99947-20-3; **20** (R_1 = H), 99946-84-6; (*E*)-**20** (R_1 = Me), 99946-85-7; (*Z*)-**20** (R_1 = Me), 99946-86-8; (*E*)-**22**, 99947-24-7; (*Z*)-**22**, 99947-25-8; (*E*)-**23** (R_1 = Ph), 99946-87-9; (*Z*)-**23** (R_1 = Ph), 99946-88-0; **25**, 99947-27-0; $MeSCH(SO_2Tol)Et$, 94816-47-4; $MeSCCl(SO_2Tol)Et$, 99946-81-3; $MeSCH(SO_2Tol)Pr$, 99946-79-9; $MeSCCl(SO_2Tol)Pr$, 99946-82-4; $MeSCH(SO_2Tol)(CH_2)_2Ph$, 99946-80-2; $MeSCCl(SO_2Tol)(CH_2)_2Ph$, 99946-83-5; $Me_2CH(CH_2)_3Br$, 626-88-0.

Synthesis and Stereochemistry of Carbinolamine-Containing Pyrrolo[1,4]benzodiazepines by Reductive Cyclization of *N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes

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An investigation of the reductive cyclization of *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes has been carried out, establishing that (a) electron-donating substituents are apparently required in the aromatic ring for successful carbinolamine formation, (b) this route complements the lactam (hydride) reduction approach which fails to afford carbinolamine products when electron-donating groups are present in the aromatic ring, and (c) carbinolamines are always coproduced with varying amounts of the corresponding secondary amines of type **6**. Five carbinolamine-containing compounds have been prepared by this route and details of the interconversion between the imine, carbinolamine, and carbinolamine methyl ether forms and their corresponding ^1H NMR assignments are described. In addition, the unsubstituted nitro aldehyde **3** afforded a different isolated product (the *N*-hydroxycarbinolamine methyl ether **21**), the yield of which could be increased by the addition of Me_2SO.

The carbinolamine-containing pyrrolo[1,4]benzodiazepine group of antitumor antibiotics are presently attracting increased interest from both the synthetic and biological standpoint. Well-known members of this group[1] include anthramycin, tomaymycin, the neothramycins A and B, and sibiromycin, which are thought to exert their antitumor activity through covalent binding of their N10–C11 carbinolamine functionalities within the minor groove of DNA,[2] and at least in the case of anthramycin, the precise structure of the drug–DNA adduct has been elucidated.[3] A rational approach to the development of clinically useful drugs in this series has been suggested[4] and a few groups, including our own,[5] have embarked upon the preparation of rationally designed analogues in order to test SAR predictions.

Until 1983, there were two major synthetic routes in the literature, one involving hydride reduction of the corresponding dilactam **1**[6] and the other controlled reductive cyclization of an *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**3**)[7] (Scheme I). These methods have been used for the total syntheses of anthramycin,[6] and tomaymycin[8,9] and neothramycin,[10] respectively. However, more recently Kaneko and co-workers have reported[11,12] an alternative approach involving the aluminum amalgam reduction of an imino thioether of type **2**, prepared from the corresponding dilactam **1**. In addition, work carried out by another group[13] has led to the development of two new techniques involving cyclization of amino acetals **4** and N-protected amino aldehydes **5**. Also, Mori and coworkers[14] have recently reported a new route for the synthesis of secondary amine compounds of type **6**, suggesting that this should open up a new synthetic pathway. However, there are presently no useful techniques in the literature for converting the N10–C11 secondary amine functionality to an N10–C11 carbinolamine or the equivalent.

We recently published the results of an investigation into the generality of the dilactam reduction route (**1** → **7**), demonstrating that product formation is dependent upon the nature and position of substituents in the aromatic ring.[5] We discovered that this route was unsuccessful for analogues containing electron-donating groups in the aromatic ring and only afforded carbinolamine-type products when electron density could be reduced on the N10 nitrogen via an external bridge from N10 to a C9

(1) For a review, see: Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, *52*. Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349. For newer members of this class of compounds, see: Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.; Miyamoto, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 665. Shimizu, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Fujimoto, K. *J. Antibiot.* **1982**, *35*, 972.

(2) Petrusek, R. L.; Anderson, G. L.; Garner, T. F.; Quinton, F. L.; Fannin, L.; Kaplan, D. J.; Zimmer, S. G.; Hurley, L. H. *Biochemistry* **1981**, *20*, 1111.

(3) Graves, D. E.; Pattaroni, C.; Krishnan, B. S.; Ostrander, J. M.; Hurley, L. H.; Krugh, T. R. *J. Biol. Chem.* **1984**, *13*, 8202.

(4) Thurston, D. E.; Hurley, L. H. *Drugs Future* **1983**, *8*, 957.

(5) Thurston, D. E.; Kaumaya, P. T. P.; Hurley, L. H. *Tetrahedron Lett.* **1984**, *25*, 2649.

(6) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641.

(7) Lown, J. W.; Joshua, A. V. *Biochem. Pharmacol.* **1979**, *28*, 2017.

(8) Tozuka, Z.; Takasugi, H.; Takaya, T. *J. Antibiot.* **1983**, *36*, 276.

(9) Tozuka, Z.; Yazawa, H.; Murata, M.; Takaya, T. *J. Antibiot.* **1983**, *36*, 1699.

(10) Miyamoto, M.; Kondo, S.; Naganawa, H.; Maeda, K.; Ohno, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 340.

(11) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, *24*, 5165. Kaneko, T.; Wong, H.; Doyle, T. W. *J. Antibiot.* **1984**, *37*, 300.

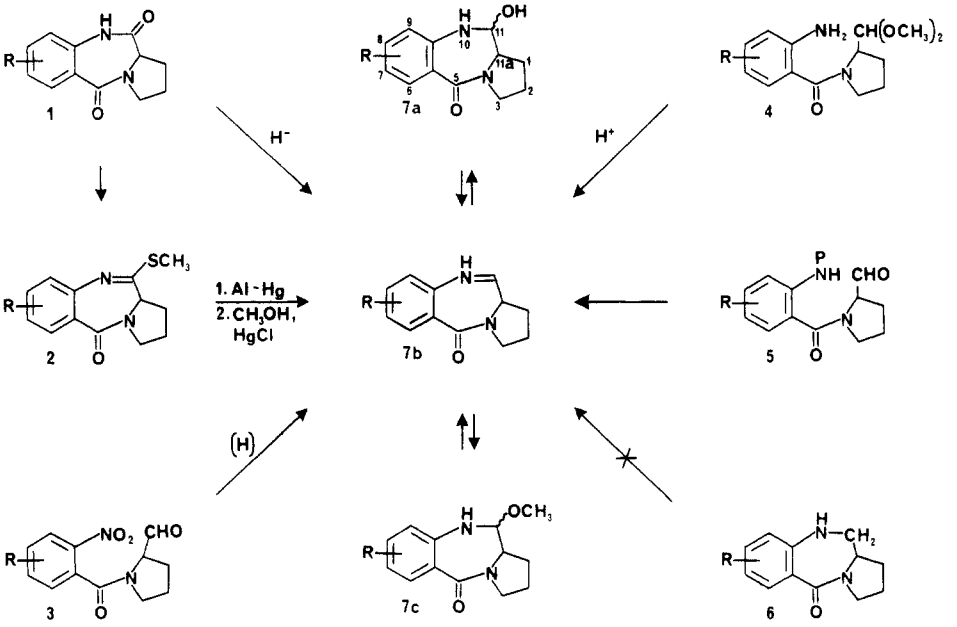
(12) Kaneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C.; Bradner, W. T. *J. Med. Chem.* **1985**, *28*, 388.

