Solid-Phase Synthesis of a Library of Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones with Potential Antitubercular Activity

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Received October 31, 2005

A versatile combinatorial approach was developed and utilized for the rapid synthesis of pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (PBD-5,11-dione) libraries **10**, **15**, and **19** containing 210 compounds with varied substitutions in A, B, and C rings. The key aspect of the synthetic strategy includes Staudinger, intermolecular aza-Wittig reaction followed by imine reduction and base-mediated cyclative cleavage results in the formation of final resin-free compounds. This strategy provides a highly efficient and practical protocol for the parallel synthesis of PBD-5,11-diones on solid support. The modifications in the C-ring of the PBD scaffold produced three types of sublibraries. Reactions were monitored by FT-IR spectroscopy on the resin beads. Further, from a generated library of 210 compounds, 142 compounds have been selected and evaluated for in vitro activity against *Mycobacterium tuberculosis*, and some of these compounds have exhibited promising activity.

Introduction

Recently, solid-phase chemistry has become an attractive synthetic tool for the rapid generation of combinatorial libraries of small organic molecules,[1] particularly in the research of drug discovery.[2] Presently, the most important challenge in combinatorial chemistry is to develop general methods that provide access to libraries of biologically relevant and structurally diverse molecules. Combinatorial libraries based on heterocyclic motifs have become a popular objective in library design, because a large number of drugs may contain one or more heterocyclic rings. However, in comparison with traditional solution-phase chemistry, the synthetic strategy reported on solid support is still inadequate. As a result, currently, there is a major effort with the objective of increasing the variety of organic transformations that could be performed on solid phase.

The benzodiazepine moiety has received much attention in the synthetic community, mainly because of its representation as a member of the family of "privileged scaffolds".[3] In fact, the first heterocyclic templates prepared on a solid support have been of 1,4-benzodiazepines,[4] followed by a large number of reports on the synthesis of a similar skeleton. Pyrrolo[2,1-*c*][1,4]benozodiazepine-5,11-dione is merely the proline fused 1,4-benzodiazepine-2,5-dione scaffold (Figure 1). However, not much efforts have been made for the development of solid-phase synthesis of such pyrrolo[2,1-*c*][1,4]benozodiazepine-5,11-diones. This tricyclic ring system has been used for a number of pharmaceutical applications, such as a template for the design and assembly of peptidomimetic agents,[5] anxiolytic drugs,[6] anticonvulsants,[7] and herbicides.[8]

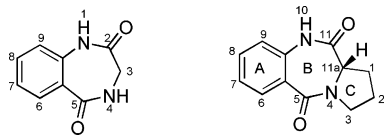

Figure 1. Benzodiazepine and pyrrolo[2,1-*c*][1,4]benzodiazepine ring system.

In the past few years, we have been involved in the development of solid-phase synthetic methodologies for the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system.[9] In the present investigation, a solid-phase approach for the desired N(10)-substituted pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione analogues that involves the generation of iminophosphorane as the key intermediate has been developed. The finding by Staudinger[10] about the iminophosphorane in the beginning of the century has become an important tool for the construction of nitrogen-containing heterocycles and their usefulness as reagents as well as intermediates in organic synthesis.[11] Recently, application of iminophosphoranes in solid-phase synthesis[12] has emerged as a result of their high potential for the synthesis of nitrogen-containing heterocycles under mild and neutral conditions. We herein report an efficient solid-phase synthetic procedure for a pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione ring system involving the aza-Wittig strategy and base-mediated cyclative cleavage,[13] allowing diversity in the A, B, and C rings. Moreover C-ring modifications provide three types of sublibraries.

Results and Discussion

A large number of methodologies have been developed for the solution-phase synthesis of the tricyclic PBD-5,11-

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10.1021/cc0501458 CCC: $37.00
Published on Web 12/09/2006

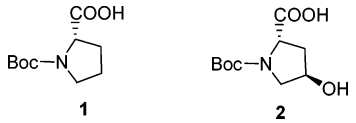


Figure 2. Set of prolines **2**{*1*−*2*} for the library.

diones employing different type of approaches ranging from deprotective to reductive cyclizations.[14] However, there are very few reports on the solid-phase synthesis of these biologically important compounds.[9,15] In the literature, not much attention has been given for PBD-5,11-diones with diversity at the N(10)-position. We recently reported a synthetic strategy for PBD-5,11-diones[9a] using Wang resin through amide formation and a reductive cyclization process with diversity at the N(10)-position. The diversity at the N(10)-position has been introduced with alkyl halides using sodium hydride in DMF. Employing this strategy, alkylation of the amide bond nitrogen is a difficult task; therefore, this can be circumvented through the aza-Wittig strategy using triphenylphosphine (Staudinger) and different aldehydes, followed by base-mediated cyclative cleavage that led to the development of the present methodology.

Merrifield resin (**1**) was coupled to the Boc-protected L-proline (**2**{*1*}, Figure 2) in the presence of potassium fluoride to give the corresponding resin-bound proline acid (**3**{*1*}). This transformation was ascertained by the data obtained from FT-IR analysis [1745 ($COOCH_3$) and 1659 (NBoc) cm^{-1}]. Similarly, **1** was coupled to Boc-protected 4-hydroxy-L-proline (**2**{*2*}) to give (**3**{*2*}), which showed additional stretching at 3425 cm^{-1} in the FT-IR. The Boc group of (**3**{*1*}) was deprotected upon treatment with trifluoroacetic acid (TFA/CH_2Cl_2, 3:7), followed by its washing with triethylamine (1% Et_3N/THF) to give the resin-bound proline acid, which exhibits the amine and carbonyl functional groups in the FT-IR (3428 and 1731 cm^{-1}). The deprotection of the Boc group from the resin-bound 4-hydroxy-L-proline acid (**3**{*2*}) was carried out in a similar way. The Boc-deprotected resin-bound proline acid (**4**) was coupled with different 2-azidobenzoic acids (**5**{*1*−*11*}, Figure 3), employing DCC and DMAP to afford the desired resins (**6**), but at this stage, the filtration became problematic. To obviate this problem, water-soluble derivatives, such as ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and HOBt, were employed as the alternative reagents for this coupling step (Scheme 1). Moreover, the water-soluble urea that was produced was easily removed by filtration. A strong azido stretching vibration in the range between 2100 and 2200 cm^{-1}, as indicated by IR spectra, confirmed the formation of resin-bound 2-azidobenzoyl proline acids **6**, as illustrated in Scheme 1.

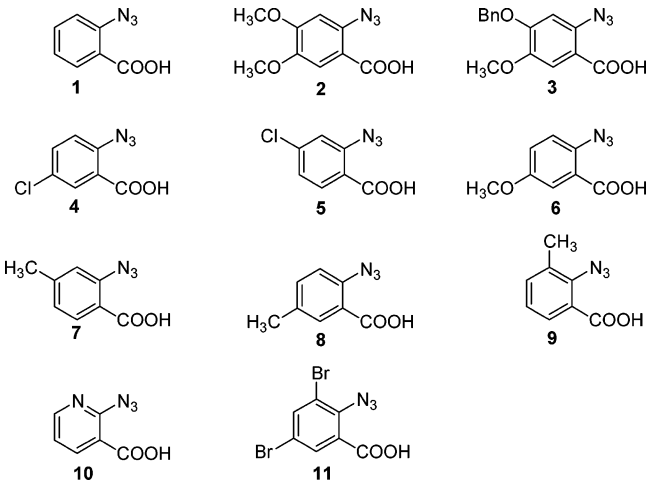


Figure 3. Set of 2-azidobenzoic acids **5**{*1*−*11*} for the library.

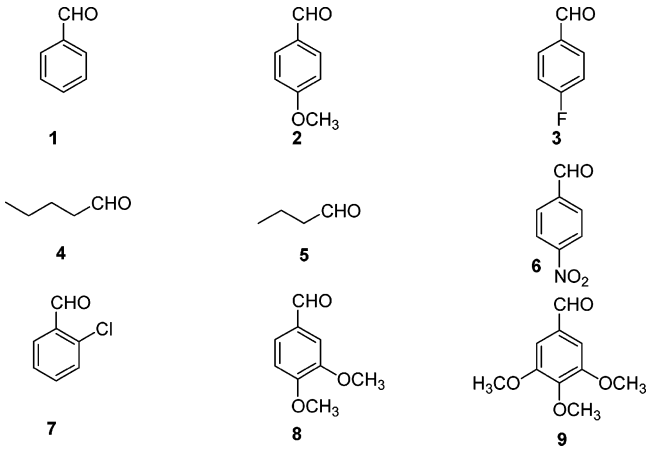
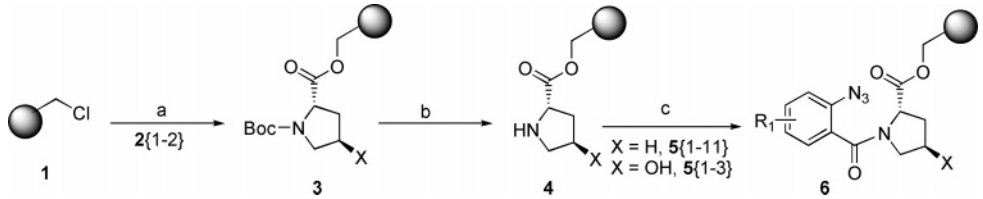


Figure 4. Set of aldehydes **7**{*1*−*9*} for the library.

