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THE NEWER SYNTHETIC STRATEGIES FOR DNA BINDING PYRROLOBENZODIAZEPINE ANTIBIOTICS (REVIEW)

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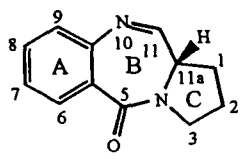
Modern synthetic approaches to DNA binding pyrrolobenzodiazepine antibiotics have been discussed.

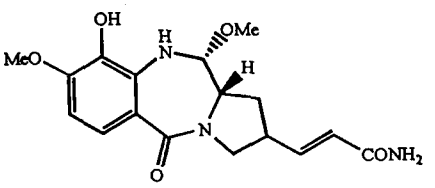
INTRODUCTION

There have been spectacular advances in the understanding of the interactions of small nonpeptide molecules with DNA in the last two decades. Although sufficient DNA sequence specificity has been achieved by proteins to permit their participation in the precise control in gene expression and other genetic events, the ability to design and synthesize a nonpeptide small molecular-weight molecule that would bind to a desired DNA sequence of reasonable size (up to about 15-16 base pairs) would be a significant achievement in medicinal chemistry.

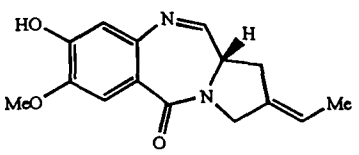
In recent years there has been considerable interest in ring systems such as the pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs, I) that can recognize and bind to a specific sequence of DNA [1]. These compounds have generally been referred as antitumor antibiotics of the anthramycin family. This family is comprised of biosynthetically derived compounds produced by *Streptomyces* species, representative compounds of this series are anthramycin (II), tomaymycin (III), sibiromycin (IV), chicamycin A (V), neothramycin A (VIa) and B (VIb), and DC-81 (VII) [2].



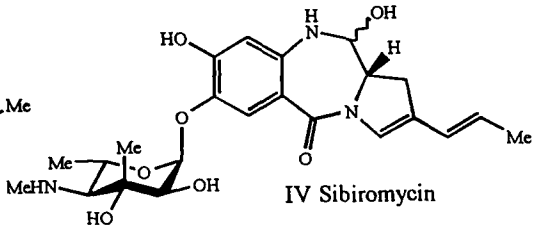
I



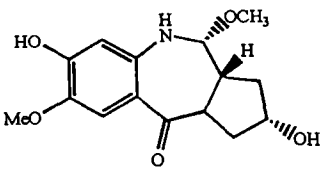
II Anthramycin



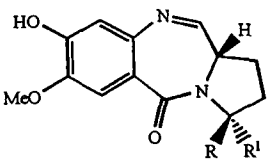
III Tomaymycin



IV Sibiromycin



V Chicamycin A



VIa Neothramycin A (R= H, R^1 = OH)
VIb Neothramycin B (R= OH, R^1 = H)
VII DC-81(R= R^1= H)

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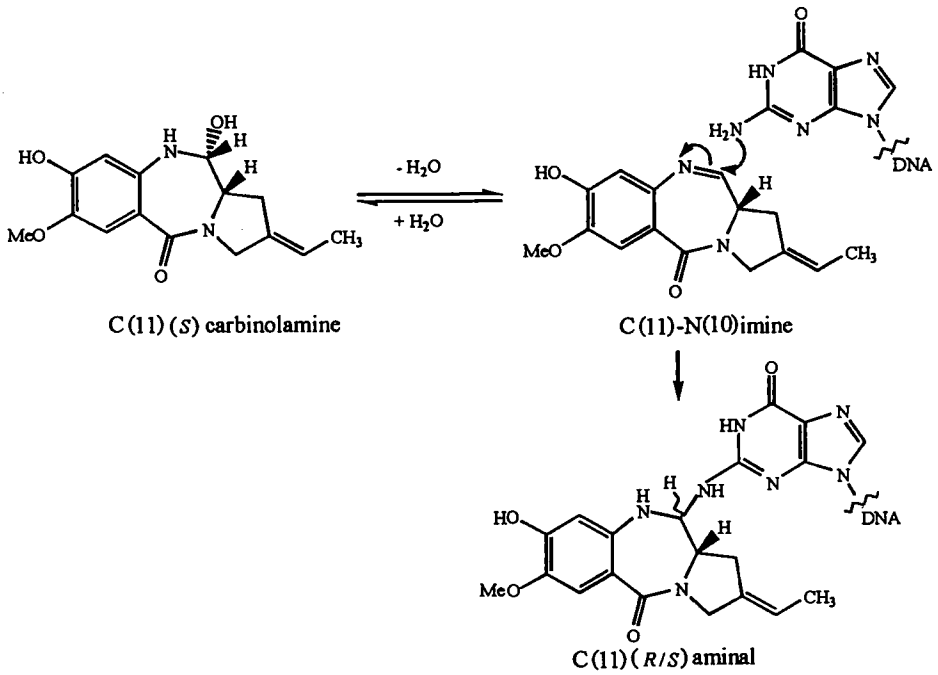
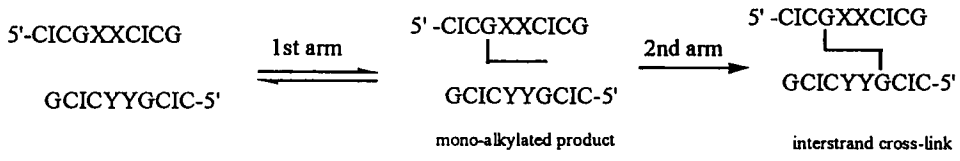
The PBDs differ in the number, type, and position of the substituents in both the aromatic A rings and pyrrolo C rings and in the nature of the C ring which is either fully saturated or unsaturated at C(2)—C(3) (endocyclic) or at C(2) (exocyclic). The cytotoxic and antitumor activities of monomeric PBDs are attributed to their ability to form covalent DNA adducts via an acid labile amine bond to the electrophilic imine C(11)-position involving the exocyclic 2-N of guanine base in the minor groove of duplex DNA.

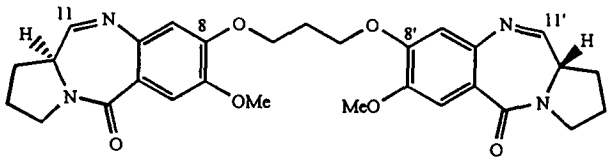
All naturally occurring compounds possess the (*S*)-configuration at C(11a) which provides the molecule with a right-handed twist when viewed from the C-ring towards the A-ring. This enables the PBD to mirror the curvature of B-form DNA and maintain isohelical contact with the walls and floor of the minor groove [3]. The structure of anthramycin and DNA adduct has been studied using indirect methods [4]. Molecular modelling, solution NMR, fluorimetry, and DNA foot-printing experiments indicate that PBD compounds are generally sequence specific with a binding site preference for 5′-PuGPu (particularly 5′-AG or 5′-GA) sequences [5]. A correlation between DNA sequence specificity, relative induced distortion of DNA, and kinetics of covalent binding has been studied [6]. PBDs have been shown to inhibit DNA processing enzymes, with activity in accord with structure-activity prediction [4], although the role of DNA adduct formation is not clearly known.