(13) Holden, K. G.; Hoover, J. R. E. SmithKline Beckman Corp., personal communication.

(14) Mori, M.; Purvaneckas, G.-E.; Ishikura, M.; Ban, Y. *Chem. Pharm. Bull.* **1984**, *32*, 3840.

0022-3263/86/1951-0705$01.50/0

Scheme I



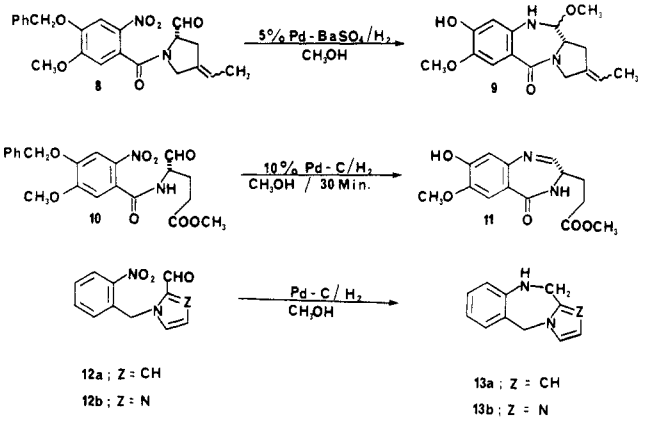
oxygen substituent or presumably via electron-withdrawing substituents in the aromatic ring. This route was therefore of limited value, and it is also noteworthy that various dilactam derivatives of known natural products have been prepared but could not be converted to the corresponding carbinolamines by direct reduction with simple hydride reducing agents.[15] However, the new route of Kaneko and co-workers[11,12] allows the conversion of a dilactam precursor to a carbinolamine in six steps.

The work reported here is concerned with a study of the generality of the reductive cyclization technique (**3** → **7**). We have been able to elucidate certain aspects of the mechanism of this reaction and have established that it complements the hydride reduction route discussed above, in that it is successful for compounds possessing electron-donating substituents in the aromatic ring, although yields are fairly modest (15–59%) and HPLC purification is required to separate the products from varying amounts of the corresponding secondary amine byproducts of type **6**. In addition, in our hands, the unsubstituted nitro aldehyde **3** afforded a different isolated product to that reported in the literature.[7] We have also been able to assign and correlate proton NMR chemical shifts and coupling constants for five different carbinolamine compounds, their methyl ethers, and also the corresponding imine forms.

Results and Discussion

The first example of a controlled reductive cyclization of an *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde was reported by Lown and Joshua[7] in 1979, who apparently isolated the unsubstituted imine **7b** (R = H) in 8.5% yield, by hydrogenation of the nitro aldehyde **3** (R = H) in methanol, at atmospheric pressure over 5% Pd–$BaCO_3$ catalyst for 17 h. After many attempts, under varying conditions, we were unable to repeat this reaction. However, instead we isolated the previously unknown[16] *N*-hydroxycarbinolamine methyl ether **21** (Scheme III) or after longer reduction time (≃ 6 h), the secondary amine **6** (R = H).[7,14]

Scheme II



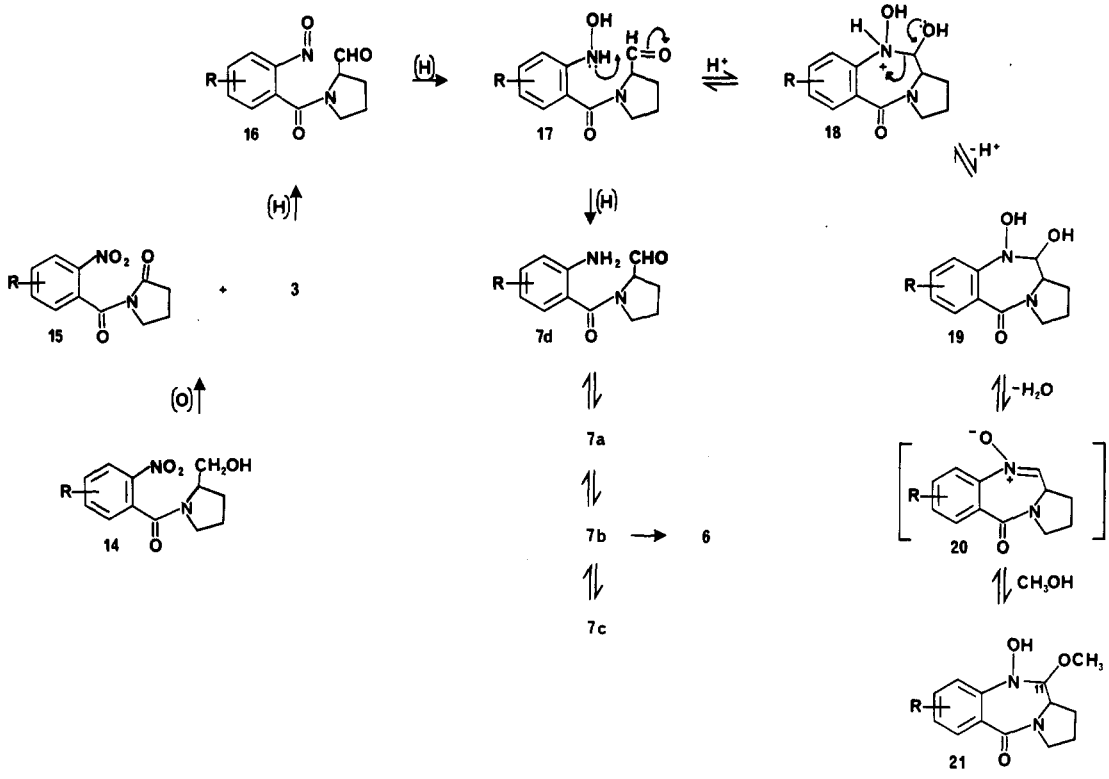
This result was intriguing, as it was inconsistent with the work of Tozuka and co-workers[8,9] and Miyamoto and co-workers,[10] who reportedly prepared tomaymycin methyl ether (**9**) and **11**, an intermediate in the synthesis of neothramycin, by reductive cyclization of the corresponding nitro aldehydes **8** and **10**, using 5% Pd–$BaSO_4$ and 10% Pd–C, respectively (Scheme II). In addition, Kaneko and co-workers have reported[12] the synthesis of a bicyclic imine of type **11** in 30% yield, by hydrogenation of a corresponding nitro aldehyde, in methanol, at 10 psi over 10% Pd–C. The formation of imines in the last two examples is surprising, as with a nonpoisoned catalyst (and particularly at a higher pressure), rapid formation of the corresponding secondary amine would be anticipated. For example, it is clear from the work of Lown[7] and from studies in our own laboratory that reduction of nitro aldehydes under similar conditions always affords the corresponding secondary amines of type **6** in nearly quantitative yield. Similarly, Artico and co-workers[17] have reported that catalytic hydrogenation of 1-(2-nitrobenzyl)-pyrrole-2-carboxaldehyde (**12a**) with Pd–C (strength not

(15) Massa, S.; De Martino, G. *Farmaco, Ed. Sci.* **1978**, *34*, 666. Kariyone, K.; Yazawa, H.; Kohsaka, M. *Chem. Pharm. Bull.* **1971**, *19*, 2289. Carey, F. A.; Giuliano, R. M. *J. Org. Chem.* **1981**, *46*, 1366.