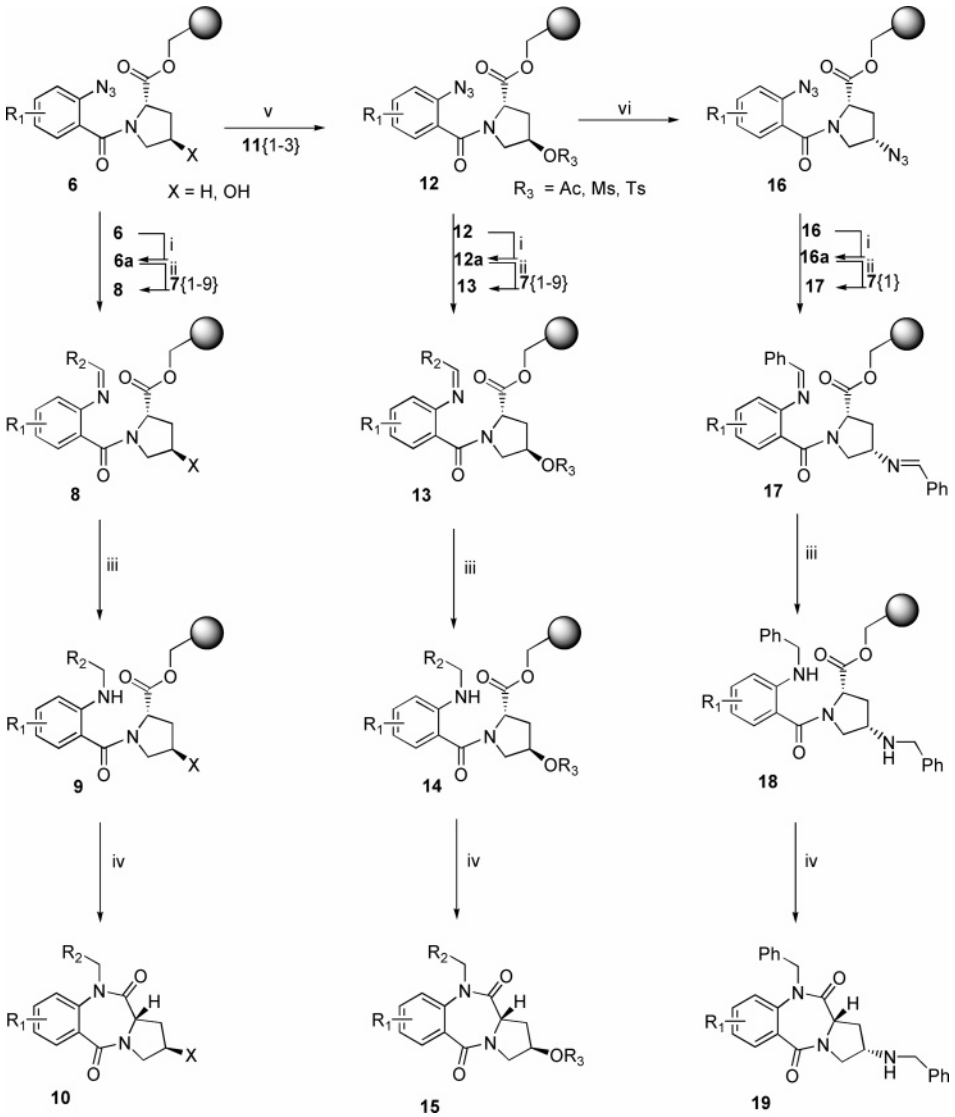
The obtained compounds **6** were then treated with a 5-fold excess of triphenylphosphine in dry toluene at room temperature to produce the iminophosphorane intermediates bound to the solid support and condensed with different aldehydes (**7**{*1*−*9*}), as shown in Figure 4, to yield the corresponding imines (**8**). This step was repeated in CH_2Cl_2 under reflux conditions to ensure that the entire iminophosphorane intermediate was converted to the imino compound. These imines (**8**) were later reduced with $NaCNBH_3$ in 1% AcOH−DMA to give the amino-substituted products (**9**), and this step was further repeated for complete reduction. Resin-bound amino compounds (**9**) were cyclized by treating the resin with lithiated 5-phenyl-2-oxazolidinone to afford the desired PBD-5,11-diones **10**, as illustrated in Scheme 2. It is interesting to note that lithiated oxazolidinone was earlier used in the solid-phase synthesis to carry out amide alkylation reactions.[16] However, in the present methodology, this reagent has been employed for the first time for the cyclative

Scheme 1. Synthesis of Different Resin-Bound *N*-(2-azidobenzoyl)pyrrolidine-2-carboxylic Acids[a]



[a] Reagents and conditions: (a) KF, DMF, 50 °C, 24 h; (b) 30% TFA/CH_2Cl_2, 45 min; (c) 2-azidobenzoic acids 5, EDCI, HOBt, DMF, rt, 15−24 h.

Scheme 2. Synthesis of PBD-5,11-dione Libraries **10**, **15**, and **19**[a]



[a] Reagents and conditions: (i) TPP, toluene, 3 h, rt; (ii) aldehydes 7, CH_2Cl_2, 4 h; (iii) $NaCNBH_3$, 1% AcOH−DMA, 4 h, rt; (iv) lithiated oxazolidinone, THF, 0 °C, 2 h; (v) chlorides **11**, Et_3N, DMAP, CH_2Cl_2, 0 °C, overnight; (vi) NaN_3, DMF, 50 °C, overnight.

Table 1. Purity[a] and Yield[b] Data of Cleaved Final Compounds **10**{*1,2,1*−*9*} with Varied Reagents

	purity/yield (%)			
compd	oxazolidinone	K_2CO_3	NaOMe	KO*t*Bu
10{*1,2,1*}	50/70	95/55	91/45	90/44
10{*1,2,2*}	49/62	95/43	84/40	89/38
10{*1,2,3*}	48/72	93/51	89/45	91/46
10{*1,2,4*}	49/65	95/41	84/36	89/40
10{*1,2,5*}	48/65	97/35	80/36	89/36
10{*1,2,6*}	46/78	93/52	81/45	85/49
10{*1,2,7*}	46/71	90/46	75/39	86/42
10{*1,2,8*}	42/66	81/40	69/30	81/33
10{*1,2,9*}	40/60	71/37	65/29	73/31

[a] Purity was indicated by HPLC[18] of the crude reaction mixture. [b] Overall yields after column purification from the Merrifield resin (loading capacity of the Merrifield resin (**1**) is 2.0 mmol/g).

cleavage. In this study, apart from oxazolidinone, other reagents such as K_2CO_3, NaOMe, and KO*t*Bu, have also been employed for the cyclative cleavage step, and the results obtained for this single study are illustrated in Table 1. Furthermore, it was observed that employing oxazolidinone gave better yields (overall yields from the Merrifield resin) in comparison to the other bases. This reagent provided the required mild and efficient reaction conditions in comparison to the other inorganic reagents. These inorganic reagents provided the products in moderate yields and excellent purities; however, the library generation with diversity in the C-ring of PBD tricyclic ring system is problematic with these inorganic reagents. Nevertheless, removal of 5-phenyl-2-oxazolidinone was a difficult task, and attempts to remove it from the crude products through its salt formation or recrystallization were not successful. Interestingly, the purity of crude product **10**{*1,1,1*} increased from 39 to 80% by shaking it with dilute HCl for 1 h. However, there was a drastic fall in the yield of the compound compared to the yield obtained through silica column chromatography. In addition, the recovered 5-phenyl-2-oxazolidinone from the column was reused once again for the cleavage process afterconverting to its lithiated salt. The lithium salt of 5-phenyl-2-oxazolidinone was prepared by the treatment of *n*-BuLi of 5-phenyl-2-oxazolidinone, which in turn was prepared by the reaction of phenyl glycinol with diethyl carbonate, as reported in the literature.[17] Overall, this

Table 2. Diversity of PBD-5,11-dione Libraries **10**, **15**, and **19**

acid (**5**)	aldehyde (**7**)	C(2)-position	library	library type
{*1*−*11*}	{*1*−*9*}	H	11 × 9 = 99	**10**
{*1*−*3*}	{*1*−*9*}	OH	3 × 9 = 27	**10**
{*1*−*3*}	{*1*−*9*}	OAc	3 × 9 = 27	**15**
{*1*−*3*}	{*1*−*9*}	OMs	3 × 9 = 27	**15**
{*1*−*3*}	{*1*−*9*}	OTs	3 × 9 = 27	**15**
{*1*−*3*}	{*1*}	NHBn	3 × 1 = 3	**19**
			total = 210	

procedure was performed in a stepwise manner involving the addition of triphenylphosphine; aldehyde; reducing agent; and, finally, followed by cleavage without the observation of any sideproducts. To demonstrate the versatility of this procedure, 2 different types of prolines, 11 different types of azidobenzoic acids, and 9 different types of aldehydes (Figure 2, 3, and 4) were employed toward the synthesis of PBD-5,11-diones, thus generating a 126-compound library (Scheme 2, Table 2).

Additionally, the hydroxyl groups of resin-bound *N*-(2-azidobenzoyl)-4-hydroxypyrrolidine-2-carboxylic acids **6**{*2,1*−*3*} were activated to obtain different types of esters **12** by treatment with the respective chlorides **11**{*1*−*3*} (Figure 5) in the presence of triethylamine, as shown by the disappearance of the hydroxyl stretching in the FT-IR. It was observed that the acetylation and tosylation of this hydroxyl group took a longer time, and in some cases, the conversions were partial. This problem was overcome by the addition of a catalytic amount of DMAP in this esterification process. These compounds (**12**) were treated with a 5-fold excess of triphenylphosphine in dry toluene at room temperature to produce the iminophosphoranes, and this, upon condensation with different aldehydes (**7**{*1*−*9*}), gave the corresponding imines (**13**), and, as mentioned earlier for the preparation of imines (**8**), the step was repeated again. The imines were later reduced with $NaCNBH_3$ in 1% AcOH−DMA to give the amino resins (**14**). Finally the PBD-5,11-diones (**15**) with diversity in the C-ring were obtained by cyclative cleavage of amino resins (**14**) employing lithiated 5-phenyl-2-oxazolidinone. Three types of carbonyl and sulfonyl chlorides (Figure 5) were selected and used for the preparation of the corresponding ester derivatives of the hydroxyproline moiety to generate an 81-compound library by employing the above synthetic strategy (Scheme 2, Table 2).

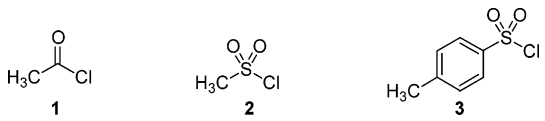


Figure 5. Set of acetyl, mesyl, and tosyl chlorides **11**{*1*−*3*} for the library.

Additionally, the mesyl group of *N*-(2-azidobenzoyl)-4-methylsulfonyloxypyrrolidine-2-carboxylic acid resins **12**{*2,1*−*3,2*} was treated with NaN_3 to give the bis-azido resins (**16**), as indicated by the strong azide stretching vibrations in the range between 2100 and 2190 cm^{-1} in the FT-IR. In this transformation, disappearance of antisymmetric stretching vibrations of the sulfonyl group at 1373 cm^{-1} and theappearance of an azide stretching at 2100 cm^{-1} were observed in the IR spectra. These compounds were treated with a 10-fold excess of triphenylphosphine in dry toluene at room temperature to produce the iminophosphoranes, and these,

Table 3. Antimycobacterial Activity of PBD-5,11-dione Library

	MIC (μg/mL)				
		M. tb.[a] clinical isolates			
compd	*M. tb.*[a] H37Rv ATCC 27294	sensitive	resistant	*M. a.*[a] ATCC 49601	*M. i.*[a] ATCC 13950
10{*1,1,9*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,2,8*}	8.0	8.0−16.0	8.0−16.0	16.0	8.0
10{*1,3,3*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,3,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,4,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,4,7*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,6,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,6,6*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,8,2*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,9,7*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*1,11,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*2,1,1*}	>16.0	>16.0	>16.0	>16.0	>16.0
10{*2,1,9*}	8.0	8.0−16.0	8.0−16.0	>16.0	>16.0
10{*2,2,2*}	8.0	8.0−16.0	8.0−16.0	>16.0	>16.0
10{*2,3,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
15{*2,3,1,3*}	4.0	4.0−8.0	4.0−8.0	>16.0	>16.0
15{*2,1,2,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
15{*2,1,2,9*}	4.0	4.0−8.0	4.0−8.0	>16.0	>16.0
15{*2,2,2,9*}	1.0	1.0−2.0	1.0−2.0	8.0	8.0
15{*2,3,2,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
15{*2,3,2,9*}	2.0	2.0−4.0	2.0−4.0	16.0	8.0
15{*2,1,3,4*}	>16.0	>16.0	>16.0	>16.0	>16.0
15{*2,2,3,1*}	>16.0	>16.0	>16.0	>16.0	>16.0
15{*2,3,3,2*}	4.0	4.0−8.0	4.0−8.0	>16.0	>16.0
15{*2,3,3,9*}	4.0	4.0−8.0	4.0−8.0	>16.0	>16.0
isoniazid	0.25	0.125−0.25	8.0->16.0	>16.0	8.0

[a] *M. tb.*, *Mycobacterium tuberculosis*; *M. a.*, *Mycobacterium avium*; *M. i.*, *Mycobacterium intracellulare*.