In recent years many synthetic PBDs have been prepared to study their recognizing and bonding capabilities. However, such compounds have generally shown selectivity for only relatively short DNA stretches [7], indicating the need for the development of a better sequence recognizing PBDs. In this endeavor a PBD dimer has been synthesized by Thurston and co-workers as a highly efficient DNA interstrand cross-linking agent [8]. This dimer consists of two DC-81 subunits which join head to head through A ring C(8) positions by various flexible alkanediyl-dioxy linkages which could be considered as a DNA template-directed drug design [9].



Among these dimers 1,3-propanediyledioxy linked compounds (e. g. VIII) have been extensively studied towards its DNA cross-linking ability, cytotoxicity and antitumor activity [10]. The carbinolamine containing PBD was first synthesized in 1968 [11] (total synthesis of anthramycin) while the synthesis of various other PBDs posed many synthetic problems.



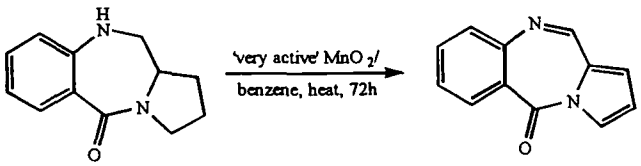
VIII DSB-120

An elaborate review of the synthetic literature of the PBDs has appeared in 1994 [12]. The purpose of the present review is to survey the most recent developments toward the synthetic strategies of PBDs. This could assist the appropriate strategy to be selected for a particular target molecule. Further, in this review an effort is being made to outline the various synthetic routes developed in the last four years with their merits and limitations. Accordingly, these recent methods have been classified based on their synthetic strategy and reaction type. Various approaches to the synthesis of PBD antibiotics have been investigated, including hydride reduction of seven-membered cyclic dilactams [13], reductive cyclization of acyclic nitroaldehydes [14], reduction of cyclic iminothioethers [15, 16], cyclization of aminoacetals or thioacetals [17, 18], and palladium-catalyzed carbonylation of 2-haloanilides [19, 20]. Most of the methods met with varying degrees of success, with each having different limitations.

I. OXIDATION OF CYCLIC SECONDARY AMINES

Oxidation by Activated Me_2SO (*Swern's oxidation*)

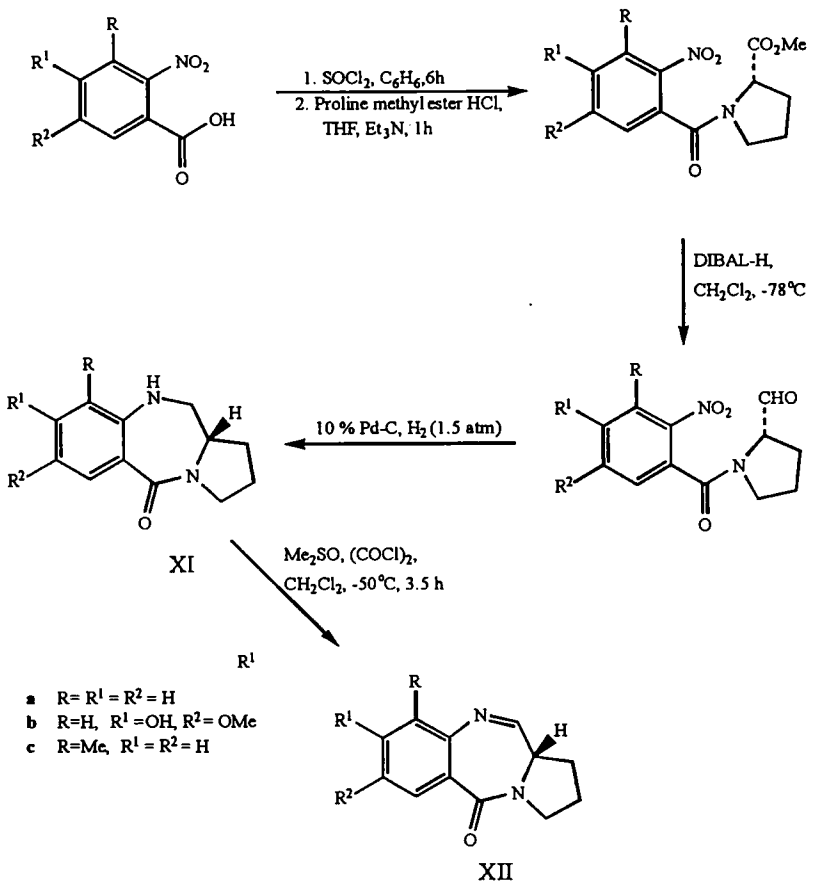
Earlier, this approach has not been extensively investigated. This approach is attractive as PBD secondary amines are readily prepared in high yields by a number of different methods including the reductive cyclization of N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes and also palladium-catalyzed carbonylation reaction. The literature investigation has demonstrated that very active MnO_2 is capable of oxidizing the unsubstituted amine IX to the fully unsaturated PBD X.



IX X

A milder oxidation method was successfully carried out in this laboratory for the desired conversion of PBD cyclic amines into imines [21]. This is a successful application of the activated Me_2SO reagent (*Swern's oxidation*) for the oxidation of cyclic secondary amines to the corresponding PBD imines. Employing this methodology, DC-81 (XIIb≡VII) has also been synthesized as described in Scheme 1. Further, this method does not endanger the stereochemical integrity of the C(11a) position. In this approach in comparison to most successful methods, the simultaneous cyclization with imine formation has been avoided. Therefore, in this method the remote chance of racemization at the C(11a) position has been excluded and the desired stereochemistry is preserved. Furthermore,

Scheme 1



unlike the other successful methods such as the reductive cyclization of amino dithioacetals, this method is devoid of protective and deprotective steps.