(16) The structure of the *N*-hydroxycarbinolamine methyl ether **21** was first assigned and communicated to us by Jack D. Leber and John R. E. Hoover of the SmithKline Beckman Corp., PA, who originally isolated the carbinolamine form of this compound via an alternative method.

(17) Artico, M.; De Martino, G.; Giuliano, R.; Massa, S.; Porretta, G. C. *J. Chem. Soc., Chem. Commun.* **1969**, 671.

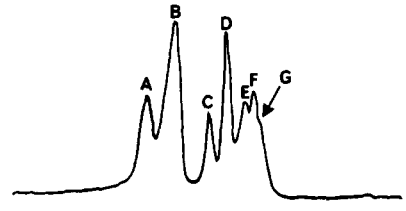
Scheme III



reported) affords the secondary amine **13a** and similar treatment of 1-(2-nitrobenzyl)imidazole-2-carboxaldehyde (**12b**) (10% Pd–C) has been shown to afford the corresponding secondary amine **13b**.[18] These inconsistencies prompted us to investigate substituent effect and the mechanism of the reductive cyclization process.

We began with a reinvestigation of the reductive cyclization experiment of Lown and Joshua.[7] The parent nitro aldehyde **3** (R = H) was originally prepared by pyridinium chlorochromate (PCC) oxidation of the corresponding nitro alcohol **14** (Scheme III). However, in our hands we obtained, in addition to the nitro aldehyde **3** (56%; $[\alpha]^{36}_{D}$ −121.4°), the pyrrolidone **15** in 6% yield. According to the reported procedure, a solution of **3** in methanol was hydrogenated over 5% Pd–$BaCO_3$. Despite numerous attempts using different batches of catalysts, different grades of solvents, and various reaction times, none of the imine **7b** (R = H) could be isolated. However, on some occasions we were able to obtain a white solid, mp 177–178 °C, in various yields, which was identified[16] as the previously unknown *N*-hydroxycarbinolamine methyl ether.[21] The *N*-hydroxylamine aldehyde **17** once formed, presumably cyclizes to **19**, which then reacts with solvent (via the iminium ion **20**) to form the methyl ether **21**.

The NOH and C11 protons were clearly visible as a singlet and doublet at δ 9.01 and 4.70 (J = 9 Hz), respectively, suggesting the 11*S*,11a*S* configuration or the equivalent enantiomer (vide infra). Furthermore, if reduction was allowed to continue for a longer time period, quantitative conversion to the secondary amine **6** occurred. We therefore studied the time course of this reaction by RP-HPLC, using the isolated *N*-hydroxycarbinolamine methyl ether **21** and an authentic sample of the carbinolamine **7a** (R = H) prepared via a different route.[19] After



A = Unknown, B = Secondary Amine (6)
C = Unknown, D = Nitro Aldehyde (3)
E = Carbinolamine, F = N-Hydroxycarbinolamine Methyl Ether (21), G = N-Hydroxycarbinolamine.

Figure 1. RP-HPLC trace obtained after 10 min of reduction of nitro aldehyde **3** using 5% Pd–$BaSO_4$.

many runs we were able to reproducibly establish a sequence of intermediates. Beginning with pure (single peak by RP-HPLC) nitro aldehyde **3**, a reduction was carried out in methanol, over 5% Pd–$BaSO_4$ catalyst (0.07 g per 1 mM of nitro aldehyde). Figure 1 shows a RP-HPLC trace after 10 min in which the nitro aldehyde peak (D) is decreasing in intensity as the secondary amine peak (B) increases. Additional peaks A, C, E, F, and G appeared, and E, G, and F were identified as the carbinolamine **7a** (R = H) and the *N*-hydroxycarbinolamine **19**[20] and its methyl ether **21**, respectively, by spiking experiments with authentic samples. Of the two unidentified peaks (A and C), A appeared rapidly after reduction commenced and was the largest peak present at 5 min (20% total). By 10 min it was in a ratio of 1:2 with secondary amine (B) and had completely disappeared by 90 min leaving *N*-hydroxycarbinolamine **19** along with smaller amounts of carbinolamine **7a**. After 3 h, in addition to secondary amine (B), the *N*-hydroxycarbinolamine methyl ether (F) was the major surviving species (30% total), and complete conversion to the secondary amine **6** had occurred by 6 h. The

(18) Stefancich, G.; Artico, M.; Massa, S.; Corelli, F. *Synthesis* **1981**, 321.

(19) The carbinolamine **7a** was prepared via a novel technique involving the deprotection of an amino dithioacetal under mild conditions. This route will be described in a future publication.

(20) We express our gratitude to Dr. John Hoover of the SmithKline Beckman Corp., PA, for supplying an authentic sample of the *N*-hydroxycarbinolamine **19**.

Table I. Diagnostic ^{1}H NMR Data for the Racemic 11*R*,11a*S* and 11*S*,11a*S* Carbinolamines (CA), Carbinolamine Methyl Ethers (ME), and Imine Forms [23a–e (R′ = H or CH_3), 27a–e]

		ME C11-OCH_3		ME H11			CA H11			
compd	imine H11	*R*	*S*	*R*	*S*	ratio[a] *R*:*S* ME	*R*	*S*	ME N10-H[b]	CA N10-H[b]
23a	7.92[c,d,e]		3.38[f,e]		4.43[c,g,e]			4.73[c,h,e]	5.69[i,e]	5.27[i,e]
23b	7.80[c,j,k]	3.29[f,k]	3.40[f,k]	4.61[c,l,k]	4.38[c,m,k]	1:1.4	5.13[f,n]	4.87[c,m,n]	5.0[i,k]	5.75[i,k]
23c	7.76[c,j,k]	3.27[f,k]	3.38[f,k]	4.52[c,l,k]	4.38[c,m,k]	1:1.5	4.96[c,l,k]	4.75[c,m,k]	5.23[i,k]	5.82[i,k]
23d	7.78[c,o,p]									
	7.83[c,o,k]		3.38[f,k]		4.35[q,r,m,k]	0:1		4.73[c,m,k]	5.14[i,k]	4.48[i,k]
23e			3.35[f,k]		4.47[c,m,k]		5.13[f,n]	4.88[c,m,n]	5.35[i,k]	