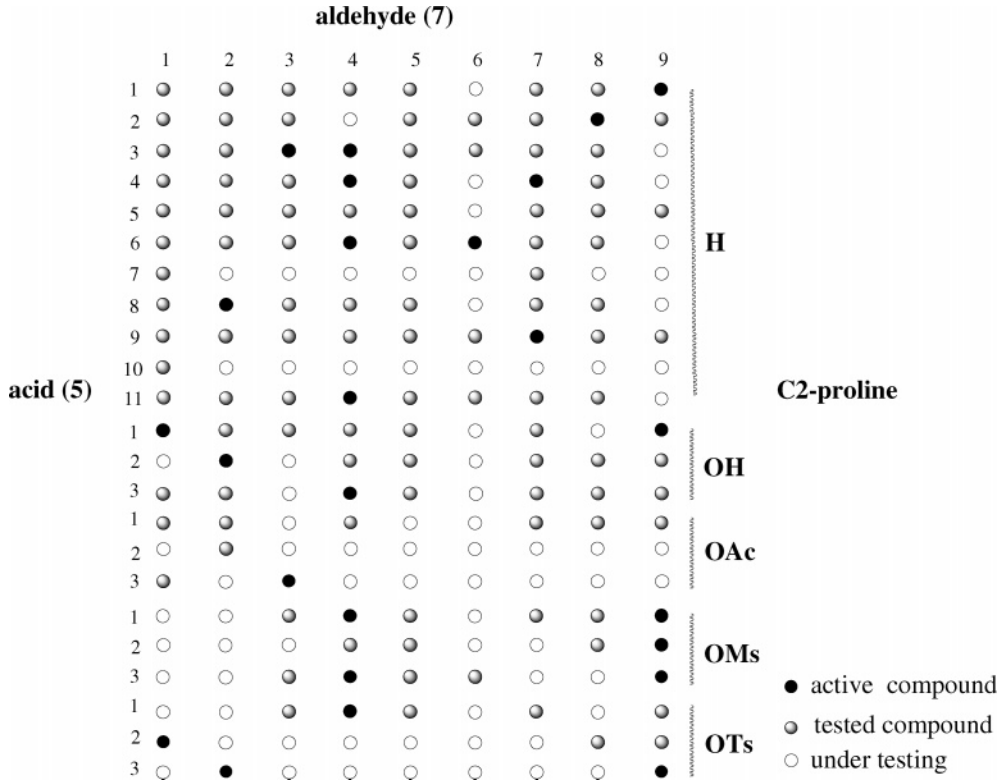


Figure 6. Antimycobacterium activity data for the PBD-5,11-diones of **10**, **15**, and **19**.

upon condensation with benzaldehyde **7**{*1*}, gave the corresponding imine resins (**17**), and, as mentioned earlier for imines (**8**), the step was repeated again. These imine resins were later reduced with $NaCNBH_3$ in 1% AcOH−DMA to give the amino resins (**18**), which, upon cyclative cleavage with lithiated 5-phenyl-2-oxazolidinone, gave the desired C-ring 2-amino substituted PBD-5,11-diones (**19**). By employing this process, three types of compounds with 2-amino substitution in the proline moiety of the PBD-5,11-diones were synthesized (Scheme 2, Table 2).

Library Design and Synthesis. The building blocks for the library synthesis (prolines, 2-azidobenzoic acids, aldehydes, carbonyl and sulfonyl chlorides) were selected and used for the generation of a 210-compound library with satisfactory yields of final products **10**, **15**, and **19**, consisting of 3 sublibraries (126 + 81 + 3) as shown in Table 2. The coupling of azidobenzoic acids to the polymer-bound proline moieties and esterification of the hydroxyl group were carried out manually in batches. The subsequent steps involving intermediates, such as iminophosphoranes, imines, amines, and cyclative cleavage reactions, were performed in a semiautomated fashion using the MSW 500 synthesizer (Chemspeed). All final compounds were purified by column chromatography and characterized by proton NMR and mass spectroscopy. The building blocks for the library construction, such as Boc protected proline acids[19] (**2**{*1*−*2*}) and 2-azidobenzoic acids[20] (**5**{*1*−*11*}), were obtained from the available literature procedures; however, aldehydes (**7**{*1*−*9*}) and acid chlorides (**11**{*1*−*3*}) were obtained from commercial sources.

Antimycobacterium Activity. Tuberculosis is becoming a major threat to human health around the world, claiming more than 2 million lives annually.[21] This steadily increasing rate of tuberculosis is attributed to the prevalence of multiple-drug resistance in pathogenic microorganisms. Due to this, the World Health Organization (WHO) has declared a public health emergency and has created a sense of urgency and interest in the discovery and development of new antibacterial agents.[22] Since the existing drugs attack very few targets, the development of new molecules that can act on newer targets is an immediate requirement. Accordingly, the resistant strains could be treated, and the treatment course could be shortened, as well.[23] In view of the ongoing program for the design and synthesis of an antitubercular compounds library, particularly based on heterocyclic scaffolds,[24] such as PBD-5,11-diones, it has been considered of interest to evaluate their antitubercular activity. From a generated library of 210 compounds, 142 compounds have been selected and evaluated for in vitro activity against *Mycobacterium tuberculosis* H37Rv at 50 μg/mL concentration by using an agar diffusion assay procedure. Among those 142 compounds, 25 compounds have been shown to completely inhibit the growth of *M. tuberculosis* (H_{37}Rv ATCC 27294) at 50 μg/mL concentrations (Figure 6).

These 25 compounds were later evaluated for antimycobacterial activity against three different mycobacterium (*M. tuberculosis* ATCC27294, *Mycobacterium avium* ATCC 49601, and *Mycobacterium intracellulare* ATCC 13950) species at a concentration of 25 and 12.5 μg by diffusion assay. Among these, nine compounds demonstrated good to mild inhibition of the *Mycobacterium* cultures. These nine molecules were then tested by the agar dilution assay[25] to determine the minimum inhibitory concentration against a panel of sensitive and resistant clinical isolates. Compound **15**{*2*,*2*,*2*,*9*} was the most active compound, with an MIC value of 1.0 μg/mL against ATCC 27294, and it showed a

MIC value of 1.0−2.0 μg/mL for a drug-sensitive and -resistant strain of *M. tuberculosis* with respect to isoniazid.

Conclusion

In summary, a versatile approach for the solid-phase synthesis of PBD-5,11-diones has been developed. The synthetic strategy includes the preparation of a large array of resin-bound 2-azidobenzoyl proline acids, the generation of iminophosphoranes from these corresponding proline acids, and the solid-phase aza-Wittig reaction of the iminophosphorane intermediates to imino derivatives, followed by their reduction to the corresponding amino compounds, which undergo intramolecular cyclization by the cleavage of the resin. The diversity at the N(10)-position can be created in a facile manner by employing this methodology. Moreover, the N-alkylation and esterification at the C(2)-position has been achieved by employing this synthetic sequence. The reaction conditions used in this protocol are mild, and compounds are obtained in good yields. This method can be potentially used for the generation of large number of pyrrolobenzodiazepine-based compounds using an automated synthesizer.

From the generated library of 210 compounds, 142 compounds have been screened in vitro for activity against *M. tuberculosis*. Some of the C2-substituted compounds showed interesting in vitro activity against *M. tuberculosis*. The possible improvement of antitubercular activity of this basic PBD-5,11-dione structure through suitable modulation of the C2-substituents as well as additional functionalization suggests further exploration of this class of compounds. In view of this, further efforts for the generation of a larger library of 2-alkylamino- and 2-aryloxy-substituted PBD-5,-11-diones are underway in our laboratory. The complete screening of this library against *M. tuberculosis* and related microbes is in progress, and results from the screening will be reported elsewhere.

Experimental Section

Merrifield resin (2 mmol/g, 60−120 mesh, 1% DVB) was obtained from Advanced Chemtech Ltd. All building blocks (except 2-azidobenzoic acids), reagents, and solvents were purchased from Aldrich, Lancaster, and other standard commercial sources and were procured as such without further purification. Anhydrous THF, CH_2Cl_2, toluene, and DMF were prepared by distillation under nitrogen atmosphere over sodium/benzophenone, CaH_2, sodium/P_2O_5, and CaH_2/molecular sieves, respectively, and were used for reactions. Sodium azide was handled with care for the preparation of various 2-azidobenzoic acids and C2-alkylamino diversity by wearing safety glasses, face mask, and gloves, and reactions were performed in a fume hood. IR spectra were recorded on a Nicoler FT-IR spectrometer. All the polymer-bound intermediates were monitored by FT-IR. The final products were purified by column chromatography using Acme silica gel 60−120 mesh for compounds **10**{*1,1*−*11,1*−*9*} and 100−200 mesh for the rest of the compounds. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200, Bruker WH Avance 300, and Varian Unity 400 MHz spectrometers using tetramethyl silane as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethyl silane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in Hertz (Hz). High-resolution mass spectra were recorded on a QSTAR XL MS/MS system (Biosciences, USA) in the ESI mode. Mass spectra were recorded on a Quattro-LC, Micromass (Manchester UK) (ESI); for molecular weight above 400, on an LSIMS-VG-Autospec (Micromass, Manchester UK) (FAB), and below 400, on aVG 70-70 H (EI). HPLC data[22] of final crude samples of **10**{*1,2,1*−*6*} were analyzed on a Shimadzu LC-10AT VP system controller instrument. Other final crude samples were analyzed on a Shimadzu LC-10AT VP system controller instrument (auto sampler). Optical rotations was recorded on a SEPA-300 (Horiba) high sensitivity polarimeter fixed with a sodium lamp of wavelength 589 nm. The yields of the purified products were determined on the basis of the loading of the polymeric support starting from the Merrifield resin. The following abbreviations were used: TPP, triphenylphosphine; Ac, acetyl; Ms, mesyl; Ts, tosyl; AcOH, acetic acid; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; and DMA, *N*,*N*-dimethylacetamide.