Oxidation by TPAP

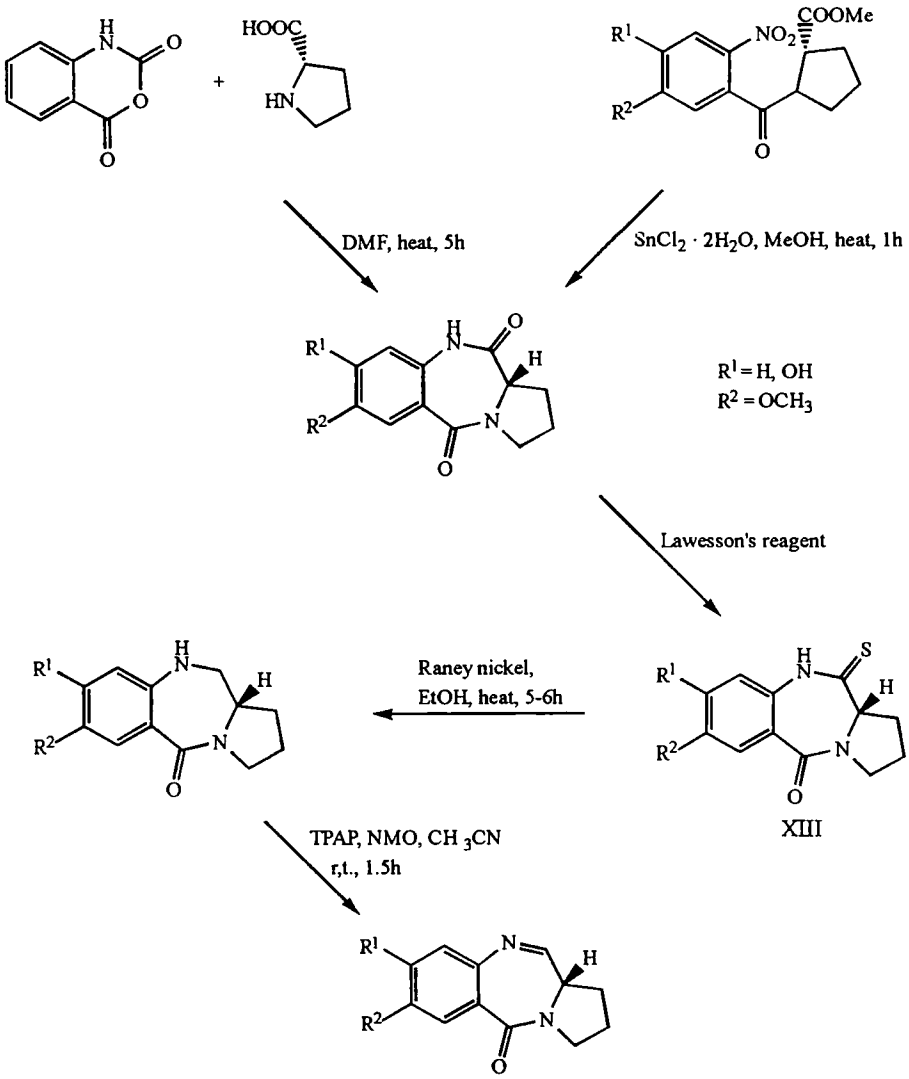
In the search for more practical and efficient methodologies, another new oxidative method has been developed in this laboratory employing tetra-*n*-propylammonium perruthenate (TPAP). As discussed in the above oxidation method, this method has various advantages; the most significant advantage is the complete absence of side products and also is devoid of aqueous work-up for the sensitive imine moiety. In this study the cyclic secondary amines have also been synthesized by an altogether new approach involving the reductive desulfurization of PBD-5-one-11-thione XIII by Raney nickel (Scheme 2).

II. REDUCTIVE CYCLIZATIONS

Reductive Cyclization of N-(2-Nitrobenzoyl)-pyrrolidine-2-carboxaldehyde

This approach involves the controlled reductive cyclization of N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde via catalytic hydrogenation or chemical reduction. The earlier reports for such reductions by catalytic hydrogenation of N-(2-nitrobenzoyl)pyrrole-2-carboxaldehyde (XIV) over Pd-C catalyst afforded 10,11-dihydro derivatives XV, i.e., the secondary amines in low yields (Scheme 3).

Scheme 2

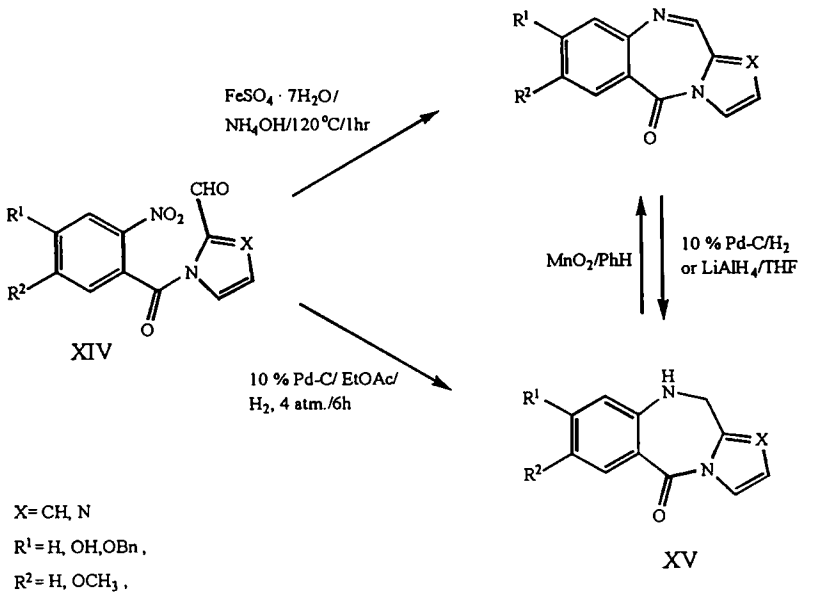


Later, Miyamoto and co-workers reported [23] the first total synthesis of N(10), C(11) imine-containing PBD via reductive cyclization for neothramycin A and B (Scheme 4). Employing this approach the total synthesis of both *E* and *Z*-tomaymycins has also been accomplished [24].

Thurston and Langley have carried out a detailed investigation on the mechanism of the reductive cyclization of N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes (XVI) [25]. Studies on this type of reductive cyclizations in our laboratory employing iron powder and acetic acid afforded the PBD imines in good yields [26]. This method has also been extended towards the synthesis of 5-thio PBD imine derivatives XVII which was not successful in employing the iminothioether approach (Scheme 5). The limitation in this methodology has been that the PBD imine is produced with an optical rotation value somewhat lower than the product obtained by the diethylthioacetal deprotective cyclization route. This has been attributed due to the racemization taking place to some extent in acidic reaction conditions [27].

Another convenient methodology via simultaneous reduction of aromatic nitro functionality and protection of the aldehydic group for the formation of the seven-membered ring of the PBD is achieved at this laboratory em-

Scheme 3

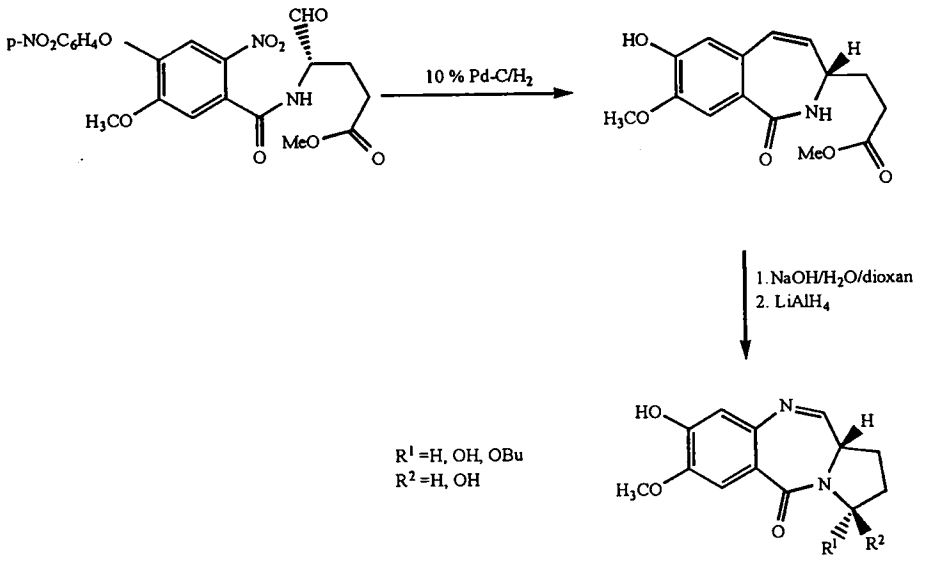


ploying $FeCl_3 \cdot 6H_2O$ and N,N-dimethylhydrazine. This procedure has been applied for the preparation of benzylated DC-81 and the natural product DC-81 (VII) demonstrating the generality of this method. This approach (Scheme 6) is a far more useful and convenient method for the preparation of natural and synthetic DNA binding PBD imines compared to the previously reported protocols.