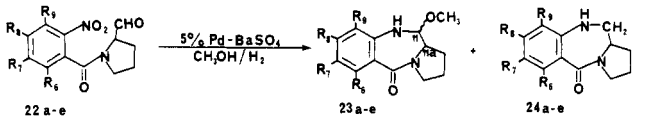
[a] Calculated by comparison of C11-OCH_3 signal heights. [b] Exchangeable with D_2O. [c] Doublet. [d] J = 4.2 Hz. [e] Me_2SO-d_6. [f] Singlet. [g] J = 9.45 Hz. [h] J = 9.5 Hz. [i] Broad singlet. [j] J = 4 Hz. [k] CD_3CN. [l] J = 6 Hz. [m] J = 9 Hz. [n] CD_3CN/D_2O. [o] J = 5 Hz. [p] $CDCl_3$. [q] Doublet of doublets. [r] J = 2 Hz.

behavior of the unidentified peak A suggested that it might be a precursor of the *N*-hydroxycarbinolamine (or its methyl ether) which itself is converted to the secondary amine (B). We therefore tentatively identified A as the nitroso compound **16**, a known type of intermediate in the reduction of nitro groups.[21] When pure (isolated) *N*-hydroxycarbinolamine methyl ether **21** was dissolved in methanol and hydrogenated over 5% Pd–$BaSO_4$, slow conversion to secondary amine **6** occurred. This suggests that **21** is in equilibrium with a small amount of the acyclic *N*-hydroxy aldehyde **17** which is rapidly reduced to the amino aldehyde **7d** and related species **7a–c** and then on to the secondary amine **6**. Conversion of **21** to the acyclic form **17** is probably slow; a buildup of carbinolamine does not occur and only secondary amine **6** is isolated. However, we were unable to rule out the possibility of direct reduction of **21** to the secondary amine **6**, without the occurrence of a ring-opening process. In addition, we were able to show that pure (isolated) carbinolamine **7a** (R = H), when hydrogenated in methanol over 5% Pd–$BaSO_4$, rapidly reduced to the secondary amine **6**, also supporting the proposed pathway in Scheme III.

During one of these runs, some nitro aldehyde was used that had been prepared via Swern-type oxidation[22] of alcohol **14**. On this occasion HPLC showed the appearance of only a trace amount of secondary amine and most of the nitro aldehyde converted to the *N*-hydroxycarbinolamine methyl ether **21** as judged by RP-HPLC. This time we were able to isolate the *N*-hydroxycarbinolamine methyl ether **21** in 60% yield. The most likely explanation for the increase in yield was the presence of trace amounts of Me_2SO in the aldehyde sample resulting from the Swern oxidation. This was confirmed by spiking PCC-prepared aldehyde with small amounts of Me_2SO prior to reduction, and this observation is in agreement with other reports of the Me_2SO-promoted partial reduction of aromatic nitro compounds to hydroxylamines.[21]

It follows from the above discussion that **17**, once formed (Scheme III), can either be further reduced to the amino aldehyde **7d** leading to species **7a–c** or cyclize to **19** (and **21**) via the protonated intermediate **18**. Based on our previous work which demonstrated that a protonated amine (rather than a nitrogen anion) is the leaving group in the ring-opening process of a species of type **18**, it seemed likely that factors leading to an increase in the electron density (e.g., base strengthening) on the N10 nitrogen, such as electron-donating substituents in the aromatic ring, would favor protonation of the species **18** and hence maintain the equilibrium **17** ⇌ **18** toward **17**. Of further interest, was the optical activity of the isolated secondary amine **6** ($[\alpha]^{36}_D$ +339.58°), which suggests that the reductive cyclization process proceeds with retention of configuration at the C11a position, assuming that **6** is derived from the imine **7b**, as depicted in Scheme III.

Scheme IV



22	23	24	R_6	R_7	R_8	R_9
a	a	a	H	H	CH_3	OH
b	b	b	H	H	H	CH_3
c	c	c	H	CH_3	H	H
d	d	d	CH_3	H	H	H
e	e	e	H	H	H	OCH_3

Five nitro aldehydes were therefore prepared[22] (**22a–e**), each containing electron-donating groups (Scheme IV). These compounds were hydrogenated in methanol over 5% Pd–$BaSO_4$, and in each case moderate yields (15–59%) of the corresponding carbinolamine methyl ethers **23a–e** were obtained along with varying amounts of the corresponding secondary amines **24a–e**.[23] However, in each case, only these two species were observed by MP-HPLC with a notable absence of *N*-hydroxy compounds, thereby supporting the concept that nitrogen protonation in a species of type **18** may direct the course of reaction. In the interest of high yields and convenience, the substituted aldehydes **22a–e** were prepared by bis(triphenylphosphine) copper borohydride reduction[24] of the corresponding acid chlorides. This preparative method afforded essentially racemic aldehydes with a consequent lack of optical activity in the final cyclized products. However, these racemic aldehydes served to investigate the reductive cyclization process, which apparently proceeds with a retention of configuration at C11a, based on the formation of optically active secondary amine **6**, as previously indicated.

During extensive investigations to optimize yields, we found that the type and amount of catalyst, the volume of solvent, and reaction time were all critical. Catalyst activity appeared to vary from batch to batch, and storage

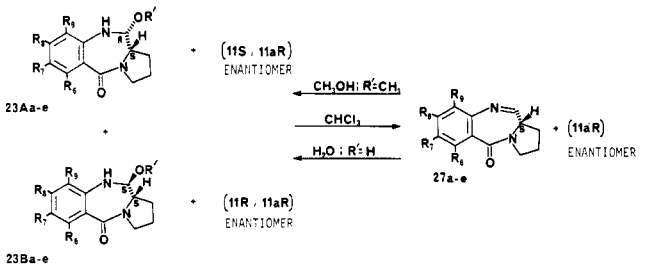
(21) Rylander, P. N. "Catalytic Hydrogenation in Organic Synthesis"; Academic Press: New York, 1979; pp 115–117 and references therein.

(22) In an attempt to obtain higher yields of the aldehyde and to avoid the separation of byproducts, we also investigated Swern oxidation of the nitro alcohol **14** and bis(triphenylphosphine) copper borohydride, Dibal, and $LiAlH_4$ reduction of the corresponding acid chloride, methyl ester, and imidazole derivatives, respectively. However, although in most cases the yield of aldehyde was improved, various degrees of racemization was observed at the aldehyde-bearing carbon. A detailed study of this phenomenon and how it relates to the DNA binding and biological activity of pyrrolo[1,4]benzodiazepine analogues in general, will form the basis of a future publication. For this study of the reductive cyclization process, nitro aldehydes **22a–e** were prepared via bis(triphenylphosphine) copper borohydride reduction of the corresponding (2*S*)-*N*-(2-nitrobenzoyl)proline derivatives, derived from simple condensation of (2*S*)-proline with the corresponding 2-nitrobenzoyl chlorides.

(23) The HPLC-separated, crude secondary amine products were identified by MS and ^{1}H NMR but were not purified and fully characterized for reporting in this publication.

(24) Sorrell, T. N.; Pearlman, P. S. *J. Org. Chem.* **1980**, *45*, 3449.

