert*butyl 2-methyl-3-oxohexanothioate by a known method,[12] was supported on silica gel[13] and treated with azadiene **2**, affording a mixture of the 5,8-dihydro-1,8-diazaanthraquinone **8** (46 %) and its aromatic derivative **9** (24 %). Aromatization of isolated **8** to **9** was performed in 63 % yield by stirring with a suspension of manganese dioxide in dichloromethane. Finally, compound **9** was transformed into diazaquinomycin A in 30 % overall yield by treatment with percarbamide in trifluoroacetic acid, followed again by tosyl chloride in acetonitrile-water (Scheme 2).



Reagents and conditions: i. SiO_2, CH_2Cl_2, r.t., 5 min. ii. MnO_2, CH_2Cl_2, r.t., 30 min. iii. H_2O_2.urea, TFA, r.t., 24 h. iv. TsCl, CH_3CN-H_2O, 60 °C, 24 h.

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