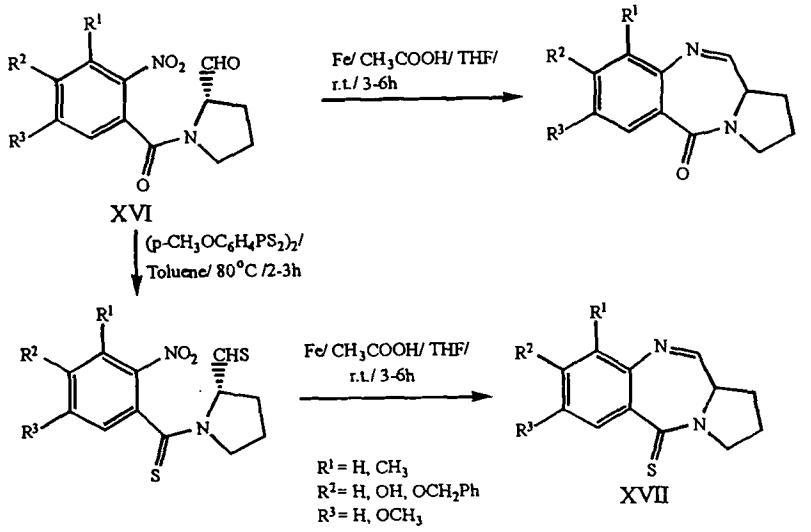
Intramolecular aza-Wittig reaction

The intramolecular aza-Wittig reaction of N-(*o*-azidobenzoyl) α-amino acid esters and their applications to the synthesis of benzylated DC-81 as well as DC-81 has been reported [28, 29] by two groups independently. Both the groups have employed triphenylphosphine (TPP) for their intramolecular aza-Wittig reaction (Schemes 7 and 8).

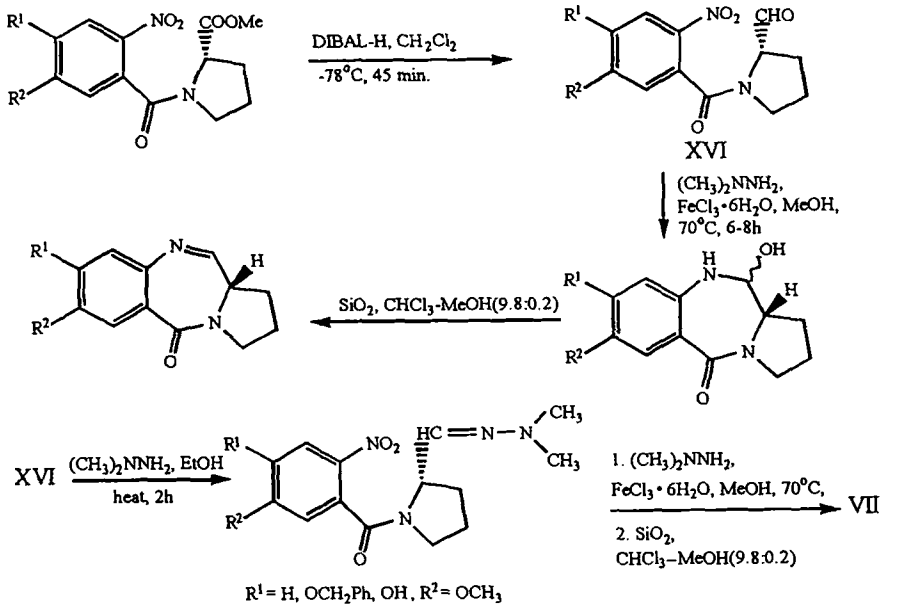
Scheme 4



Scheme 5



Scheme 6



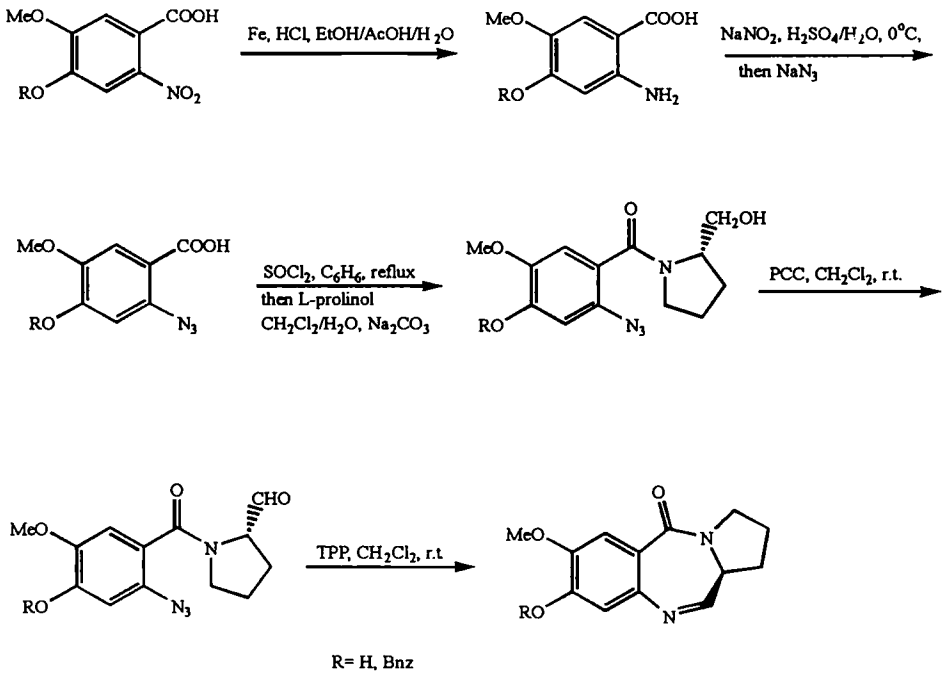
The intramolecular aza-Wittig approach is a new alternative and powerful method for the preparation of PBD imines. The azidobenzamide derivative XVIII on conversion to its ethyl ester XIX was oxidized to give its carbonyl analogue XX. This upon sequential treatment with TPP, reduction with DIBAL-H and further heating did not afford the PBD (Scheme 9).