Scheme V



under anhydrous conditions was important for maintaining reduction efficiency. The optimal amount of catalyst and solvent volume were found to be 0.35 g and 100 mL, respectively, per 1 mM of nitro aldehyde. The reaction time was also found to be critical, with longer times leading to higher yields of the corresponding secondary amines. In each case, the carbinolamine and secondary amine products were isolated by simple filtration and evaporation of solvent at 40 °C. The carbinolamines were then purified by MP-HPLC using CH_3CN/H_2O (1:1) as the mobile phase. On evaporation of the appropriate fractions, the pure product in each case was obtained essentially in the carbinolamine form, presumably due to the aqueous solvent system.

In most cases, ^1H NMR of these isolates in CD_3CN/D_2O showed H11 doublets at δ 4.73–4.88 (J = 9 Hz) and singlets at approximately δ 5.1, corresponding to the racemic 11*R*,11*S* and 11*S*,11*S* forms, respectively (**23Aa–e** and **23Ba–e**, R′ = H) (Scheme V and Table I). In the 11*S*,11a*S* conformations and the corresponding 11*R*,11a*R* enantiomers, the H11 proton must subtend an angle of approximately 170° to H11a as predicted (within reasonable experimental error) from the Karplus equation[25] and studies with Dreiding models. This also supports the original configurational assignments of anthramycin[26] and tomaymycin.[27] Similarly, in the 11*R*,11a*S* conformations and the corresponding 11*S*,11a*R* enantiomers, the H11 proton subtends an angle of approximately 90–95° to H11a, and so no coupling is observed.

If instead, the HPLC-purified products were dissolved directly in deuterated chloroform, the corresponding imines **27a–e** were observed, typified by doublets for the C11 protons at δ 7.76–7.92 (J = 4 Hz). The dehydrating effect of chloroform and silica gel has also been reported by Tozuka and co-workers[8] and Kaneko and co-workers,[11] respectively, and may be due to slightly acidic conditions.

Finally, if the appropriate fractions from MP-HPLC were extracted into chloroform and then evaporated, followed by the addition of methanol and further evaporation, a mixture of the carbinolamine methyl ethers **23Aa–e** and **23Ba–e** (R′ = CH_3) was formed. ^1H NMR in CD_3CN typically revealed doublets for the racemic 11*S*,11a*S* forms at approximately δ 4.35–4.47 and doublets for the racemic 11*R*,11a*S* forms at δ 4.51–4.61. Only the doublets due to the racemic 11*R*,11a*S* forms collapse to singlets on exchange with D_2O, implying a lack of coupling between the C11 and C11a protons. In two cases, we were able to estimate the ratio of racemic 11*R*,11a*S* methyl ether to racemic 11*S*,11a*S* methyl ether as approximately 1:1.5. However, the C6-methyl analogue afforded exclusively the racemic 11*S* form. A study of Dreiding models indicates that in the (11aS)-pyrrolo[1,4]benzodiazepine system, the β-face of the C11 position is always the less hindered, with the α-face appearing in closer proximity to the C3 protons of the pyrrolidine ring. This may explain the approximately 1.5:1 predominance of the racemic 11*S*,11a*S* isomers in compounds **23b** and **23c**. However, a model of the 6-methyl analogue (**23d**) indicates a steric compression between the 6-methyl and C5-carbonyl functionalities. Displacement of the carbonyl to either side of the C6-methyl apparently causes the α-face of the C11 position to move into closer proximity to the C3 protons of the pyrrolidine ring, which may explain the lack of a racemic 11*R*,11a*S* form for this compound. Finally, the addition of D_2O to a solution of either the imine or carbinolamine methyl ether forms in CD_3CN caused the appearance of signals corresponding to the carbinolamine forms.

In conclusion, we report that we have been unable to isolate the unsubstituted carbinolamine (or its equivalent) according to the method of Lown and Joshua, isolating instead a low yield of the *N*-hydroxycarbinolamine methyl ether **21** or on prolonged reduction, the secondary amine **6**. However, in the presence of Me_2SO a much higher yield of **21** could be isolated. For successful carbinolamine formation, electron-donating substituents are apparently required in the aromatic ring, and careful attention to the type and amount of catalyst, volume of solvent, and reaction time are critical. However, the yields are generally modest and HPLC separation of secondary amine byproducts is required. Finally we report details of the interconversion between imine, carbinolamine, and carbinolamine methyl ether forms and their corresponding NMR assignments. The results of biological testing will be published elsewhere.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 1330 diffraction grating spectrophotometer, and peak positions are reported in reciprocal centimeters (cm^{-1}). Proton magnetic resonance (^1H NMR) spectra, unless otherwise stated, were recorded on a Varian Associates Model EM-390 spectrometer. A few spectra were recorded on a Nicolet NT-200 200-MHz spectrometer and are designated as such in the text. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (Me_4Si) as an internal standard. Coupling constants (J values) are given in hertz and spin multiplicities are described as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), or m (multiplet). Low-resolution mass spectral (MS) data were obtained with electron ionization (EI) on a Dupont 21-491 spectrometer coupled to an Incos data system. High-resolution MS data were obtained on a Dupont 21-110B spectrometer with EI and the same data system. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Flash chromatography was performed according to the method of Still[28] using Sigma Chromatographic Grade 230–240 mesh silica gel (No. S-0507). Reverse-phase analytical HPLC (RP-HPLC) and preparative medium-pressure HPLC (MP-HPLC) were carried out with PRP-1 (No. 79426, #202, Hamilton, Reno, NV) and RP-8 (Lobar LiChroprep, Size B (310-25) 40-63uM, EM Reagents) columns, respectively. The catalyst used, unless otherwise stated, was 5% palladium on barium sulfate purchased from the Aldrich Chemical Co. Inc. (#20,572-9; Lot No.: 3231EK) and stored over a desiccant, in vacuo. All solvents were dried and distilled prior to use.

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidinemethanol (14).[29] A

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(28) Clark Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(29) This procedure represents an improvement over the original method of Lown and Joshua[7] which afforded, in our hands, large amounts (>50%) of the ester byproduct.

solution of 2-nitrobenzoyl chloride (20.42 g, 0.11 mol) in acetonitrile (40 mL) was added dropwise over 1.5 h to a vigorously stirred suspension of (2*S*)-pyrrolidinemethanol (10.12 g, 0.1 mol) and anhydrous potassium carbonate (33.46 g, 0.242 mol) in acetonitrile (80 mL) under an atmosphere of dry nitrogen, at −20 °C, and in a CCl_4/dry ice bath. The reaction mixture was stirred for a further 45 min at −20 °C, then diluted with water (200 mL), and extracted with chloroform (4 × 50 mL). The combined organic phase was washed with water (2 × 40 mL), HCl (10%, 1 × 50 mL), water (1 × 50 mL), and brine (1 × 30 mL), dried ($MgSO_4$), and treated briefly with charcoal. Evaporation of the solvent in vacuo afforded **14** (R = H) (22.4 g, 89%) as a pale yellow solid: mp 101–102 °C (from benzene/hexane); IR (Nujol) 3430 (OH), 1620 (C=O), 1523, 1355 (NO_2), 1055 (C–O), 851, 795, 769, 699; ^{1}H NMR ($CDCl_3$) 1.68–2.39 (m, 4 H), 3.15–3.34 (m, 2 H), 3.78–3.98 (m, 2 H), 4.20–4.60 (m, 2 H), 7.30–7.93 (m, 3 H), 8.27 (d, 1 H, J = 9 Hz); MS, m/e (relative intensity) 250 (M^+, 14), 232 (39), 219 (100), 150 (85), 134 (29), 120 (20), 104 (43), 76 (39); $[\alpha]^{36}_D$ −164.61° (*c* 0.049, $CHCl_3$). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.58; H, 5.65; N, 11.20. Found: C, 57.63; H, 5.69; N, 11.16.