Resin-Bound (*S*)-*N*-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic Acid 3{*1*}. To a stirred suspension of Boc-protected proline acid (**2**{*1*}, 430 mg, 2.0 mmol) in DMF (10 mL) was added anhydrous KF (116 mg, 2.0 mmol) and Merrifield resin (**1**) (500 mg, 1.0 mmol). The mixture was maintained at 50 °C for 24 h, and the resin was filtered. The resin was washed thoroughly with DMF (3 × 15 mL); DMF/water (3 × 15 mL); DMF (3 × 15 mL); MeOH (3 × 15 mL); and finally, with CH_2Cl_2 (3 × 15 mL) and dried. FT-IR: cm^{-1} 2924.4, 1745.9, 1659.2, 1601.7, 1493.96, 1279.8, 1109.2, 1023.7, 752.7, 693.3, 542.4, 415.5.

Resin-Bound (2*S*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic Acid 3{*2*}. To a stirred suspension of Boc-protected hydroxy-L-proline acid (**2**{*2*}, 462 mg, 2.0 mmol) in DMF (10 mL) was added anhydrous KF (116 mg, 2.0 mmol) and Merrifield resin (**1**) (500 mg, 1.0 mmol). The mixture was maintained at 50 °C for 24 h and the resin was filtered. The resin was washed thoroughly with DMF (3 × 15 mL); DMF/water (3 × 15 mL); DMF (3 × 15 mL); MeOH (3 × 15 mL); and finally, with CH_2Cl_2 (3 × 15 mL) and dried. FT-IR: cm^{-1} 3343.5, 2903.2, 1748.4, 1693.6, 1493.3, 759.3.

Resin-Bound (*S*)-Pyrrolidine-2-carboxylic Acid 4{*1*}. Deprotection of the Boc group of proline acid resin (672 mg) occurs on treatment with TFA/CH_2Cl_2 (3:7) (10 mL) for 45 min. The resin (**4**{*1*}) was filtered and washed with CH_2Cl_2 (3 × 15 mL); 1% Et_3N in THF (3 × 15 mL); and finally, with CH_2Cl_2 (3 × 15 mL) and dried. FT-IR: cm^{-1} 3428.7, 2923.4, 2856.2, 1731.7, 1597.2, 1449.1, 1369.5, 1275.4, 1139.97, 1022.5, 752.2, 696.9, 540.7.

Resin-Bound (2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic Acid 4{*2*}. Deprotection of the Boc group of proline acid resin (690 mg) occurs on treatment with TFA/CH_2Cl_2 (3:7) (10 mL) for 45 min. The resin (**4**{*2*}) was filtered and washed with CH_2Cl_2 (3 × 15 mL); 1% Et_3N in THF (3 × 15 mL); and finally, with CH_2Cl_2 (3 × 15 mL) and dried. FT-IR:

cm^{-1} 3422.8, 3025.9, 2923.3, 1734.6, 1599.3, 1494.0, 1446.3, 1373.3, 1264.9, 1164.9, 1076.7, 1022.6, 754.7, 697.3, 540.0.

General Procedure for the Preparation of Resin-Bound *N*-(2-Azidobenzoyl)pyrrolidine-2-carboxylic Acids 6. To a suspension of 2-azido benzoic acid substrates (**5**{*1*−*11*}, 4.0 equiv) in DMF (10−15 mL), EDCI (4.0 equiv), HOBt (4.0 equiv), and resin were added, and the mixture was stirred for 15−24 h at room temperature. The resin was filtered and washed successively with DMF (3 × 15 mL); DMF/water (3 × 15 mL); MeOH (3 × 15 mL); MeOH/water (3 × 15 mL); MeOH (3 × 15 mL); CH_2Cl_2 (3 × 15 mL); and finally, with ether (3 × 15 mL) and dried.

General Procedure for the Preparation of Resins 8 and 9. The resin-bound *N*-(2-azidobenzoyl)pyrrolidine-2-carboxylic acid (**6**) was partitioned into nine equal parts, and these were transferred into nine vessels of the parallel synthesizer for the generation of iminophosphoranes. The imnophosphorane generation occurs in the following manner: TPP (5.0 equiv) was added for every vessel containing a suspension of *N*-(2-azidobenzoyl)pyrrolidine-2-carboxylic acid resin (**6**) (0.11 mmol) in dry toluene (3 mL), and the mixture was allowed to shake for 3−5 h at room temperature to give the iminophosphorane resins. These were filtered, rinsed with toluene and CH_2Cl_2 under dry conditions, and then dried in vacuo. To the iminophosphorane resins in CH_2Cl_2 (3 mL), nine aldehydes (**7**{*1*−*9*}, 5.0 equiv) were added, and the mixture was allowed to shake at room temperature for 4−6 h. The resin was then filtered and washed with CH_2Cl_2 (3 × 10 mL). This step was repeated in CH_2Cl_2 (3 mL) under reflux conditions for 4−6 h in nitrogen atmosphere to get the imino resins **8**. The reduction of these imino resins **8** with $NaCNBH_3$ (10.0 equiv) in 1% AcOH−DMA (3 mL) at room temperature for 4−8 h afforded the amino resins **9**. These were filtered and washed with 1% AcOH−DMA (3 × 10 mL), DMA (3 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL) and dried. The above step was repeated once again for completion of the reduction process.

General Procedures for the Cleavage of PBD-5,11-diones 10. Cleavage with Oxazolidinone. To the suspension of amino resins (**9**) in dry THF at 0 °C, the generated lithiated 5-phenyl-2-oxazolidinone (1.1 equiv, 1 M) was added dropwise over a period of 10 min, and the mixture was allowed to reach ambient temperature. These mixtures were subjected to shaking at room temperature for 2−3 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution. The resin mixture was filtered and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrates were evaporated to afford the crude products, which were further purified by column chromatography to get the final products **10**.

Cleavage with K_2CO_3. To the suspension of amino resins (**9**) in THF/MeOH/H_2O (2:2:1) (5 mL), K_2CO_3 (5 equiv) was added, and the mixture was allowed to shake at room temperature for 6 h. The mixture was filtered and washed with CH_2CL_2. The filtrate was washed with water (2 × 10 mL) and brine (10 mL), then dried (Na_2SO_4) and evaporated in vacuo to leave the final PBD-5,11-diones (**10**).

Cleavage with NaOMe. A suspension of amino resins (**9**) in MeOH/THF (1:1) (5 mL) was treated with sodium methoxide (2 equiv) and allowed to shake for 4−5 h. The mixture was filtered and washed with CH_2Cl_2. The filtrate was washed with 5% HCl (10 mL), water (2 × 10 mL), and brine (10 mL), then dried (Na_2SO_4) and evaporated in vacuo to give the final PBD-5,11-diones (**10**).

Cleavage with KO*t*Bu. A suspension of amino resins (**9**) in toluene (5 mL) and KO*t*Bu (2 equiv) was added, and the mixture was heated under reflux for 2 h. The mixture was cooled, acidified with 5% HCl, and filtered thoroughly with CH_2Cl_2. The filtrate was washed with 5% HCl (10 mL), water (2 × 10 mL), and brine (10 mL), then dried (Na_2SO_4) and evaporated in vacuo to afford the final PBD-5,11-diones.

Resin-Bound (*S*)-*N*-(2-iminophosphoranebenzoyl)pyrrolidine-2-carboxylic Acid 6a{*1,1*}. To the resin-bound (*S*)-*N*-(2-azidobenzoyl)pyrrolidine-2-carboxylic acid (**6**{*1,1*}, 80 mg) in toluene (3 mL), TPP (144 mg, 0.55 mmol) was added, and the mixture was allowed to shake at room temperature for 3 h. The generated iminophosphorane resin was filtered, rinsed with toluene (3 × 10 mL) and CH_2Cl_2 (3 × 10 mL) under dry conditions, and then dried in vacuo. FT-IR: cm^{-1} 3654.4, 3305.8, 2882.4, 1744.5, 1661.2, 1621.8, 1547.7, 1230.9, 1121.4, 985.9, 686.4, 527.0.

Resin-Bound (*2S*)-1-(2-[Phenylmethylidene]aminobenzoyl)pyrrolidine-2-carboxylic Acid 8{*1,1,1*}. To iminophosphorane resin **6a**{*1,1*} in CH_2Cl_2 (3 mL), benzaldehyde (**7**{*1*}, 58 mg, 0.55 mmol) was added, and the mixture was allowed to shake at room temperature for 4 h. The resin was then filtered and washed with CH_2Cl_2 (3 × 10 mL) and dried in vacuo. FT-IR: cm^{-1} 2921.8, 2737.1, 1727.8, 1615.4, 1505.3, 1477.7, 1261.0, 1178.2, 1148.3, 1015.1, 832.2, 772.9, 693.5, 606.6, 530.7.

Resin-Bound (*2S*)-1-[2-(Benzylamino)benzoyl]pyrrolidine-2-carboxylic Acid 9{*1,1,1*}. The reduction of the generated imino resin **8**{*1,1,1*} with $NaCNBH_3$ (69 mg, 1.1 mmol) in 1% AcOH−DMA (3 mL) at room temperature for 4 h affords the amino resin **9**{*1,1,1*}. FT-IR: cm^{-1} 3436.9, 3024.9, 2922.6, 1725.3, 1615.0, 1450.4, 1299.9, 1155.2, 1086.5, 1026.3, 755.6, 694.6, 538.7.

(11a*S*)-10-Benzyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{*1,1,1*}. The final product was cleaved from the resin employing lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,1,1*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.87 (dd, J = 2.37 Hz, J = 7.89 Hz, 1H), 7.08−7.43 (m, 8H), 5.18 (d, J = 15.78 Hz, 1H), 4.95 (d, J = 15.78 Hz, 1H), 4.10−4.20 (m, 1H), 3.75−3.90 (m, 1H), 3.47−3.65 (m, 1H), 2.65−2.85 (m, 1H), 1.90−2.30 (m, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz) 169.4, 165.0, 139.8, 136.9, 131.9, 130.6, 130.2, 128.7, 127.2, 126.7, 125.8, 122.3, 57.2, 52.3, 46.6, 26.8, 23.8. FT-IR: cm^{-1} 2981.7, 1664.8, 1633.9, 1598.9, 1459.2, 1247.9, 1209.2, 761.2. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$ 307.1446, found 307.1452. Purity/cleavage with K_2CO_3 > 97%; t_R = 3.34 min. Purity/cleavage with oxazolidinone > 49%. t_R = 3.89 min. $[\alpha]_D^{27}$ −43.00 (*c* 0.5, $CHCl_3$).

(11a*S*)-7,8-Dimethoxy-10-(4-methoxybenzyl)-1,2,3,10,-11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{*1,2,2*}. Prepared as described earlier for the

preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,2*}, 85 mg), TPP (144 mg, 0.55 mmol), 4-methoxybenzaldehyde (**7**{*2*}, 74 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,2,2*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (s, 1H), 7.10 (d, J = 8.31 Hz, 2H), 6.80 (d, J = 8.31 Hz, 2H), 6.59 (s, 1H), 5.16 (d, J = 15.10 Hz, 1H), 4.70 (d, J = 15.10 Hz, 1H), 4.11−4.14 (m, 1H), 3.90 (s, 3H), 3.73−3.80 (m, 4H), 3.66 (s, 3H), 3.50−3.60 (m, 1H), 2.74−2.80 (m, 1H), 1.94−2.20 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.5, 165.0, 158.9, 151.5, 146.7, 133.9, 129.6, 128.6, 123.0, 114.1, 111.4, 105.6, 57.5, 56.0, 55.9, 55.2, 52.2, 46.6, 26.7, 23.8. FT-IR: cm^{-1} 1674.0, 1636.9, 1514.3, 1455.7, 1435.3, 1249.5, 755.1. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_5$ $[M + H]^+$ 397.1763, found 397.1770. Purity/cleavage with K_2CO_3 > 92%. t_R = 11.53 min. Purity/cleavage with oxazolidinone > 47%. t_R = 6.37 min. $[\alpha]_D^{27}$ +7.00 (*c* 1, $CHCl_3$).