Recently in our laboratory, a new method for the reduction of the azido functionality has been developed for the first time employing trimethylsilyl iodide (TMSI) [30]. This has been extended towards the synthesis of PBD imines *via* intramolecular aza-Wittig reaction involving iminosilane intermediate instead of the usual imino phosphorane intermediate.*

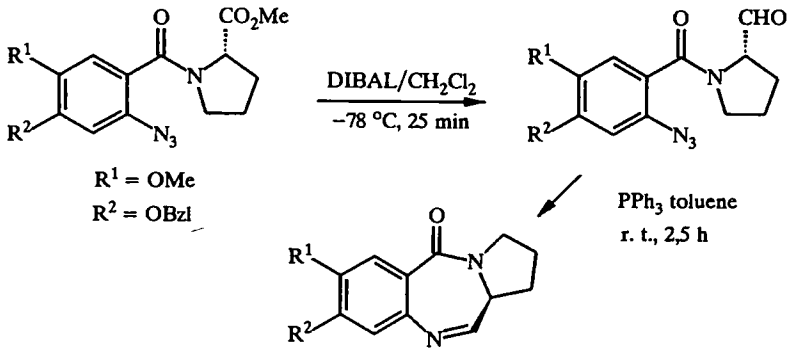
Another ring closure for the synthesis of PBD imine XII *via* the Staudinger aza-Wittig approach has also been reported [31]. In this procedure the precursor for the aza-Wittig cyclization, the azidoaldehyde XX has been obtained

*A. Kamal and N. Laxman, unpublished results.

Scheme 7



Scheme 8



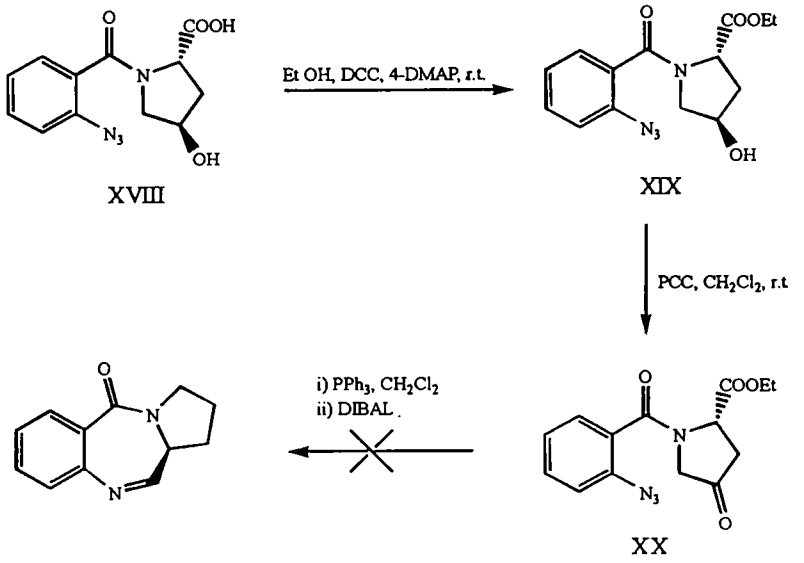
by the oxidation of azidoprolinol derivatives XXI *via* Dess-Martin periodinane oxidative process. This approach has been extended towards the synthesis of functionalized PBD imines (Scheme 10).

Azido Reductive Cyclizations

A new modified approach [32] based on the formation of the seven-membered ring through an azido reductive process has also been developed recently in this laboratory. In this method the azido functionality has been reduced employing hexamethyldisilathiane (HMDST) accompanied with cyclization to the PBD methylether (XXII). This procedure does not disturb the (*S*)-configuration of the chiral C(11a) position as it is carried out under extremely mild conditions and also involves a simple and rapid work-up procedure (Scheme 11).

Recently, another azidoreductive cyclization [33] has been carried out for the synthesis of PBD's employing benzyltriethylammonium tetrathiomolybdate, $[PhCH_2NEt_3]_2MoS_4$ (Scheme 12).

Scheme 9

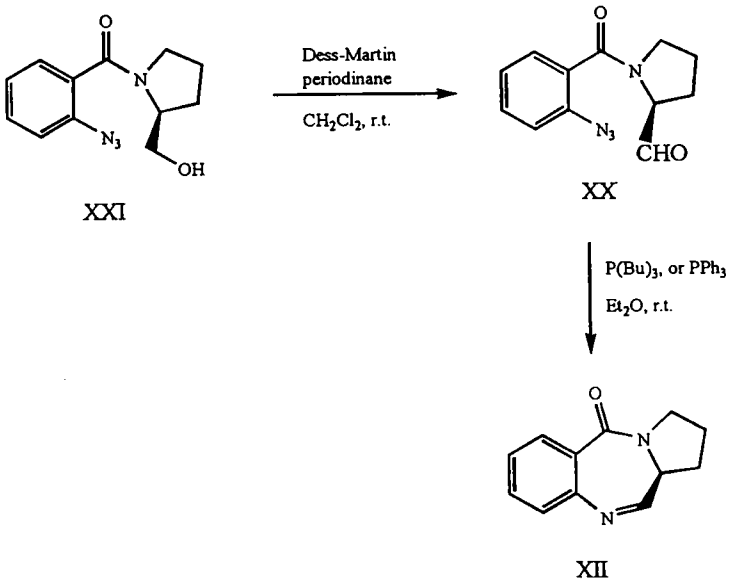


III. DEPROTECTIVE CYCI IZATIONS

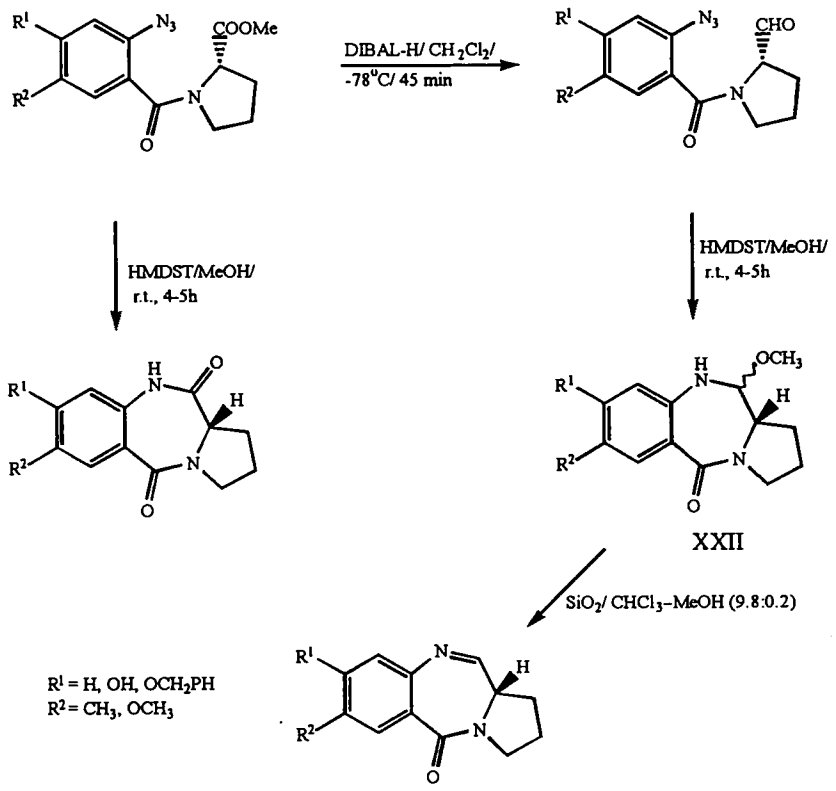
Cyclization of N-(2-Aminobenzoyl)pyrrolidone-2-carboxaldehyde Dialkyl Acetals