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde (3, R = H). Method A: Pyridinium Chlorochromate. A solution of **14** (2.75 g, 10.99 mmol) in dichloromethane (28 mL) was added dropwise over 10 min to a vigorously stirred suspension of pyridinium chlorochromate (3.58 g, 16.61 mmol) and anhydrous sodium acetate (1.1 g, 13.41 mmol) in dichloromethane (440 mL) under an atmosphere of dry nitrogen. Stirring was continued at room temperature for 8.5 h when TLC (silica gel; 15% MeOH/$CHCl_3$) indicated maximum extent of reaction. The solution was filtered through Celite, treated briefly with charcoal, dried, and evaporated in vacuo (at 35 °C) to afford a black oily residue (3 mL), consisting of two components. Separation was effected by chromatography on silica gel (70 g; 2% MeOH/$CHCl_3$) to afford **N-(2-Nitrobenzoyl)-2-pyrrolidone (15)** (0.15 g, 6%), the faster running component, as a white crystalline solid: mp 98–99 °C (from ethanol/H_2O); IR (Nujol) 1749, 1690 (C=O), 1615, 1575 (C=C), 1520, 1350, (NO_2), 1325, 1020, 860, 790; ^{1}H NMR ($CDCl_3$) 1.90–2.32 (m, 2 H), 2.34–2.67 (m, 2 H), 4.01 (t, 2 H, J = 8 Hz), 7.23–7.84 (m, 3 H), 8.21 (d, 1 H, J = 9 Hz); MS, m/e (relative intensity) 234 (M^+, 3), 188 (100), 160 (9), 150 (19), 119 (10), 76 (37). Anal. Calcd for $C_{11}H_{10}N_2O_4$: 234.0640. Found 234.0633. The slower running component, **3** (R = H), was obtained as a colorless oil (1.52 g, 56%), which was crystallized from ether as white needles: mp 97.5–98 °C: IR (neat) 1730, 1625 (C=O), 1575 (C=C), 1525, 1346 (NO_2), 852, 791, 765, 745, 703; ^{1}H NMR ($CDCl_3$) 1.8–2.41 (m, 4 H), 3.31 (t, 2 H, J = 7 Hz), 4.74 (t, 1 H, J = 7 Hz, fine coupling J = 2.5 Hz), 7.50–7.98 (m, 3 H), 8.29 (d, 1 H, J = 8 Hz), 9.88 (d, 1 H, J = 2.5 Hz) (minor rotamer 1:4.9, visible at δ 9.45, J = 2.5 Hz); MS, m/e (relative intensity) 248 (low temperature only), 219 (84), 200 (63), 185 (66), 171 (20), 150 (100), 104 (36), 76 (49); $[\alpha]^{36}_D$ −121.40° (*c* 0.049, $CHCl_3$). Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.00; H, 4.88; N, 11.25.

Method B: Swern Oxidation. Dry Me_2SO (2.66 g, 34.05 mmol) in dry CH_2Cl_2 (6.3 mL) was added dropwise over 20 min to a stirred solution of oxalyl chloride (2.14 g, 16.86 mmol) in dry CH_2Cl_2 (15.8 mL), under an argon atmosphere at −45 °C (acetonitrile/dry ice bath). After the mixture was stirred for an additional 15 min, **14** (3 g, 11.99 mmol) in dry CH_2Cl_2 (13 mL) was added dropwise over 45 min. The mixture was stirred for a further 45 min at −45 °C, and triethylamine was then added dropwise over 0.5 h, followed by stirring for a further 15 min at −45 °C. The mixture was allowed to return to room temperature and water added (65 mL). The lower organic phase was separated and dried ($MgSO_4$) and the solvent evaporated in vacuo to afford the crude aldehyde as a yellow oil (3.48 g). The oil was passed over a short pad of silica gel (MCB, SX0143L-1, 100–200 mesh, 18 g) by using 6% $CH_3OH/CHCl_3$. The appropriate fractions were combined and evaporated in vacuo to afford purified aldehyde **3** (R = H) as a pale yellow oil (2.82 g, 95%), $[\alpha]^{36}_D$ − 8.163° (*c*, 0.049, $CHCl_3$).

10-Hydroxy-11-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (21). The nitro aldehyde **3** (R = H) prepared by Swern oxidation (1.19 g, 4.79 mmol) was dissolved in methanol (50 mL) and hydrogenated at atmospheric pressure over 10% Pd–C catalyst (0.49 g, Aldrich Chemical Co., #20,569-9). After 1.5 h, TLC indicated incomplete reaction. A further amount of catalyst (0.41 g) was added and hydrogenation continued until starting material had disappeared. The reaction mixture was then filtered through Celite and the filtrate evaporated in vacuo to afford the *N*-hydroxy compound **21** as a white solid (0.75 g, 63%): mp 177–178 °C (needles from methanol); IR (Nujol) 3212 (OH), 1622 (C=O), 1597 (C=C), 1071, 956, 755, 715; ^{1}H NMR (Me_2SO-d_6) 1.74–2.28 (m, 4 H), 3.0–3.80 (m, 3 H), 3.69 (s, 3 H), 4.70 (d, 1 H J = 9 Hz), 6.98–7.27 (m, 1 H), 7.35–7.67 (m, 3 H), 9.01 (s, 1 H); MS, m/e (relative intensity) 248 (M^+, 12), 216 (93), 199 (100), 187 (69), 171 (98), 162 (70), 148 (67), 130 (67), 117 (52), 104 (76), 90 (55), 82 (55), 76 (63), 70 (55). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.51; N, 11.28. Found: C, 62.90; H, 6.55; N, 11.23.