(11a*S*)-8-Benzyloxy-7-methoxy-10-(4-flurobenzyl)-1,2,3,-10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,3,3***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,3*}, 92 mg), TPP (144 mg, 0.55 mmol), 4-fluorobenzaldehyde (**7**{*3*}, 68 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,3,3*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27−7.31 (m, 4H), 7.17 (d, J = 6.69 Hz, 2H), 6.90 (d, J = 6.69 Hz, 4H), 6.51 (s, 1H), 4.98 (s, 2H), 4.85 (d, J = 15.60 Hz, 1H), 4.69 (d, J = 15.60 Hz, 1H), 4.08 (d, J = 5.95 Hz, 1H), 3.92 (s, 3H), 3.74 (t, J = 8.94 Hz, 1H), 3.47−3.56 (m, 1H), 2.72 (t, J = 8.17 Hz, 1H), 1.93−2.15 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.2, 164.8, 164.2, 159.3, 150.1, 147.2, 135.7, 133.1, 132.7, 128.6, 128.4, 128.0, 126.7, 123.1, 115.7, 115.3, 111.5, 107.5, 70.6, 57.2, 56.0, 51.6, 46.5, 26.6, 23.7. FT-IR: cm^{-1} 2926.9, 1675.5, 1633.9, 1605.1, 1512.0, 1459.9, 1434.8, 1378.3, 1257.0, 1218.8, 1161.5, 1040.6, 1015.7, 755.1. HRMS (ESI) calcd for $C_{27}H_{26}FN_2O_4$ $[M + H]^+$ 461.1876, found 461.1887. Purity/cleavage with K_2CO_3 > 95%. t_R = 8.53 min. Purity/cleavage with oxazolidinone > 48%. t_R = 5.08 min. $[\alpha]_D^{27}$ +154.25 (*c* 1, $CHCl_3$).

(11a*S*)-7-Chloro-10-pentyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,4,4***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,4*}, 80 mg), TPP (144 mg, 0.55 mmol), velaraldehyde (**7**{*4*}, 47 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,4,4*} was purified by column chromatography using ethyl acetate−hexane (2.5:7.5) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (d, J = 3.02 Hz, 1H), 7.43 (dd, J = 2.27 Hz, J = 8.31 Hz, 1H), 7.19 (d, J = 8.31 Hz, 1H), 4.14−4.26 (m, 1H), 3.98 (d, J = 6.04 Hz, 1H), 3.73−3.83 (m, 1H), 3.44−3.61 (m, 2H), 2.67−2.78 (m, 1H), 1.90−2.22 (m, 3H), 1.38−1.65 (m, 2H), 1.13−1.34 (m, 4H), 0.85 (t, J = 7.55 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.7, 163.7, 137.8, 132.2, 131.9, 131.3, 129.9, 123.9, 57.3, 48.2, 46.6, 28.6, 27.4, 26.6, 23.7, 22.0, 13.8. FT-IR: cm^{-1} 2930.1, 2873.7, 1673.2, 1640.6, 1445.3, 1376.1, 1243.9, 1200.8, 1127.8, 1038.1, 943.2, 843.3, 680.2. HRMS (ESI) calcd for $C_{17}H_{22}ClN_2O_2$ $[M + H]^+$ 321.1369, found 321.1367. Purity/cleavage with K_2CO_3 > 96%. t_R = 10.10 min. Purity/cleavage with oxazolidinone > 45%. t_R = 4.19 min. $[\alpha]_D^{27}$ +17.00 (*c* 1, $CHCl_3$).

(11a*S*)-8-Chloro-10-butyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,5,5***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,5*}, 80 mg), TPP (144 mg, 0.55 mmol), butaraldehyde (**7**{*5*}, 40 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,5,5*} was purified by column chromatography using ethyl acetate−hexane (2.5:7.5) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, J = 7.55 Hz, 1H), 7.24 (s, 2H), 4.16−4.28 (m, 1H), 3.98 (d, J = 6.04 Hz, 1H), 3.72−3.82 (m, 1H), 3.46−3.65 (m, 2H), 2.65−2.78 (m, 1H), 1.90−2.20 (m, 3H), 1.40−1.60 (m, 2H), 1.20−1.33 (m, 2H), 0.89 (t, J = 7.55 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.9, 164.2, 140.5, 137.7, 131.6, 129.5, 126.0, 122.6, 57.3, 48.2, 46.6, 29.9, 26.6, 23.8, 19.8, 13.5. FT-IR: cm^{-1} 2927.4, 1678.8, 1638.7, 1588.9, 1440.1, 1375.6, 1234.3, 1204.5, 1093.9, 843.4, 709.2. HRMS (ESI) calcd for $C_{16}H_{20}ClN_2O_2$ $[M + H]^+$ 307.1213, found 307.1220. Purity/cleavage with K_2CO_3 > 98%. t_R = 6.82 min. Purity/cleavage with oxazolidinone > 49%. t_R = 4.16 min. $[\alpha]_D^{27}$ +43.75 (*c* 1, $CHCl_3$).

(11a*S*)-7-Methoxy-10-(4-nitrobenzyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,6,6***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,6*}, 80 mg), TPP (144 mg, 0.55 mmol), 4-nitrobenzaldehyde (**7**{*6*}, 82 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,6,6*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 8.18 Hz, 2H), 7.27−7.32 (m, 3H), 7.02 (d, J = 8.92 Hz, 1H), 6.94 (dd, J = 2.33 Hz, J = 8.17 Hz, 1H), 5.13 (d, J = 15.61 Hz, 1H), 5.03 (d, J = 15.61 Hz, 1H), 4.17 (d, J = 5.95 Hz, 1H), 3.83 (s, 3H), 3.78−3.80 (m, 1H), 3.49−3.59 (m, 1H), 2.69−2.76 (m, 1H), 1.97−2.17 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.5, 163.5, 156.2, 146.0, 143.4, 131.1, 130.6, 126.5, 122.8, 122.4, 118.4, 112.0, 56.0, 54.5, 50.6, 45.6, 25.5, 22.6. FT-IR: cm^{-1} 2925.9, 1678.9, 1639.9, 1607.9, 1520.2, 1494.4, 1454.9, 1345.5, 1259.9, 1045.9, 1017.1, 753.8. HRMS (ESI) calcd for $C_{20}H_{20}N_3O_5$ $[M + H]^+$ 382.1402, found 382.1401. Purity/cleavage with K_2CO_3 > 99%. t_R = 9.09 min. Purity/cleavage with oxazolidinone > 44%. t_R = 4.47 min. $[\alpha]_D^{27}$ +210.75 (*c* 1, $CHCl_3$).

(11a*S*)-8-Methyl-10-(2-chlorobenzyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,7,7***}**.** Prepared as described earlier for the prepa-

ration of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,7*}, 79 mg), TPP (144 mg, 0.55 mmol), 2-chlorobenzaldehyde (**7**{*7*}, 76 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,7,7*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, J = 7.43 Hz, 1H), 7.24−7.28 (m, 1H), 7.10−7.20 (m, 2H), 6.94−7.00 (m, 2H), 6.87 (s, 1H), 5.15 (d, J = 16.35 Hz, 1H), 5.06 (d, J = 16.35 Hz, 1H), 4.18 (dd, J = 2.93 Hz, J = 8.17 Hz, 1H), 3.72−3.78 (m, 1H), 3.48−3.56 (m, 1H), 2.68−2.74 (m, 1H), 2.27 (s, 3H), 1.90−2.12 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.8, 164.9, 142.7, 139.3, 130.2, 129.6, 128.5, 127.9, 126.9, 126.8, 57.3, 49.8, 46.5, 26.7, 23.8, 21.4. FT-IR: cm^{-1} 2928.7, 1681.6, 1638.4, 1441.5, 1378.4, 1257.5, 1040.1, 753.9. HRMS (ESI) calcd for $C_{20}H_{20}ClN_2O_2$ $[M + H]^+$ 355.1220, found 355.1213. Purity/cleavage with K_2CO_3 > 93%. t_R = 6.50 min. Purity/cleavage with oxazolidinone > 43%. t_R = 4.47 min. $[\alpha]_D^{27}$ +3.25 (*c* 1, $CHCl_3$).

(11a*S*)-7-Methyl-10-(3,4-dimethoxybenzyl)-1,2,3,10,11,-11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,8,8***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,8*}, 78 mg), TPP (144 mg, 0.55 mmol), 3,4-dimethoxybenzaldehyde (**7**{*8*}, 91 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,8,8*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (s, 1H), 7.17 (d, J = 8.78 Hz, 1H), 7.09 (d, J = 8.78 Hz, 1H), 6.69 (d, J = 8.05 Hz, 1H), 6.56−6.62 (m, 2H), 5.10 (d, J = 15.37 Hz, 1H), 4.88 (d, J = 15.37 Hz, 1H), 4.11 (d, J = 5.87 Hz, 1H), 3.73−3.86 (m, 8H), 3.48−3.60 (m, 1H), 2.35 (s, 3H), 2.10−2.20 (m, 1H), 1.95−2.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): 170.3, 164.4, 148.3, 145.1, 139.7, 135.9, 132.6, 130.2, 129.9, 119.1, 111.0, 109.9, 57.2, 55.7, 51.7, 46.5, 26.7, 23.7, 20.6. FT-IR: cm^{-1} 2928.4, 1675.9, 1639.4, 1515.2, 1445.6, 1379.7, 1260.2, 1141.1, 1026.4, 770.2. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_4$ $[M + H]^+$ 381.1814, found 381.1815. Purity/cleavage with K_2CO_3 > 85%. t_R = 8.13 min. Purity/cleavage with oxazolidinone > 39%. t_R = 5.35 min. $[\alpha]_D^{27}$ −9.25 (*c* 1, $CHCl_3$).