Deprotective cyclization to the PBD imine or carbinolamine has been earlier considered as the most widely used methodology. However, one of the major problems associated with this method is that the deprotection of the

Scheme 10



Scheme 11

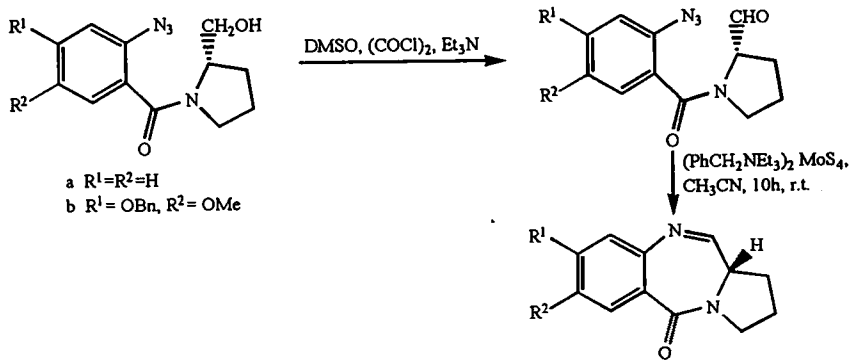


acetal can lead to racemization at the C(11a) position of the product, particularly under acidic conditions. Many reports [34] have been published for the synthesis of the PBD imine via deprotection of the aminoacetals (Scheme 13).

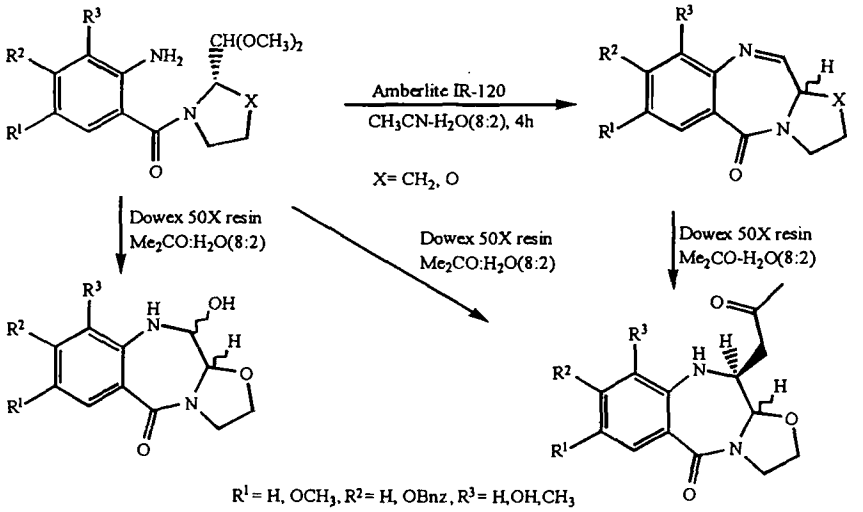
Cyclization of N-(2-Aminobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetals

This particular method has been mainly developed to overcome the limitations of the previously described techniques. [13-15]. This is a method which has been generally applicable and not dependent on the type or pattern of

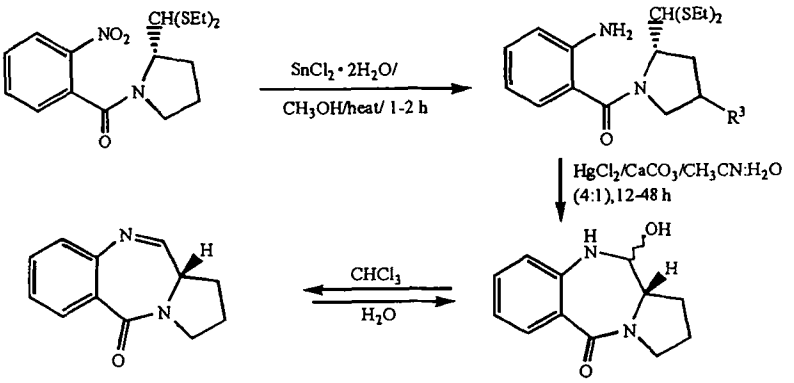
Scheme 12



Scheme 13



Scheme 14



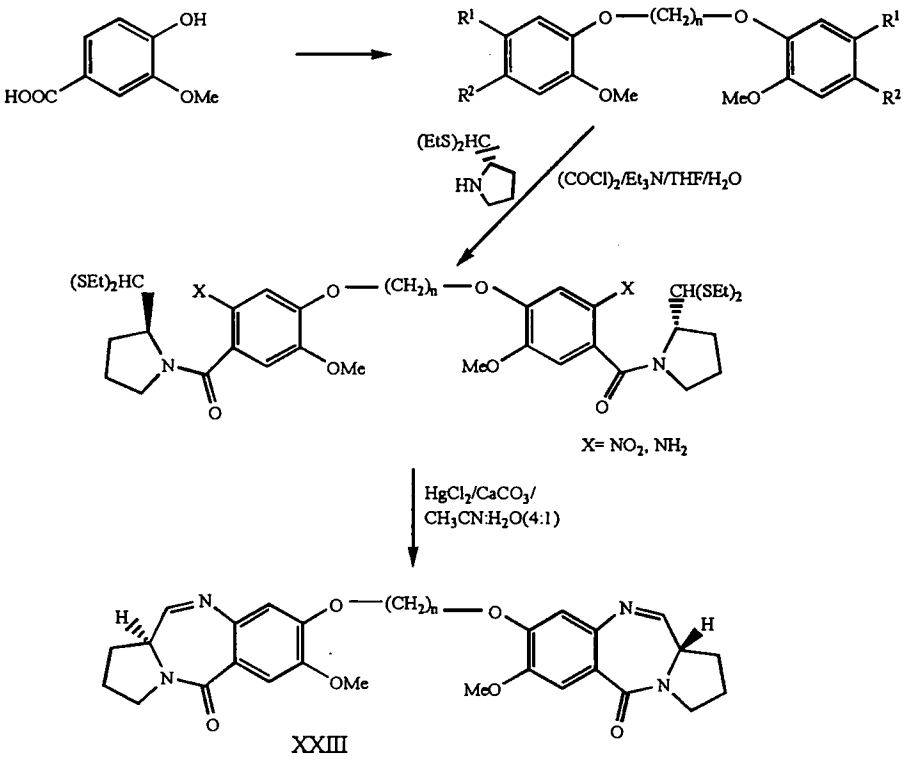
ring substitute that involved nonhydrogenolytic conditions to preserve the points of unsaturation in the molecule which could maintain the stereochemical integrity at C(11a) of the product, and has been adaptable to a convergent synthesis (Scheme 14).

