Tetrahedron Letters,Vol.30,No.32,pp 4185-4188,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

APPLICATION OF A SET-INDUCED PHOTOSPIROCYCLIZATION METHODOLOGY TO HARRINGTONINE RING CONSTRUCTION

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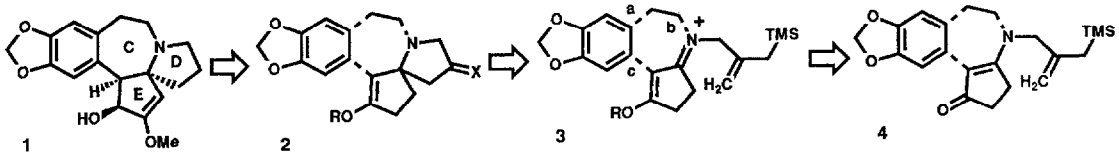
SUMMARY. A route for construction of the pentacyclic skeleton of the harringtonine alkaloids based upon a photo-SET induced spirocyclization process has been developed.

Cephalotaxine (**1**)[1] and other members of the harringtonine alkaloid family possess several interesting structural features in their pentacyclic skeleta. Particularly noteworthy in this regard is the DE-spirocyclic amine grouping which is multiply linked to a benzazepine ring system in these substances. In addition, members of this alkaloid family have been the subjects of intense biological investigation owing to their potential cancer chemotherapeutic properties.[2] As a result of these characteristics, synthetic approaches to cephalotaxine and its derivatives[3] have been scrutinized since shortly after their characterization in 1969.[1] The recent reports[3d,e] of novel synthetic entries to these substances has prompted us to disclose the preliminary results of efforts underway in our laboratory aimed at developing a potentially efficient route for harringtonine ring construction.

In previous studies we have found that the mechanistically interesting, single electron transfer (SET) induced photochemistry of allylsilane-iminium salt systems[4a,b] can be used advantageously in alkaloid synthesis.[4c] Observations which demonstrated that this process could serve as a method for spirocyclic amine construction[5] led us to design the cephalotaxine (**1**) synthetic strategy outlined in Scheme 1. Routes based on this design would employ photospirocyclization reactions of N-silylallyl iminium salts **3**, derived from ß-enaminone precursors **4**, in key ring building steps. Results from earlier[5] and continuing investigations of photocyclization reactions related to **3** → **2** have allowed further refinement of this strategy. Specifically, due to an interesting mechanistic feature (see below) photocyclizations of salts related to **3** which contain fully elaborated benzazepine ring systems (*i.e.*, a, b, c are bonds) are unsuccessful. In contrast, similarly structured salts which lack the benzazepine C-ring (*i.e.*, a, b or c are no-bonds) photocyclize efficiently. This feature along with other considerations has guided us to a harringtonine synthetic strategy which is based upon the photochemistry of the silylallyl-iminium salt **11** (Scheme 2), a substance which can be readily prepared starting with the known[3b] iodopiperonyl ethanol **5**. The preparation of **11**, its photoconversion to spirocyclic amine **12**, and transformations to elaborate the harringtonine pentacyclic skeleton found in enol ester **15** are outlined in Scheme 2 and discussed below.

Several methods have been explored to prepare the 2-arylcyclopentan-1,3-dione **7** which serves as an important intermediate in this sequence.[6] A procedure based upon the Kuwajima cyclopentanedione synthetic methodology[7] employing BF_3-catalyzed addition of 1,2-bis-trimethylsilyloxycyclobutene to aldehyde **6** followed by pinacol

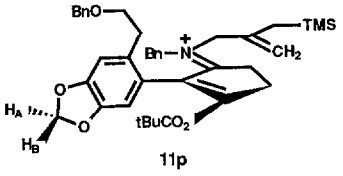
Scheme 1.



rearrangement was found to be superior for this purpose. The requisite aldehyde **6** was produced from the known iodopiperonyl ethanol **5**[3b] by sequential O-benzylation, lithiation and formylation. The dione **7** formed from **6** in this way was then transformed to an acid senstive ß-chlorenone **8** derivative by use of a procedure (NaOH, ClCOCOCl) adapted from Rapoport's method[8] for synthesis of similarly unstable carboxylic acid chlorides. The silylmethallyl amine **9**, needed for conversion of the vinylogous acid chloride **8** to ß-enaminone **10**, was prepared starting with the known[9] mesylate of 2-(trimethylsilylmethyl)propen-3-ol by use of azide displacement and LAH-reduction. Reaction of this amine with the chloroenone **8** followed by N-benzylation furnished the tertiary ß-enaminone **10**.

The O-pivaloyl iminium perchlorate **11**, a key intermediate in this strategy for harringtonine ring construction, can be efficiently prepared by using a procedure we had developed as part of our earlier studies in this area.[5] Accordingly, $AgClO_4$ facilitated O-acylation of ß-enaminone **10** with pivaloyl chloride provides the desired perchlorate salt **11** as an *ca.* 1:1 mixture of E and Z-isomers. Selection of the pivaloyl enol ester function was based on our expectation that it would be durable under ensuing reaction conditions and that it could be advantageously removed at later stages of a cephalotaxine synthetic sequence.