(11a*S*)-9-Methyl-10-(3,4,5-trimethoxybenzyl)-1,2,3,10,-11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{***1,9,9***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,9*}, 79 mg), TPP (144 mg, 0.55 mmol), 3,4,5-trimethoxybenzaldehyde (**7**{*9*}, 108 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,9,9*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20−7.27 (m, 1H), 7.01−7.10 (m, 2H), 6.26 (s, 2H), 5.26 (d, J = 15.61 Hz, 1H), 4.75 (d, J = 15.61 Hz, 1H), 4.12 (d, J = 5.96 Hz, 1H), 3.80−3.86 (m, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 3.49−3.58 (m, 1H), 2.66−2.74 (m, 1H), 2.51 (s, 3H), 2.12−2.28 (m, 1H), 1.98−2.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.9, 160.3, 156.0, 153.3, 142.0, 132.9, 126.5, 114.1, 104.5, 94.2, 60.7, 56.0, 46.4, 44.0, 38.4, 29.6, 21.0, 20.9. FT-IR: cm^{-1} 2923.9, 2852.3, 1658.4, 1597.6, 1459.6, 1418.3, 1125.6, 759.5. HRMS (ESI) calcd for $C_{23}H_{27}N_2O_5$ $[M + H]^+$ 411.1919, found 411.1937. Purity/cleavage with K_2CO_3 > 83%. t_R = 7.41 min. Purity/cleavage with oxazolidinone > 40%. t_R = 5.28 min. $[\alpha]_D^{27}$ +281.00 (*c* 0.3, $CHCl_3$).

(11a*S*)-10-Benzyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]pyridodiazepine-5,11-dione 10{***1,10,1***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,10*}, 77 mg), TPP (144 mg, 0.55 mmol), benzaldehyde (**7**{*1*}, 58 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,10,1*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (dd, J = 2.23 Hz, J = 4.46 Hz, 1H), 8.24 (dd, J = 2.23 Hz, J = 8.17 Hz, 1H), 7.11−7.20 (m, 6H), 5.37 (d, J = 14.87 Hz, 1H), 5.32 (d, J = 14.87 Hz, 1H), 4.05−4.09 (m, 1H), 3.78−3.85 (m, 1H), 3.52−3.61 (m, 1H), 2.77−2.84 (m, 1H), 1.98−2.22 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.3, 164.6, 147.1, 141.3, 137.0, 133.3, 129.1, 125.3, 124.6, 127.2, 125.5, 56.8, 51.2, 47.3, 26.2, 23.2. FT-IR: cm^{-1} 2922.9, 2853.1, 1735.9, 1672.4, 1638.7, 1431.4, 1384.1, 1260.0, 1098.4, 1021.3, 758.7. HRMS (ESI) calcd for $C_{18}H_{18}N_3O_2$ $[M + H]^+$ 308.1399, found 308.1391. Purity/cleavage with K_2CO_3 > 82%. t_R = 6.68 min. Purity/cleavage with oxazolidinone > 45%. t_R = 6.68 min. $[\alpha]_D^{27}$ +48.75 (*c* 0.2, $CHCl_3$).

(11a*S*)-7,9-Dibromo-10-(4-methoxybenzyl)-1,2,3,10,11,-11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,-11-dione 10{***1,11,2***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*1,11*}, 95 mg), TPP (144 mg, 0.55 mmol), 4-methoxybenzaldehyde (**7**{*2*}, 74 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*1,11,2*} was purified by column chromatography using ethyl acetate−hexane (3:7) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 2.23 Hz, 1H), 7.85 (d, J = 2.97 Hz, 1H), 6.82 (d, J = 8.92 Hz, 2H), 6.66 (d, J = 8.92 Hz, 2H), 5.46 (d, J = 14.87 Hz, 1H), 4.40 (d, J = 14.87 Hz, 1H), 3.96 (dd, J = 1.49 Hz, J = 7.43 Hz, 1H), 3.72 (s, 3H), 3.51−3.57 (m, 1H), 3.36−3.43 (m, 1H), 2.61−2.69 (m, 1H), 1.89−2.11 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.6, 163.5, 159.2, 142.6, 138.7, 136.0, 132.2, 131.7, 129.3, 121.0, 113.8, 57.6, 55.0, 51.3, 46.3, 26.2, 23.6. FT-IR: cm^{-1} 2925.3, 2854.5, 1675.4, 1642.2, 1607.5, 1517.6, 1462.1, 1368.6, 1272.0, 1213.3, 1118.4, 770.3. HRMS (ESI) calcd for $C_{20}H_{19}Br_2N_2O_3$ $[M + H]^+$ 492.9762, found 492.9756. Purity/cleavage with K_2CO_3 > 93%. t_R = 3.93 min. Purity/cleavage with oxazolidinone > 48%. t_R = 3.92 min. $[\alpha]_D^{27}$ +127.00 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-10-(4-Fluorobenzyl)-2-hydroxy-1,2,3,10,11,-11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,-11-dione 10{***2,1,3***}**.** Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*}

employing resin (**6**{*2,1*}, 77 mg), TPP (144 mg, 0.55 mmol), 4-fluorobenzaldehyde (**7**{*3*}, 68 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*2,1,3*} was purified by column chromatography using ethyl acetate−hexane (6:4) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J = 7.31 Hz, 1H), 7.40 (t, J = 7.32 Hz, 1H), 7.08−7.28 (m, 4H), 6.95 (t, J = 8.053 Hz, 2H), 5.07 (d, J = 15.37 Hz, 1H), 4.99 (d, J = 15.37 Hz, 1H), 4.62 (bs, 1H), 4.30 (t, J = 7.321 Hz, 1H), 3.90 (d, J = 13.177 Hz, 1H), 3.60 (dd, J = 4.39 Hz, J = 12.46 Hz, 1H), 2.92−3.00 (m, 1H), 2.00−2.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.9, 165.7, 163.6, 160.4, 139.4, 132.4, 132.2, 130.4, 129.7, 126.3, 122.3, 115.8, 115.5, 69.2, 56.0, 54.0, 51.9, 34.9, 29.6. FT-IR: cm^{-1} 3416.2, 2928.8, 1678.9, 1635.0, 1510.7, 1464.8, 1222.2, 767.9. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ $[M + H]^+$ 341.1301, found 341.1306. Purity/cleavage with K_2CO_3 > 97%. t_R = 6.56 min. Purity/cleavage with oxazolidinone > 49%. t_R = 6.56 min. $[\alpha]_D^{27}$ +260.50 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-7,8-Dimethoxy-10-pentyl-2-hydroxy-1,2,3,-10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 10{*2,2,4*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*2,2*}, 82 mg), TPP (144 mg, 0.55 mmol), velaraledehyde (**7**{*4*}, 47 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*2,2,4*} was purified by column chromatography using ethyl acetate−hexane (6.5:3.5) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (s, 1H), 6.65 (s, 1H), 4.07−4.30 (m, 2H), 3.94 (s, 3H), 3.89 (s, 3H) 3.75−3.85 (m, 1H), 3.37−3.65 (m, 3H), 2.85−2.96 (m, 1H), 1.95−2.10 (m, 1H), 1.40−1.60 (m, 2H), 1.15−1.35 (m, 4H), 0.80−0.95 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.7, 165.9, 151.7, 133.1, 127.8, 111.4, 105.5, 69.8, 56.4, 56.2, 50.7, 48.6, 32.7, 31.4, 29.4, 22.5, 13.9. FT-IR: cm^{-1} 3474.6, 2926.0, 2853.2, 1636.3, 1618.2, 1460.7, 1351.0, 1219.7, 722.3. HRMS (ESI) calcd for $C_{22}H_{25}N_2O_6$ $[M + H]^+$ 413.1712, found 413.1708. Purity/cleavage with K_2CO_3 > 85%. t_R = 3.62 min. Purity/cleavage with oxazolidinone > 45%. t_R = 4.17 min. $[\alpha]_D^{27}$ +308.00 (*c* 0.75, $CHCl_3$).

(2*R*,11a*S*)-8-Benzyloxy-7-methoxy-10-butyl-2-hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiaze-pine-5,11-dione 10{*2,3,5*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**6**{*2,3*}, 90 mg), TPP (144 mg, 0.55 mmol), butaraldehyde (**7**{*5*}, 40 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **10**{*2,3,5*} was purified by column chromatography using ethyl acetate−hexane (6.5:3.5) as an eluent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25−7.42 (m, 5H), 7.07 (d, J = 7.43 Hz, 1H), 6.81 (d, J = 8.18 Hz, 1H), 5.14 (s, 2H), 4.65 (t, J = 7.43 Hz, 1H), 4.10−4.20 (m, 2H), 4.04 (s, 1H), 3.90 (s, 3H), 3.75−3.80 (m, 1H), 3.23−3.40 (m, 2H), 2.00−2.10 (m, 1H), 1.20−1.50 (m, 4H), 0.80−1.00 (m, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.2, 164.3, 157.2, 147.2, 135.3, 131.2, 128.0, 126.2, 126.0, 115.3, 114.3, 107.3, 69.3, 68.7, 57.6, 56.1, 49.8, 48.9, 34.3, 28.1, 20.7, 13.9. FT-IR: cm^{-1} 3414.2, 2929.3, 1660.3, 1617.3, 1422.5, 1261.6, 1220.0, 1182.6, 722.6. HRMS (ESI) calcd for $C_{27}H_{26}FN_2O_5$ $[M + H]^+$ 477.1826, found 477.1831. Purity/cleavage with K_2CO_3 > 97%. t_R = 4.17 min. Purity/cleavage with oxazolidinone > 44%. t_R = 4.67 min. $[\alpha]_D^{27}$ −42.95 (*c* 1.1, $CHCl_3$).

General Procedure for the C2 Esterification of *N*-(2-Azidobenzoyl)-4-hydroxypyrrolidine-2-carboxylic Acid Resins 12. The resin-bound *N*-(2-azidobenzoyl)-4-hydroxypyrrolidine-2-carboxylic acid (**6**) was prepared from Merrifield resin (1.5 g, 3 mmol, described earlier), and the resin compound (**6**) obtained was equally partitioned into three parts. CH_2Cl_2 (10 mL) was added to each part, and after cooling to 0 °C, triethylamine (3.0 equiv) was added under an inert atmosphere, and the mixture was stirred for 10 min. Later, corresponding chlorides (3.0 equiv; acetyl, mesyl, and tosyl) were added dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for overnight. It may be noted that for the generation of acyl and tosyl group compounds (**12**), a catalytic amount of DMAP was used.

General Procedure for Preparation of Compounds 15. The acetyl, mesyl, and tosyl groups containing resins (**12**) upon preparation were equally divided into nine parts and transferred into nine vessels of a parallel synthesizer for the generation of iminophosphoranes, followed by the addition of various aldehydes **7**{*1*−*9*} to give the imino resins (**13**). The amino resins (**14**) were generated by the reduction of the imino resins (**13**) with $NaCNBH_3$. The final products (**15**) were cleaved from the resin (**14**) by employing the lithiated 5-phenyl-2-oxazolidinone and purified by column chromatography using ethyl acetate−hexane.