This procedure was initially tested on various model nitro aldehydes which afforded, in about three steps, cyclized imines in good overall yields. Thurston and co-workers [35] have carried out a detailed study on the effect of A-ring substitution employing this method. Later, the same methodology has been used by Suggs and co-workers [36] to prepare C(7)-linked PBD dimers from precursor aminothioacetals. These dimers have shown DNA cross-linking activity.

Recently, Thurston and co-workers [37] have synthesized the C(8)-linked DC-81 dimers XXIII employing the above methodology (Scheme 15). These dimers are extremely cytotoxic and are fifty-fold more efficient than cisplatin. These have been claimed as irreversible DNA interstrand cross-linking agents [38].

In view of the biological importance of DC-81 "dimers" as antitumor antibiotics, an improved, economical and versatile route has been designed and developed in this laboratory [39]. Significant features of this new methodology are that the PBD dimers have been prepared from a less expensive starting material, i.e., vanillin (XXIV) instead of vanillic acid; this also brought down the additional steps of esterification and deesterification of the vanillic acid. Further, during dimerization of vanillin there is very little monoalkylation product formed employing either the dibromo or diiodoalkanes [8b]. Most importantly, the nitration of vanillin "dimer" giving compound XXV (Scheme

Scheme 15



16) was extremely successful unlike the vanillic acid dimers. In this methodology the overall yields are more than twice compared to the previously employed routes.

Another, new and novel GC-selective pyrrolobenzodiazepine EDTA conjugate has been synthesized recently that covalently binds to DNA at 5'-PuGPu sequence leading to site-specific cleavage. The synthesis of this substance has also been based on the convergent thioacetal deprotection routes [40] (Scheme 17).

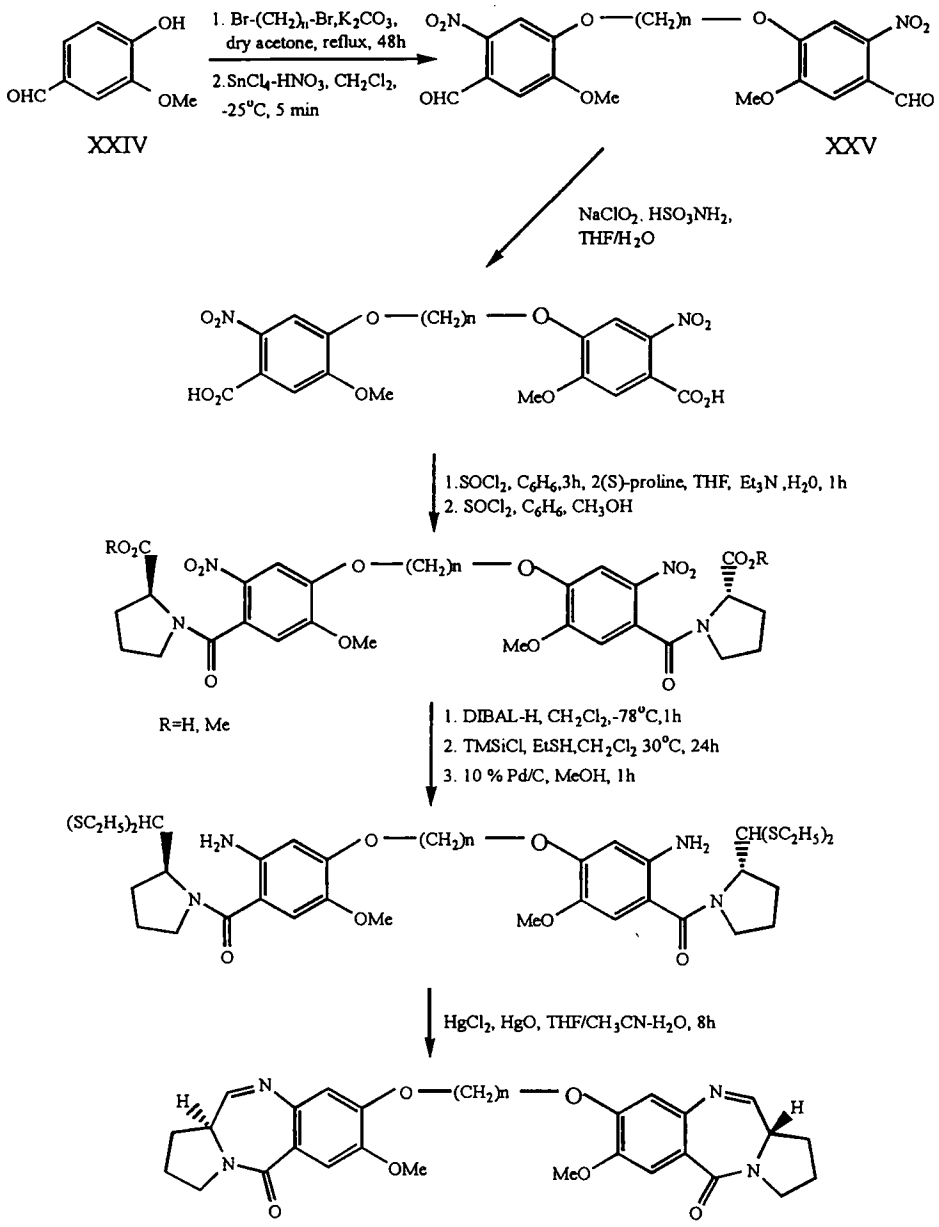
Recently, a novel epoxide-containing PBD XXVI has been synthesized *via* a new cyclization procedure [41]. In this method 9-fluorenylmethylcarbonyl (Fmoc) group has been employed to protect the amino intermediate before dithioacetal deprotection to allow the Fmoc protected carbinolamine deprotection of dithioacetals. Finally the Fmoc is cleaved by tetrabutyl-ammonium fluoride (TBAF) at room temperature to afford the PBD imines under mild conditions (Scheme 18).

IV. ENZYMATIC APPROACH

In the literature a number of enzyme systems are known for oxidizing substituted amines. This type of biooxidation is related to the well-known metabolic process of N-demethylation. It is feasible that secondary PBD imines could be converted into imines or carbinolamines *via* this process. However, attempts made in this laboratory were not very successful. Therefore, a second possibility of bioreductive cyclization of the azidoaldehydes have been attempted and successfully achieved in this laboratory [42] (Scheme 19).

