A PHOTOCHEMICAL ROUTE TO PYRROLO[1,4]BENZODIAZEPINE ANTITUMOR ANTIBIOTICS

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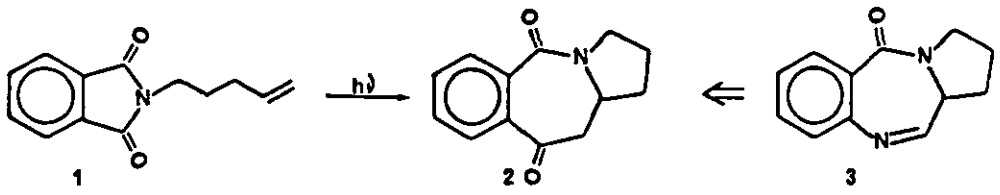
Abstract - The parent pyrrolo[1,4]benzodiazepine ring system was synthesized. The key step was the photostimulated ring expansion reaction of N-pentenylphthalimide to give a pyrrolobenzazepinedione photoproduct. Conversion of the pyrrolobenzazepinedione ring system to the pyrrolo[1,4]-benzodiazepine ring system was accomplished in several steps with the key step a Curtius rearrangement.

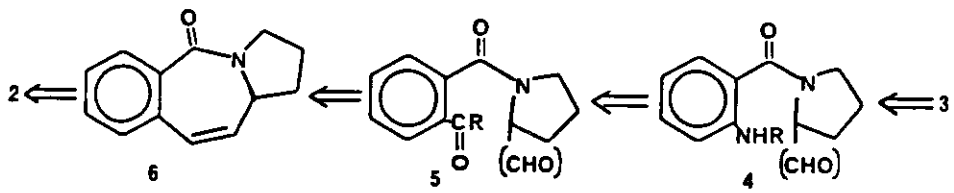
The pyrrolo[1,4]benzodiazepine family of antitumor antibiotics has elicited considerable interest due to their potent biological activity. Some members of this group include antibramycin,[1] sibiromycin,[2] tomaymycin,[3] nethramycins A and B,[4] mazethramycin,[5] chicomycins,[6] BBM-2040,[7] DC-81,[8] and dextrochrysin.[9] Many of these natural products, which are isolated from various Actimomycete bacteria, exhibit antiviral, antibacterial and antifungal properties. Most significantly, they show potent antitumor activity in a wide range of animal models as well as activity against human solid and liquid tumors.[10] For some time we have been studying various mechanistic and synthetic aspects of the photochemical addition of the alkenes to phthalimides which gives 2,5-benzazepinediones.[11] The intramolecular analog of this reaction, reported by Maruyama and Kubo,[12] affords a tricyclic product 2 which differs from the desired 3 in that it requires removal of a carbonyl group and replacement by a nitrogen.



1 2 3

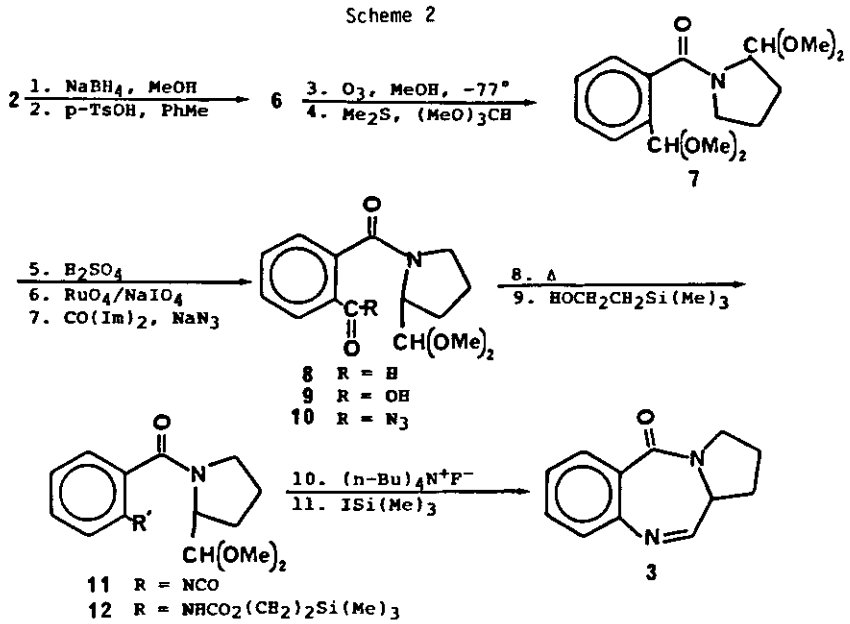
The knowledge of the directing effects of substituents on the aromatic ring in this reaction[11c] makes this approach attractive especially if a rearrangment route from the oxime of 2 or its corresponding ring expanded lactam could be developed. However, as a variety of attempts at a rearrangement route failed[13], we were forced to proceed with a less elegant ring opening -ring closure procedure to introduce the nitrogen. This approach in the synthesis of the parent antibiotic 3[14] is outlined in Scheme 1 with the key step involving nitrogen introduction via a Curtius rearrangement.

Scheme 1



The synthesis of 3 is presented in Scheme 2. Borohydride reduction of 2 and acid catalyzed dehydration gave a 75% overall yield of 6 which was subsequently ozonized and worked up with dimethyl sulfide and methyl orthoformate to give the protected dialdehyde 7 in 86% yield. The aldehydes were cleanly differentiated by acid hydrolysis (aqueous H_2SO_4 in dimethoxyethanol) to give 8 which was oxi-

Scheme 2



dized to the acid 9 ($RuO_4/NaIO_4$)[16] in 90% yield. The acid was converted to the azide 10 in 87% yield by consecutive treatment with carbonyl diimidazole[17] and sodium azide. Pyrolysis led to a clean Curtius rearrangement[18] to the isocyanate 11 which reacted with trimethylsilyl ethanol[19] to give a 90% yield the protected amino-aldehyde 12. Deprotection of the amine and aldehyde by sequential treatment of 12 with tetrabutylammonium flouride[20] (60% yield) followed by iodotrimethylsilane[21] gave a 51% yield the desired product 3, the physical properties of which were identical to those reported by Joshua and Lown[14]. We expect to shortly be able to report on the synthesis of several pyrrolo[1,4]benzodiazepine natural products including anthramycin and tomaymycin.

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