(2*R*,11a*S*)-2-Acetyloxy-10-benzyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15-{*2,1,1,1*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,1,1*}, 79 mg), TPP (144 mg, 0.55 mmol), benzaldehyde (**7**{*1*}, 58 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,1,1,1*} was purified by column chromatography using ethyl acetate−hexane (4:6) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (dd, J = 1.51 Hz, J = 7.55 Hz, 1H), 7.65−7.70 (m, 1H), 7.48−7.53 (m, 1H), 7.37−7.45 (m, 1H), 7.16−7.30 (m, 4H), 7.11 (d, J = 6.79, 1H), 5.38−5.45 (m, 1H), 5.16 (d, J = 15.86 Hz, 1H), 5.01 (d, J = 15.86 Hz, 1H), 4.32 (t, J = 6.79 Hz, 1H), 3.97−4.05 (m, 1H), 3.72 (dd, J = 4.53 Hz, J = 13.59 Hz, 1H), 3.14−3.26 (m, 1H), 2.17−2.30 (m, 1H), 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 169.9, 168.2, 164.4, 138.3, 135.6, 132.2, 130.4, 128.7, 127.4, 126.7, 126.0, 122.4, 71.8, 68.1, 55.8, 51.7, 32.5, 22.9. FT-IR: cm^{-1} 2926.7, 1733.1, 1638.9, 1618.2, 1461.8, 1268.3, 616.2. HRMS (ESI) calcd for $C_{21}H_{21}N_2O_4$ $[M + H]^+$ 365.1501, found 365.1496. Purity/cleavage with oxazolidinone > 44%. t_R = 9.76 min. $[\alpha]_D^{27}$ +81.87 (*c* 0.4, $CHCl_3$).

(2*R*,11a*S*)-2-Acetyloxy-7,8-dimethoxy-10-(4-methoxybenzyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,2,1,2*}. Prepared as

described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,2,1*}, 84 mg), TPP (144 mg, 0.55 mmol), 4-methoxybenzaldehyde (**7**{*2*}, 74 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,2,1,2*} was purified by column chromatography using ethyl acetate−hexane (4:6) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 1H), 7.11 (d, J = 8.31 Hz, 2H), 6.81 (d, J = 8.31 Hz, 2H), 6.65 (s, 1H), 5.40−5.47 (m, 1H), 5.17 (d, J = 15.10 Hz, 1H), 4.79 (d, J = 15.10 Hz, 1H), 4.31 (t, J = 6.79 Hz, 1H), 4.19−4.23 (m, 1H), 4.00−4.08 (m, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.65−3.72 (s, 3H), 3.15−3.28 (m, 1H), 2.15−2.36 (m, 1H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 172.3, 169.2, 164.6, 156.5, 155.2, 148.2, 133.8, 130.8, 128.8, 114.1, 111.2, 107.5, 71.8, 68.1, 55.9, 52.3, 51.6, 32.4, 22.9. FT-IR: cm^{-1} 2926.9, 2854.2, 1736.8, 1674.0, 1636.6, 1609.3, 1515.0, 1460.5, 1435.8, 1376.4, 1247.9, 1216.7, 1030.3, 760.3. HRMS (ESI) calcd for $C_{24}H_{26}N_2O_7$ $[M + H]^+$ 455.1818, found 455.1810. Purity/cleavage with oxazolidinone > 42%. t_R = 4.54 min. $[\alpha]_D^{27}$ +140.25 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-2-Acetyloxy-8-benzyloxy-10-(4-fluorobenzyl)-7-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,3,1,3*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,3,1*}, 89 mg), TPP (144 mg, 0.55 mmol), 4-flurobenzaldehyde (**7**{*3*}, 68 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,3,1,3*} was purified by column chromatography using ethyl acetate−hexane (4:6) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22−7.35 (m, 4H), 7.17 (d, J = 5.86 Hz, 2H), 7.00 (t, J = 8.05 Hz, 2H), 6.90 (d, J = 5.86 Hz, 2H), 6.52 (s, 1H), 5.00 (s, 2H), 4.85 (d, J = 15.37 Hz, 1H), 4.72 (d, J = 15.37 Hz, 1H), 4.43−4.55 (m, 1H), 4.20−4.32 (m, 2H), 3.93 (s, 3H), 3.56−3.64 (m, 1H), 2.90−3.00 (m, 1H), 2.07−2.20 (m, 1H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.5, 165.4, 164.3, 164.2, 156.3, 149.2, 146.9, 135.5, 132.9, 131.5, 127.8, 127.5, 127.4, 125.6, 122.4, 114.3, 114.2, 111.0, 105.4, 70.2, 64.2, 55.4, 50.7, 33.8, 21.3. FT-IR: cm^{-1} 2921.6, 2852.4, 1736.4, 1674.8, 1636.0, 1605.8, 1511.5, 1462.0, 1218.8, 1078.9, 759.2. HRMS (ESI) calcd for oxazolidinone > 37%. t_R = 21.88 min. $[\alpha]_D^{27}$ −145 (*c* 0.1, $CHCl_3$).

(2*R*,11a*S*)-2-Methylsulfonyloxy-10-pentyl-1,2,3,10,11,-11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,1,2,4*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,1,2*}, 78 mg), TPP (144 mg, 0.55 mmol), velaraldehyde (**7**{*4*}, 47 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,1,2,4*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 7.43 Hz, 1H), 7.52 (t, J = 7.43 Hz, 1H), 7.25−7.35 (m, 2H), 5.30−5.36 (m, 1H), 4.05−4.25 (m, 3H), 3.73 (t, J = 4.46 Hz, 1H), 3.58−3.68 (m, 1H), 3.13−3.27 (m 1H), 3.10 (s, 3H), 2.34−2.47 (m, 1H), 1.12−1.30 (m, 6H), 0.82 (t, J = 7.43 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.7, 165.3, 139.2, 132.4, 130.4, 126.2, 122.8, 113.9, 78.0, 55.5, 51.6, 48.8, 38.6, 33.5, 28.7, 27.5, 22.1, 13.8. FT-IR: cm^{-1} 2930.4, 2866.3, 1675.7, 1645.9, 1602.4, 1463.0, 1407.8, 1358.3, 1174.2, 1020.4, 961.4, 892.3, 835.5, 764.5. HRMS (ESI) calcd for $C_{18}H_{24}N_2O_5S$ $[M + H]^+$ 381.1484, found 381.1494. Purity/cleavage with oxazolidinone > 38%. t_R = 5.57 min. $[\alpha]_D^{27}$ +248.75 (*c* 1.2, $CHCl_3$).

(2*R*,11a*S*)-10-Butyl-7,8-dimethoxy-2-methylsulfonyloxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,2,2,5*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*} and **10**{*1,1,1*} employing resin (**12**{*2,2,2*}, 79 mg), TPP (144 mg, 0.55 mmol), butaraldehyde (**7**{*5*}, 40 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,2,2,5*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (s, 1H), 6.69 (s, 1H), 5.32−5.38 (m, 1H), 4.15−4.32 (m, 3H), 4.00 (s, 3H), 3.95 (s, 3H), 3.68 (dd, J = 4.46 Hz, J = 14.12 Hz, 1H), 3.47−3.56 (m, 1H), 3.15−3.25 (m, 1H), 3.06 (s, 3H), 2.37−2.47 (m, 1H), 1.20−1.60 (m, 4H), 0.87 (t, J = 6.99 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.5, 165.1, 152.0, 147.0, 132.9, 113.9, 111.3, 105.6, 78.1, 56.1, 55.7, 51.5, 48.5, 44.7, 38.5, 33.4, 29.8, 19.7, 13.6. FT-IR: cm^{-1} 2957.3, 1663.1, 1637.5, 1603.7, 1518.1, 1442.3, 1361.0, 1268.1, 1176.8, 1025.0, 964.4, 901.4, 752.6, 530.6. HRMS (ESI) calcd for $C_{19}H_{27}N_2O_7S$ $[M + H]^+$ 427.1538, found 427.1548. Purity/cleavage with oxazolidinone > 41%. t_R = 3.84 min. $[\alpha]_D^{27}$ +279.25 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-8-Benzyloxy-7-methoxy-2-methylsulfonyloxy-10-(4-nitrobenyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,3,2,6*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,3,2*}, 91 mg), TPP (144 mg, 0.55 mmol), 4-nitrobenzaldehyde (**7**{*6*}, 82 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,3,2,6*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J = 8.79 Hz, 2H), 7.28−7.34 (m, 4H), 7.14−7.19 (m, 2H), 7.01 (d, J = 8.05 Hz, 2H), 6.46 (s, 1H), 5.32−5.37 (m, 1H), 5.10 (d, J = 13.18 Hz, 1H), 5.03 (d, J = 13.18 Hz, 1H), 4.96 (d, J = 16.11 Hz, 1H), 4.87 (d, J = 16.11 Hz, 1H), 4.36 (t, J = 7.32 Hz, 1H), 4.26 (d, J = 13.91 Hz, 1H), 3.96 (s, 3H), 3.67 (dd, J = 4.39 Hz, J = 13.91 Hz,1H), 3.13−3.22 (m, 1H), 3.02 (s, 3H), 2.45−2.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.8, 165.3, 152.3, 149.2, 146.3, 143.6, 138.2, 132.3, 129.3, 128.8, 128.2, 127.5, 126.4, 123.9, 111.9, 107.5, 77.8, 70.9, 56.2, 55.4, 52.0, 51.8, 38.6, 33.6. FT-IR: cm^{-1} 2929.0, 1678.3, 1638.8, 1605.3, 1518.3, 1461.4, 1434.3, 1347.6, 1261.3, 1173.2, 1035.3, 970.9, 894.4, 755.0. HRMS (ESI) calcd for $C_{28}H_{28}N_3O_9S$ $[M + H]^+$ 582.1546, found 582.1569. Purity/cleavage with oxazolidinone > 39%. t_R = 7.35 min. $[\alpha]_D^{27}$ +130.50 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-10-(2-Chlorobenzyl)-2-methylphenylsulfonyloxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,1,3,7*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,1,3*}, 86 mg), TPP (144 mg, 0.55 mmol), 2-chlorobenzaldehyde (**7**{*7*}, 76 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,1,3,7*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86 (dd, J = 1.15 Hz, J = 7.55 Hz, 1H), 7.80 (s, 1H), 7.76 (s, 1H), 7.27−7.47 (m, 5H), 7.12−7.20 (m, 3H), 6.96−7.07 (m, 1H), 5.09−5.17 (m, 3H), 4.35 (t, J = 7.55 Hz 1H), 3.97−4.10 (m, 1H), 3.60 (dd, J = 4.53 Hz, J = 13.60 Hz, 1H), 3.07−3.20 (m, 1H), 2.50 (s, 3H), 2.35−2.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.3, 164.2, 144.3, 139.3, 134.2, 132.4, 130.5, 130.1, 129.8, 128.7, 127.8, 127.0, 126.4, 122.1, 78.3, 55.5, 51.5, 50.4, 33.9, 21.7. FT-IR: cm^{-1} 2924.3, 1685.1, 1641.7, 1600.4, 1463.4, 1355.4, 1259.7, 1167.7, 1096.0, 1040.2, 904.9, 760.5. HRMS (ESI) calcd for $C_{26}H_{24}ClN_2O_5S$ $[M + H]^+$ 511.1094, found 511.1102. Purity/cleavage with oxazolidinone > 42%. t_R = 12.14 min. $[\alpha]_D^{27}$ +263.00 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-7,8-Dimethoxy-10-(3,4-dimethoxybenzyl)-2-methylphenylsulfonyloxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,2,3,8*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,2,3*}, 89 mg), TPP (144 mg, 0.55 mmol), 4,5-dimethoxybenzaldehyde (**7**{*8*}, 91.30 mg, 0.55 mmol), $NaCNBH_3$ (69.12 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,2,3,8*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, J = 8.31 Hz, 2H), 7.36 (d, J = 7.55 Hz, 2H), 7.23 (s, 1H), 6.91 (t, J = 7.55 Hz, 1H), 6.73 (d, J = 7.55 Hz, 1H), 6.56−6.63 (m, 2H), 5.08−5.17 (m, 3H), 4.31 (t, J = 6.80 Hz, 1H), 4.30 (d, J = 13.60 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.58 (dd, J = 4.53 Hz, J = 12.84 Hz, 1H), 3.07−3.18 (m, 1H), 2.48 (s, 3H), 2.30−2.43 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 168.3, 164.2, 152.8, 146.8, 147.7, 144.5, 133.1, 130.8, 130.0, 128.7, 127.8, 124.3, 121.6, 119.4, 111.6, 111.3, 105.4, 78.4, 68.1, 56.0, 55.7, 51.5, 46.5, 43.4, 22.9. FT-IR: cm^{-1} 2932.1, 1675.2, 1639.8, 1618.7, 1518.2, 1460.3, 1367.0, 1269.0, 1176.7, 1029.9, 895.1, 763.0. HRMS (ESI) calcd for $C_{30}H_{33}N_2O_5S$ $[M + H]^+$ 397.1763, found 397.1765. Purity > 41%. t_R = 7.35 min. $[\alpha]_D^{27}$ +165.00 (*c* 1, $CHCl_3$).