2(*S*)-N-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes (XXVII) have been reduced employing baker's yeast to afford PBD imines in good yields. This chemoenzymatic method has been extended towards the synthesis of natural and synthetic analogues of PBD imines. This enzymatic approach is performed under extremely mild conditions and

Scheme 16

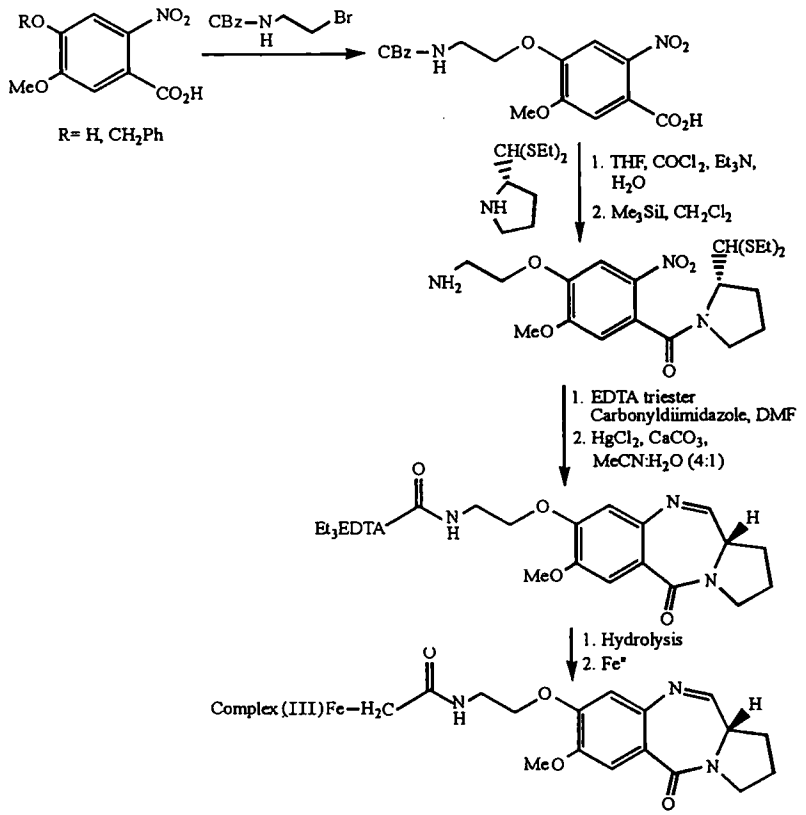


is expected to maintain the stereochemical integrity at C(11a) position without effecting the DNA-binding potential of the PBD imines unlike other chemical methods [26].

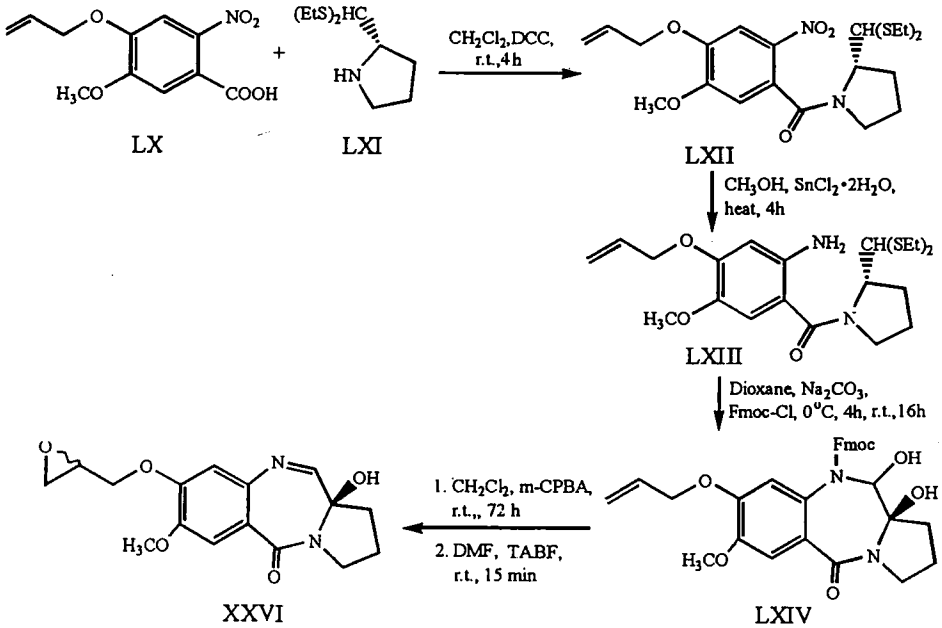
CONCLUSIONS

In most of the approaches reviewed above, the N(10)—C(11) carbinolamine moiety (or its imine equivalent) has been incorporated at the last step of the synthesis with some exceptions reported earlier. This is mainly because

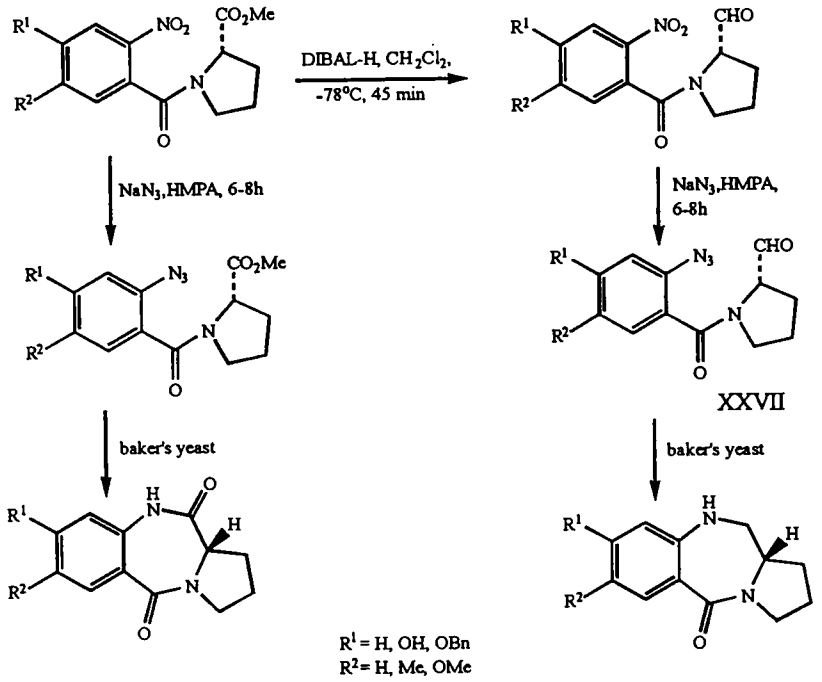
Scheme 17



Scheme 18



Scheme 19



of the reactive nature of the imine and hence has posed problems in the isolation and synthesis. The other problems include the potential loss of the stereochemistry at C(11a) due to racemization, the loss of double bonds in either pyrrolo C ring or a C(2) side chain under reductive conditions. Some of the synthetic routes reviewed above have overcome these problems to a great extent and could be widely applied for a number of natural and synthetic PBD imines. The synthesis developed in this laboratory particularly *via* the oxidation of secondary amine as well the enzymatic approaches appear to be very significant. These methods have taken care of most of the serious problems encountered during the synthesis of PBD imine antibiotics.

Some of the innovative and more recently introduced approaches for the synthesis of the PBD ring also appear to be promising. Among them the aza-Wittig approach has demonstrated its scope and general applicability.

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