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The Synthesis of a Novel Benzodiazocine *via* an Intramolecular Staudinger/Aza-Wittig Cyclization

Ian A. O'Neil,* Clare L. Murray and Andrew J. Potter

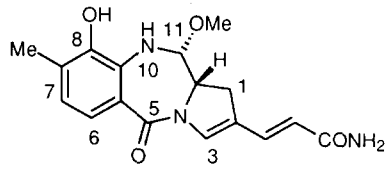
Department of Chemistry, University of Liverpool, P O Box 147, Liverpool L69 3BX U.K.

S. Barret Kalindjian

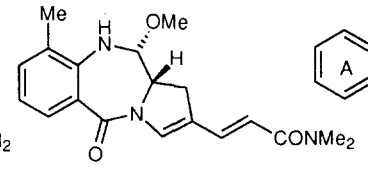
James Black Foundation, 68 Half Moon Lane, Dulwich, London SE24 9JE UK.

Abstract: The novel pyrrolobenzodiazocine (1) has been prepared by an intramolecular Staudinger/aza Wittig protocol from the precursor azido aldehyde (2) in a remarkable 93% yield. Aldehyde (2) was prepared by coupling protected homoprolinol with 2-azidobenzoic acid followed by deprotection and oxidation.

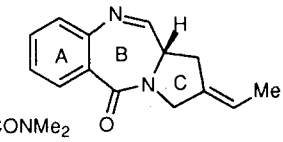
The pyrrolo[1,4]benzodiazepine ring system is found in a number of antitumour agents belonging to the anthramycin family of antibiotics. Members of this family include anthramycin, porothramycin and prothracarcin. They exert their biological activity by covalently binding to the C2-NH_2 of the guanine base in PuGPu sequences in the minor groove of DNA[1].



Anthramycin



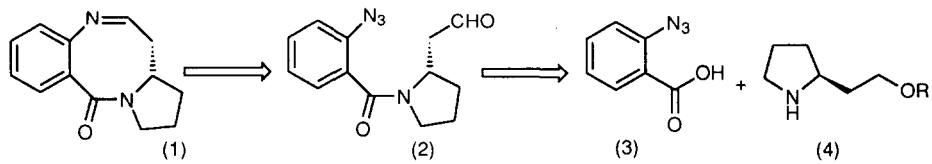
Porothramycin B



Prothracarcin

To date, the study of their mode of action and their potent biological activity has resulted in the synthesis of a wide range of analogues, particularly compounds bearing modifications in the aromatic A ring and the five membered C ring. To the best of our knowledge, no major modifications to the seven membered B ring bearing the reactive imine group have been reported. This is suprising since the imine present in this ring is crucial to the biological activity of this family of compounds. We[2] and others[3] have recently described a rapid and high yielding approach to this important ring system which utilizes a Staudinger/aza-Wittig protocol to install the sensitive imine functionality. We now wish to report the synthesis of a novel eight membered ring analogue (1) shown in Scheme 1 which utlizes this methodology.

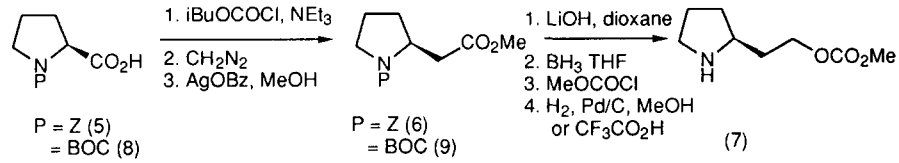
Scheme 1.



(1) (2) (3) (4)

In order to prepare the precursor azido aldehyde (2) we needed a reliable source of homoprolinol[4]. The route is shown in Scheme 2.

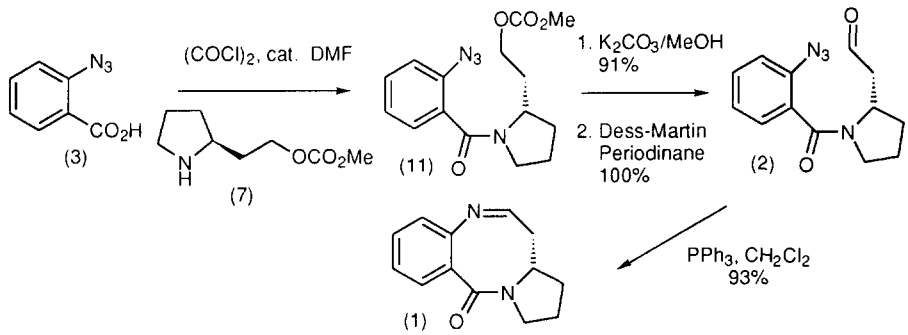
Scheme 2.



Thus, conversion of Z-proline (Z = benzyloxycarbonyl) to the acid chloride followed by addition of diazomethane gave the corresponding diazomethyl ester. Treatment of this diazo intermediate with silver benzoate in methanol yielded the methyl ester (6) in an overall yield of 98%. The use of silver benzoate was critical to the success of this reaction. Hydrolysis of the methyl ester followed by reduction of the carboxylic acid with BH_3.THF yielded the alcohol in 70% yield. Protection of the alcohol as a carbonate and removal of the Z group gave the amine (7) with a yield of 95% for the last two steps. This synthesis of *O*-protected homoprolinol is notable because the overall yield from Z-proline is 65%. This sequence was also carried out with BOC-proline (8) as the starting material with comparable yields.

Construction of the eight membered ring was then started. Conversion of 2-azidobenzoic acid to its acid chloride followed by addition of amine (7) furnished the amide (11) in 60% yield (Scheme 3).

Scheme 3.



Saponification of the carbonate with K_2CO_3/MeOH followed by oxidation of the alcohol with Dess-Martin periodinane yielded the aldehyde (2). On treatment with PPh_3 in CH_2Cl_2, aldehyde (2) underwent smooth cyclization to yield the pyrrolobenzodiazocine (1) in a remarkable 93% yield[5]. To the best of our knowledge this is the first example of the use of the Staudinger/aza-Wittig protocol for the construction of an eight membered ring,[6] and should be amenable to the synthesis of a wide range of structural analogues.

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5. Pyrrolobenzodiazocine exhibited satisfactory physical data including ^1H NMR, ^{13}C NMR, IR and high resolution MS. IR (film)/cm^{-1}, 1684, 1617. m/z (CI, NH_4^+) 215 ($M+H^+$, 100%). Found: $M+H^+$, 215.11848. $C_{13}H_{15}N_2O$, requires $M+H^+$, 215.11844. The ^1H NMR and ^{13}C NMR showed that both the imine and carbinolamine forms were present in a 3:1 ratio in $CDCl_3$. The imine proton is clearly present at δ7.94 and the C11-H (carbinolamine form) at δ4.10ppm. Full NMR details will be reported elsewhere.
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