(2*R*,11a*S*)-8-Benzyloxy-7-methoxy-2-methylphenylsulfonyloxy-10-(3,4,5-trimethoxybenzyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 15{*2,3,3,9*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**12**{*2,3,3*}, 91 mg), TPP (144 mg, 0.55 mmol), 3,4,5-trimethoxybenzaldehyde (**7**{*9*}, 108 mg, 0.55 mmol), $NaCNBH_3$ (69 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone (0.12 mL of 1 M solution in THF, 0.12 mmol). The cleaved final product **15**{*2,3,3,9*} was purified by column chromatography using ethyl acetate−hexane (5:5) as an eluent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.73 (d, J = 8.08 Hz, 2H), 7.14−7.35 (m, 8H), 6.63 (s, 1H), 6.19 (s, 2H), 4.67−5.15 (m, 5H), 4.27 (t, J = 7.35 Hz, 1H), 3.95−4.10 (m, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.70 (s, 6H), 3.47 (dd, J = 5.14 Hz, J = 13.95 Hz, 1H), 2.98−3.15 (m, 1H), 2.44 (s, 3H), 2.20−2.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.2, 164.4, 154.3, 150.1, 147.1, 144.8, 139.4, 135.2, 132.1, 130.1, 126.6, 126.3, 126.1, 125.2, 107.2, 104.3, 78.2, 68.2, 57.3, 56.6, 55.4, 55.3, 51.4, 46.7, 34.5, 21.2. FT-IR: cm^{-1} 2924.4, 2853.2, 1678.1, 1640.1, 1601.1, 1511.2, 1459.8, 1432.2, 1374.5, 1258.9, 1212.2, 1127.8, 1005.4, 757.0. HRMS (ESI) calcd for $C_{37}H_{39}N_2O_{10}S$ $[M + H]^+$ 703.2325, found 703.2327. Purity/cleavage with oxazolidinone > 32%. t_R = 7.02 min. $[\alpha]_D^{27}$ +90.00 (*c* 0.25, $CHCl_3$).

General Procedure for the Preparation of Bis Azido Resins 16. To the stirred suspension of mesylated resin (**12**) in DMF (6−8 mL) at 50 °C, NaN_3 was added, and the mixture was stirred for 8−10 h. The resin was filtered and washed with DMF (3 × 15 mL), DMF/water (3 × 15 mL), DMF (3 × 15 mL), MeOH/water (3 × 15 mL), MeOH (3 × 15 mL), and CH_2Cl_2 (3 × 15 mL) and dried. The bis azido resin (**16**) obtained was transferred to a parallel synthesizer for the generation of the iminophosphoranes.

General Procedure for the Preparation of Compounds 19. To a suspension of bis azido resins **16** in dry toluene (6−8 mL), TPP (10.0 equiv) was added, and the mixture was allowed to shake for 5−6 h at room temperature. These resins were filtered and washed with dry toluene (3 × 15 mL) and dry CH_2Cl_2 (3 × 15 mL) under nitrogen atmosphere and dried. To the generated iminophosphorane resin in CH_2Cl_2 (6−8 mL), benzaldehyde **7**{*1*} was added, and the mixture was allowed to shake at room temperature for 6−8 h, filtered, and washed with CH_2Cl_2 (6−8 mL). This step was repeated in CH_2Cl_2 under reflux conditions for 6−8 h under a nitrogen atmosphere to get the diimino resins (**17**), then reduction of this compound with $NaCNBH_3$ in 1% AcOH−DMA (5 mL) at room temperature for 5−7 h afforded the diamino resins (**18**). These were filtered and dried. The above step was repeated once again for complete amination. To the agitated mixture of compound **18** in THF (5 mL) at 0 °C, the generated lithiated 5-phenyl-2-oxazolidinone (1.1 equiv, 1 M) was added dropwise over a period of 10 min, and the mixture was allowed to reach ambient temperature. These mixtures were subjected to shaking at room temperature for 2−3 h. The reaction was quenched by the addition of saturated NH_4Cl solution. The resin mixture was then filtered and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrates were evaporated to afford the crude product, which was further purified by column chromatography to get the final product (**19**).

(2*S*,11a*S*)-10-Benzyl-2-benzylamino-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione 19{*2,1,2,1,1*}. Prepared as described earlier for the preparation of compounds **8**{*1,1,1*}, **9**{*1,1,1*}, and **10**{*1,1,1*} employing resin (**16**{*2,1,2,1*}, 310 mg), TPP (786 mg, 5.0 mmol), benzaldehyde (**7**{*1*}, 402 mg, 3 mmol), $NaCNBH_3$ (377 mg, 1.1 mmol), and lithiated 5-phenyl-2-oxazolidinone

(0.66 mL of 1 M solution in THF, 0.66 mmol). The cleaved final product **19**{*2,1,2,1,1*} was purified by column chromatography using ethyl acetate−hexane (4.5:5.5) as an eluent. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.86 (d, J = 7.55 Hz, 1H), 7.05−7.45 (m, 13H), 5.17 (d, J = 15.42 Hz, 1H), 4.93 (d, J = 15.42 Hz, 1H), 4.15−4.37 (m, 2H), 3.87 (s, 2H), 3.47−3.75 (m, 2H), 2.90−3.05 (m, 2H), 2.25−2.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.2, 163.5, 139.7, 136.8, 132.2, 130.6, 128.9, 128.8, 128.6, 128.0, 127.4, 126.7, 126.1, 122.2, 56.5, 54.9, 52.7, 51.7, 50.7, 31.9. FT-IR: cm^{-1} 3414.6, 2926.8, 2363.1, 1638.3, 1617.8, 1518.4, 1460.0, 1355.0, 1268.9, 1175.7, 768.8, 620.0. HRMS (ESI) calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.2025, found 412.2022. Purity/cleavage with oxazolidinone > 20%. t_R = 3.83 min. $[\alpha]_D^{27}$ −113.80 (*c* 1.25, $CHCl_3$).

Microbiology. Growth and Maintenance of Mycobacterial Strains. Cultures of *M. tuberculosis* (H37Rv ATCC 27294), *M. avium* (ATCC 49601), *M. intracellulare* (ATCC 13950), and clinical isolates were obtained from various medical institutions. These cultures were grown on LJ medium and maintained at −70 °C. The cultures revived from −70 °C were subcultured on Middlebrook 7H9 broth for 10 days and stored at 4 °C until used.

Drug and Compound Preparation. Stock solutions were made in dimethylsulfoxide (DMSO). It has been verified that DMSO does not suppress or delay the growth of *M. avium* or *M. tuberculosis* strains when it is added undiluted to produce 5% concentration in the medium. Isoniazid was employed as the reference drug.

In Vitro Studies. Agar Diffusion Assay. The ability of the compounds to inhibit the growth of *Mycobacterium* species was determined by an agar diffusion assay. Briefly, reference strains of *M. tuberculosis* (H37Rv ATCC 27294), *M. avium* (ATCC 49601), and *M. intracellulare* (ATCC 13950) were grown in Middlebrook 7H9 broth containing 10% ADC supplement at 37 °C on a rotary shaker at 150 rpm for 10 days. The turbidity of the culture was adjusted to 0.5 McFarland, and 0.50 mL of the individual cultures was then added to the molten Middlebrook 7H10 in 150-mm petri plates. Uniform holes were then made in the media into which the different concentrations (50, 25 and 12.5 μg/mL) of individual compounds were added. The plates were then incubated at 37 °C for 21−28 days. Compounds showing a zone of inhibition greater than or equal to the standard were considered active.

Agar Dilution Assay. Minimum inhibitory concentrations (MIC in μg/mL) of compounds against strains of *Mycobacterium* were determined by a reference agar dilution method as per the NCCLS-M24-T2 recommendations.[25] The compounds and reference drug were dissolved in DMSO and diluted twofold to obtain 10 serial dilutions of each compound. Appropriate volumes of compounds were incorporated into duplicate plates of Middlebrook 7H10 agar medium supplemented with 10% Middlebrook supplement oleic acid−albumin−dextrose−catalase (OADC) enrichment at a concentration of 0.03−16 μg/mL. Test organisms (*Mycobacterium* strains) were grown in Middlebrook 7H9 broth containing 0.05% Tween 80 and 10% ADC supplement. After 10 days of incubation at 37 °C, the broths were adjusted to a turbidity of 0.5 McFarland standard. The organisms were further diluted 10-fold in sterile water containing 0.10% Tween 80. The resulting mycobacterial suspensions were spotted (3−5 μL/spot) onto drug-supplemented 7H10 media plates. The plates were sealed and incubated at 37 °C for 3−4 weeks in an upright position. The MIC was recorded as the highest dilution/ lowest concentration of the drug that completely inhibited the growth of mycobacterial cultures.

Acknowledgment. We are thankful to Dr. Brahm S. Srivastava and Dr. Sudhir Sinha, Department of Biochemistry and Microbiology, Central Drug Research Institute, Lucknow-226001, India, for carrying out the preliminary biological activity. We are also grateful to CSIR, New Delhi for the award of research fellowships to K.L.R., V.D., N.S., and G.S.K.R.

Supporting Information Available. Table 4[26] provides structural, mass, and yield data of libraries **10**, **15**, and **19** of PBD-5,11-dione as Supporting Information. Selected resin-bound intermediates FT-IR spectra and experimental procedures and FT-IR, ^{1}H NMR, ^{13}C NMR, HRMS, and HPLC spectral data for selected library members are also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) See the Supporting Information

CC0501458