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Synthesis of Perfragilin B, A Cytotoxic Isoquinoline Quinone Isolated from the Bryozoan *Membranipora perfragilis*

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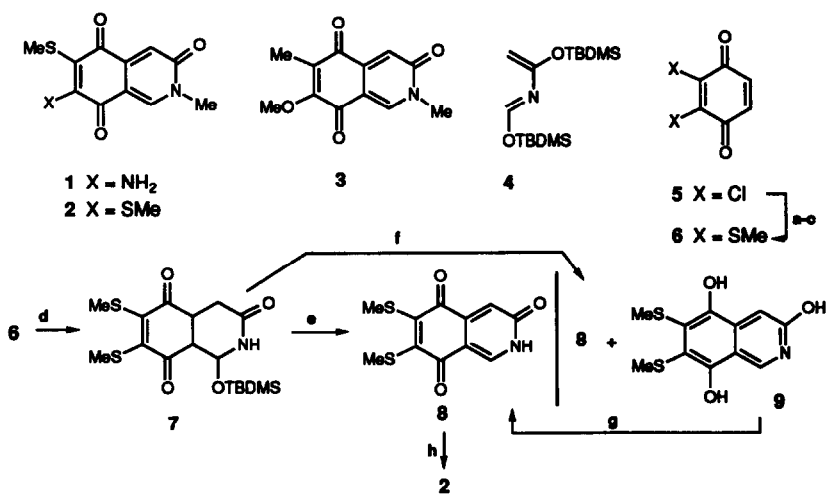
Abstract. The cytotoxic isoquinoline quinone perfragilin B (2), which was isolated from the bryozoan *Membranipora perfragilis*, has been synthesized. The key step involves a Diels-Alder reaction between a substituted 2-azabutadiene (4) and 2,3-bis(thiomethyl)-1,4-benzoquinone (6) to produce the isoquinoline skeleton.

The structures of perfragilin A and B (1 and 2, respectively), cytotoxic isoquinoline quinones isolated from the bryozoan *Membranipora perfragilis*, were recently reported.[1,2] Both compounds displayed significant levels of cytotoxicity against P-388 murine leukemia (ED_{50} 0.8, 0.07 μg/mL, respectively).[2] The skeleton of these cytotoxins is reminiscent of mimosamysin (3), an antibiotic previously isolated from terrestrial bacteria[3] and marine organisms.[4] The methylthio ether functionality of 1 and 2 is relatively uncommon. In order to obtain material for more detailed biological evaluation we have undertaken the synthesis of perfragilin B.

The strategy for synthesizing perfragilin B followed closely that utilized to prepare mimosamycin (3), the key step of which involved reaction of 4 with a substituted 1,4-benzoquinone to produce the isoquinoline skeleton.[5] Diene 4 was prepared according to a literature procedures[6,7] except that the intermediate N-acetyl formamide was prepared by addition of acetyl chloride to a solution of N,N-di-trimethylsilylformamide instead



a: C_5H_6, Et_2O, rt (90%); b: NaSMe, MeOH, phosphate buffer, pH 7 (48%); c: pyrolysis,160°C(61%); d: 4, C_6H_6, Δ 2 h, add MeOH (80%); e: $CHCl_3$/1 N HCl, Δ 2 h (50%); f: 4, C_6H_6, Δ 2 h, add conc. HCl, cool (100%, 2:3 ratio); g: $Ce(NO_3)_2^{2-}$, CH_3CN/H_2O (10%); h: K_2CO_3, MeI (xs), TDA-1,~65°C, 2 h (58%).

of the reverse addition order to minimize N,N-diacetylformamide formation.[7] 2,3-Dichloro-1,4-benzoquinone (**5**) was prepared by chlorination of 1,4-benzoquinone with sulfuryl chloride to give 5,6-dichlorocyclohex-2-ene-1,4-dione[8] which was enolized using BF_3 etherate and then oxidized with silver oxide.[9] Quinone **5** was converted to **6** as described previously.[10]

Cycloaddition of **6** and **4** in refluxing benzene followed by addition of methanol produced **7**. When a chloroform solution of **7** was treated with an equal volume of 1 N HCl and the resulting two-phased solution was refluxed for 2 h, N-demethylperfragilin B (**8**) was obtained. Methylation of **8** under conditions used in the mimosamycin synthesis[5] yielded perfragilin B (**2**). IR, ^{1}H- and ^{13}C-NMR spectral data of synthetic **2** were identical to those of the natural product.[2,11]

When the cycloaddition reaction of **6** and **4** in refluxing benzene (2 h) was terminated by addition of a few drops of conc. HCl followed by cooling of the reaction mixture as per the procedure described for synthesis of mimosamycin,[5] a mixture of **8** and **9** in a 2:3 ratio was obtained. The hydroquinone **9** was oxidized to **8** with ceric nitrate.

When **4** was reacted with **5** in an attempt to circumvent the cyclopentadiene protection step, cycloaddition of **4** across the carbonyl group occurred. Investigation of the reaction of other substituted quinones that also react with **4** at the carbonyl group is in progress.

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