1,2,3,10,11,11a-Hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (6, R = H). The nitro aldehyde **3** (R = H) prepared by Swern oxidation (0.28 g, 1.13 mmol) was dissolved in methanol (7.5 mL) and hydrogenated at atmospheric pressure over 10% Pd–C catalyst (50 mg, Aldrich Chemical Co., #20,569-9) for 1.5 h, after which TLC indicated conversion to the *N*-hydroxy compound **21**. A further 50 mg of catalyst was added and hydrogenation continued for a further 3 h, after which time TLC indicated a total conversion to the secondary amine **6** (R = H). The reaction mixture was filtered through Celite and evaporated in vacuo to afford the secondary amine **6** as a pale yellow solid (0.16 g, 70%): mp 181–182 °C (colorless plates from ethyl acetate); IR (Nujol) 3325 (NH), 1612 (C=O), 1590 (C=C), 1195, 1155, 895, 840, 738, 695; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6) 1.51–2.45 (m, 4 H), 2.97–3.95 (m, 5 H), 6.25 (br s, NH), 6.47–6.84 (m, 2 H), 7.07–7.27 (m, 1 H), 7.89 (d, 1 H, J = 9 Hz); MS, m/e (relative intensity) 202 (M^+, 19), 133 (18), 104 (35), 77 (25), 70 (100). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.99; N, 13.85. Found: C, 71.13; H, 7.02; N, 13.81. (Similar reductive cyclization of PCC-prepared aldehyde afforded **6** with $[\alpha]^{36}_D$ +339.58° (*c* 0.048, $CHCl_3$).)

(2*S*)-*N*-(2-Nitrobenzoyl)prolines: General Method. DMF (2 drops) was added to a stirred suspension of the 2-nitrobenzoic acid (0.129 mol and oxalyl chloride (19.70 g, 0.155 mol in dry benzene (120 mL) and the stirring continued for a further 3 h. The benzene was evaporated in vacuo and the resultant oil dissolved in dry THF (50 mL) and added dropwise over 1 h to a stirred suspension of (2*S*)-proline (14.9 g, 0.129 mmol), triethylamine (27.3 g, 37.6 mL, 0.27 mol) and ice/water (40 mL), cooled in an ice bath. After the addition was complete, the mixture was warmed to room temperature and stirred for an additional hour. The THF was evaporated in vacuo and the aqueous layer washed with ethyl acetate (1 × 30 mL). The aqueous phase was then adjusted to pH 3 (concentrated HCl) and extracted with ethyl acetate (4 × 50 mL). The combined organic phase was washed with H_2O (3 × 15 mL) and brine (3 × 15 mL), dried ($MgSO_4$), and evaporated in vacuo to afford the corresponding **(2*S*)-*N*-(2-nitrobenzoyl)proline**.

(2*S*)-*N*-[3-(Benzyloxy)-4-methyl-2-nitrobenzoyl]proline: IR (Nujol) 3480–2310 (COOH), 1740, 1630 (C=O), 1532, 1380 (NO_2), 1260, 1220, 1180, 1030, 950, 840, 790, 700; ^{1}H NMR ($CDCl_3$) 1.71–2.67 (m, 4 H), 2.39 (s, 3 H), 3.33–4.0 (m, 2 H), 4.58–4.79 (t, 1 H, J = 7 Hz), 5.03 (d, 2 H, J = 4 Hz), 7.20 (d, 1 H, J = 7 Hz), 7.40 (br s, 6 H); MS, m/e (relative intensity) 384 (M^+, 4), 339 (2), 236 (95), 216 (18), 209 (100), 160 (13), 149 (13), 120 (15), 105 (42), 91 (95), 77 (47); mp 105–112 °C (pale yellow plates from ethyl acetate/hexane); $[\alpha]^{36}_D$ −131.58° (*c* 0.049, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.28. Found: C, 62.63; H, 5.24; N, 7.24.

(2*S*)-*N*-(3-Methyl-2-nitrobenzoyl)proline: IR (Nujol) 3460–2300 (COOH), 1730, 1608 (C=O), 1574 (C=C), 1525, 1355 (NO_2), 1235, 1045, 960, 903, 850, 799, 735; ^{1}H NMR (CD_3CN) 1.71–2.34 (m, 4 H), 2.38 (s, 3 H), 3.40 (t, 2 H, J = 7 Hz), 4.39–4.62 (m, 1 H), 7.30–7.72 (m, 3 H); MS, m/e (relative intensity) 278 (M^+, 15), 233 (85), 217 (18), 188 (13), 164 (100), 148 (25), 135 (31),

(30) **Note added in proof**: During the review of this manuscript, Suggs and co-workers clearly demonstrated that an electron-withdrawing group (e.g., a nitro functionality) in the aromatic ring of a pyrrolo[2,1-c][1,4]benzodiazepine dilactam of type 1 will sufficiently reduce electron density on the N10 nitrogen, to allow smooth sodium borohydride reduction to a stable carbinolamine: Suggs, J. W.; Wang, Y.; Lee, K. S. *Tetrahedron Lett.* **1985**, *26*, 4871.

118 (38), 104 (26), 89 (51); mp 161–162 °C (colorless needles from ethyl acetate/hexane); $[\alpha]^{36}_D$ −197.92 (*c* 0.048, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.06. Found: C, 56.19; H, 5.10; N, 10.01.

(2*S*)-*N*-(5-Methyl-2-nitrobenzoyl)proline: IR (Nujol) 3500–2300 (COOH), 1750, 1600 (C=O), 1525, 1353 (NO_2), 1215, 1185, 855, 839; ^1H NMR ($CDCl_3$) 1.7–2.49 (m, 4 H), 2.49 (s, 3 H), 3.10–3.44 (m, 2 H), 4.82 (t, 1 H, *J* = 7 Hz), 7.19–7.50 (m, 3 H), 8.13 (d, 1 H, *J* = 8 Hz) 10.95 (s, 1 H); MS, *m/e* (relative intensity) 233 (M^+ − COOH, 31), 200 (28), 164 (100), 148 (13), 133 (23), 118 (19), 104 (22), 89 (40), 77 (17), 70 (50); mp 155–155.5 °C (colorless needles from ethyl acetate/hexane); $[\alpha]^{36}_D$ − 87.40° (*c* 0.049, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.06. Found: C, 56.14; H, 5.10; N, 10.05.

(2*S*)-*N*-(6-Methyl-2-nitrobenzoyl)proline: IR (Nujol) 3695–2320 (COOH), 1738, 1593 (C=O), 1540, 1341 (NO_2), 1220, 1183, 1092, 924, 820, 768; ^1H NMR ($CDCl_3$) 1.85–2.40 (m, 4 H), 2.43 (s, 3 H), 3.20 (t, 2 H, *J* = 6 Hz), 4.81–4.98 (m, 1 H), 6.21 (br s, 1 H), 7.37–7.71 (m, 2 H), 8.10 (d, 1 H, *J* = 9 Hz); MS, *m/e* (relative intensity) 278 (M^+, 7), 233 (79), 230 (33), 217 (20), 200 (66), 174 (25), 164 (100), 160 (17), 149 (56), 133 (67), 118 (56), 106 (48), 89 (62); mp 208.5–209 °C (colorless needles from ethyl acetate/hexane); $[\alpha]^{36}_D$ −172.92° (*c* 0.048, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.06. Found: C, 56.10; H, 5.09; N, 10.03.