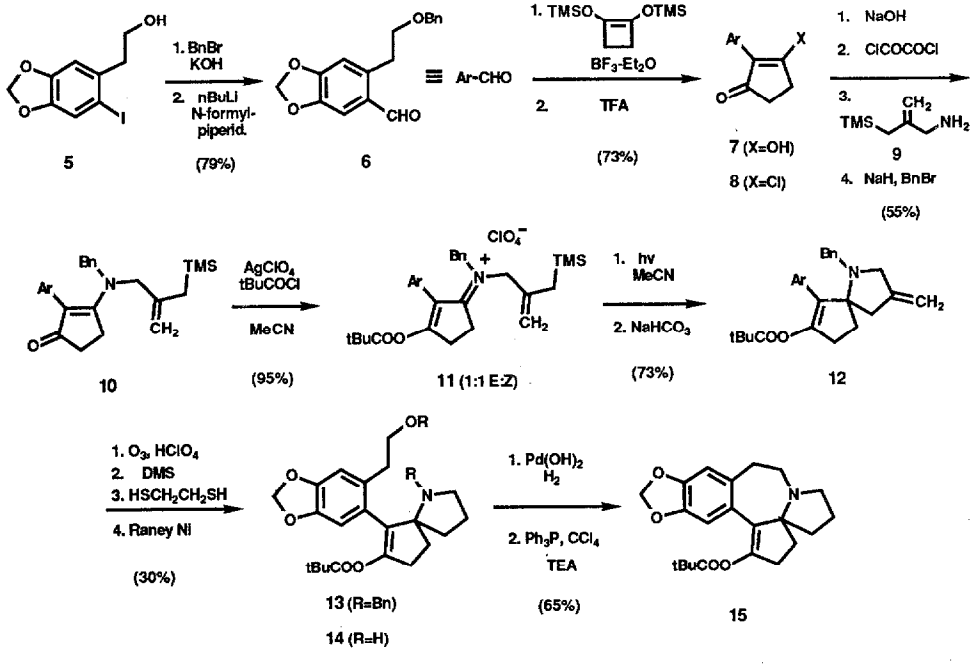
As mentioned above and detailed more thoroughly in an earlier report,[5c] β-enaminone derived iminium salts related to **3** (Scheme 1) do not undergo SET-induced photocyclization when the piperonyl and iminium cation groups are conjugated. Lack of reactivity in systems of this type is due to inefficient intramolecular SET between the allylsilane donor and iminium cation acceptor groupings. Thus, conjugation of the piperonyl and iminium cation functions causes the singlet excited state energy and ground state reduction potential of the iminium salt to be sufficiently low so as to prevent fast SET. However, SET initiated photocyclization occurs in these salts when conjugation of the piperonyl and iminium cation groups is prevented by steric crowding. Iminium salt **11** exemplifies this situation. The piperonyl and iminium cation chromophores in **11** exist in a biphenyl-like, perpendicular orientation, depicted in **11p** , as demonstrated by the UV-spectrum which



11p

contains a λ_{max} at 284 nm (MeCN) that closely matches those of non-aryl-substitued analogs.[5] More indicative of this conformational/configurational preference is the ^1H NMR spectrum of **11** which shows that the protons in the methylenedioxy (O-CH_2-O) group of both E and Z-isomers are diastereotopic.[10] The origin of this phenomenon is the chirality in **11** associated with the presence of the center of perpendicular asymmetry. In full accord with these observations, the iminium salt **11** is photoreactive. Irradiation of **11** in MeCN followed by $NaHCO_3$ work-up leads to smooth generation of the spirocyclic amine **12**.[11]

Scheme 2



Completion of the sequence for harringtonine ring construction requires the availability of methods to remove the exocyclic methylene function and to form the azepine C-ring. Our current procedure for excision of the methylene group involves ozonolytic cleavage followed by ethylene dithioketal formation and Raney nickel desulfurization. This sequence

provides the bis-benzyl blocked amino alcohol **13** which can be readily transformed to its unblocked derivative **14** by catalytic hydrogenolysis.[12] As designed, azepine ring formation occurs smoothly when the amino-alcohol **14** is treated with Ph_3P and CCl_4. This provides the enol ester **15** , a substance which has the harringtonine pentacyclic skeleton. The strategy embodied in this sequence appears to be applicable to the synthesis of interesting members of this alkaloid family. Efforts are currently underway to test this proposal.

Acknowledgement. This research was supported by a grant from the National Institutes of Health (GM-27251). We thank Professor P. Fuchs for kindly providing spectra which were used for comparative purposes.

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(10) Chemical shift (coupling constant) data for the methylene dioxy-protons of the E and Z-isomers of **11** are 5.93 and 5.92 ppm (J = 10.6 Hz) and 5.83 and 5.82 ppm (17.6 Hz). Interestingly, the enaminone **10** also exists in a perpendicular conformation/configuration as seen by the existence of diastereotopic methylene dioxy protons.

(11) This reaction is carried out to only *ca.* 50% conversion owing to the photochemical instability of the photoproduct **12** (λ_{max} = 291 nm). Work-up ($NaHCO_3$) followed by chromatography (F-20 alumina) yields **12** and **10** (derived from unreacted **11**) in isolated yields of 46% and 40%, respectively. The effective yield of **12** is therefore 73% based upon one recycle of **10**.

(12) Hydrogenation of the enol ester function in **13** does not occur under these conditions owing to the extreme steric inaccessibility of this π-bond. Also, we have found that this hydrogenolysis is a highly capricious process (success rate *ca.* 70%).

(Received in USA 3 April 1989)