(2*S*)-*N*-(3-Methoxy-2-nitrobenzoyl)proline: IR (Nujol) 3600–2500 (COOH), 1742, 1640 (C=O), 1580 (C=C), 1532, 1378 (NO_2), 1287, 1175, 1080, 981, 908, 851, 798, 761, 748; ^1H NMR (CD_3CN), 1.68–2.43 (m, 4 H), 3.40 (t, 2 H, *J* = 7 Hz), 3.90 (s, 3 H), 4.35–4.58 (m, 1 H), 6.83–7.75 (m, 3 H); MS, *m/e* (relative intensity) 249 (M^+ − COOH, 61), 180 (100), 167 (18), 150 (23), 135 (18), 119 (20), 106 (51), 92 (18), 76 (59); mp 184 °C (colorless needles from ethyl acetate/hexane); $[\alpha]^{36}_D$ −171.49° (*c* 0.048, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.79; N, 9.51. Found: C, 53.06; H, 4.84; N, 9.49.

Preparation of *N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes Using Bis(triphenylphosphine) Copper Borohydride: General Method. DMF (2 drops) was added to a stirred suspension of the (2*S*)-*N*-(2-nitrobenzoyl)proline (17.97 mmol) and oxalyl chloride (2.74 g, 1.9 mL, 2.59 mmol) in dry benzene (30 mL) and the stirring continued for a further 3 h. The benzene was evaporated in vacuo and the resultant oil dissolved in a solution of triphenylphosphine (10.47 g) in dry acetone (150 mL). This solution was cooled to 0 °C and bis(triphenylphosphine) copper borohydride[24] (13.25 g, 21.97 mmol) was added in small portions over 10 min with vigorous stirring. After the reaction was complete (30 min, TLC) the reaction mixture was filtered and reduced to 50% volume by evaporation in vacuo. The mixture was then filtered and the acetone completely evaporated to afford an oily residue, which was taken up in ethyl acetate (40 mL) and subjected to flash chromatography on silica gel (ethyl acetate) to afford the corresponding aldehyde.

***N*-[3-(Benzyloxy)-4-methyl-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde (22a, 9-OCH_2Ph)**: IR (neat) 1735, 1640 (C=O), 1545, 1361 (NO_2), 1265, 1180, 800, 740, 700; ^1H NMR (200 MHz, $CDCl_3$) 1.69–2.27 (m, 4 H), 2.37 (s, 3 H), 3.26–3.52 (m, 2 H), 4.50–4.62 (m, 1 H), 5.03 (d, 2 H, *J* = 3.1 Hz), 6.97–7.47 (m, 7 H) 9.60 (d, 1 H, *J* = 2.2 Hz); MS, *m/e* (relative intensity) 368 (M^+, 7), 339 (18), 270 (24), 160 (9), 105 (17), 91 (100), 70 (39) (pale yellow oil). Anal. Calcd for $C_{20}H_{20}N_2O_5$: 368.1372. Found: 368.1373.

***N*-(3-Methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (22b)**: IR (neat) 1730, 1630 (C=O), 1578 (C=C), 1525, 1355 (NO_2), 1295, 1179, 1115, 1035, 850, 795, 740, 675; ^1H NMR (CD_3CN) 1.70–2.25 (m, 4 H), 2.40 (s, 3 H), 3.48 (t, 2 H, *J* = 6 Hz), 4.12–4.57 (m, 1 H), 7.18–7.70 (m, 3 H), 9.58 (d, 1 H, *J* = 3 Hz); MS, *m/e* (relative intensity) 262 (M^+, 3), 233 (59), 164 (100), 118 (6), 89 (12); mp 96–97 °C (colorless plates from benzene/ether). Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.63; H, 5.42; N, 10.65.

***N*-(5-Methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (22c)**: IR (Nujol) 1725, 1625 (C=O), 1585 (C=C), 1512, 1340 (NO_2), 910, 830, 758, 729; ^1H NMR ($CDCl_3$) 1.75–2.35 (m, 4 H), 2.48 (s, 3 H), 3.31 (t, 2 H, *J* = 7 Hz), 4.48–4.74 (m, 1 H), 7.18–7.53 (m, 2 H), 8.11 (d, 1 H, *J* = 9 Hz), 9.78 (d, 1 H, *J* = 3 Hz); mp 113–115 °C (colorless plates from benzene/ether). Anal. Calcd for $C_{13}H_{14}N_2O_4 \cdot CH_3OH$: C, 57.12; H, 6.18; N, 9.52. Found: C, 57.11; H, 6.18; N, 9.49.

***N*-(6-Methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (22d)**: IR (Nujol) 1735, 1628 (C=O), 1530, 1380 (NO_2), 1280, 1125, 1075, 810, 740, 730; ^1H NMR ($CDCl_3$) 1.68–2.42 (m, 4 H), 2.51 (s, 3 H), 3.20 (t, 2 H, *J* = 7 Hz), 4.80–5.03 (m, 1 H), 7.26–7.69 (m, 2 H), 8.07 (d, 1 H, *J* = 9 Hz), 9.82 (s, 1 H); MS, *m/e* (relative intensity) 233 (M^+ − CHO, 22), 164 (100), 118 (8), 106 (2), 89 (16); (pale yellow oil). Anal. Calcd for $C_{13}H_{14}N_2O_4$: 262.0954. Found: 262.0957.

***N*-(3-Methoxy-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (22e)**: IR (neat) 1733, 1634 (C=O), 1580 (C=C), 1532, 1365 (NO_2), 1288, 1075, 855, 800, 765, 745; ^1H NMR ($CDCl_3$) 1.68–2.50 (m, 4 H), 3.28–3.63 (m, 2 H), 3.96 (s, 3 H) 4.49–4.73 (m, 1 H) 6.90–7.78 (m, 3 H), 9.70 (d, 1 H, *J* = 2 Hz); MS, *m/e* (relative intensity) 249 (M^+ − CHO, 24), 230 (7), 215 (10), 180 (100), 150 (3), 133 (5), 106 (20), 76 (28); (pale yellow oil).

Reductive Cyclization of *N*-(2-Nitrobenzoyl)-pyrrolidine-2-carboxaldehydes: General Method. A suspension of the nitro aldehyde (1.9 mmol) and 5% Pd-$BaSO_4$ catalyst (0.66 g) in methanol (200 mL) was hydrogenated at atmospheric pressure (hydrogenation time given below). The reaction was monitored by TLC and stopped after the complete disappearance of starting material. In each case the catalyst was removed by passage through Celite and the filtrate worked up to afford either the carbinolamine, carbinolamine methyl ether, or imine forms, as discussed in the text.

Racemic (11*R*,11a*S*)- and (11*S*,11a*S*)-9-hydroxy-11-methoxy-8-methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*c*][1,4]-benzodiazepin-5-ones (23a) and the corresponding carbinolamine and imine forms: IR (mixture of imine, carbinolamine, and methyl ether forms, Nujol) 3500–2300 (NH, OH), 1605 (shoulder at 1615, C=O), 1555, 1195, 1075; ^1H NMR (200 MHz, mixture of imine, 11*S* carbinolamine, 11*S* methyl ether, and corresponding enantiomers, Me_2SO-d_6) 1.78–2.40 (m), 2.18 (s), 2.96–3.79 (m), 3.38 (s, 11*S* OCH_3), 4.43 (d, *J* = 9.45 Hz, methyl ether H11), 4.73 (d, *J* = 9.5 Hz, 11*S* carbinolamine H11), 5.27 (br s, carbinolamine N10 H, exchangeable), 5.69 (br s, 11*S* methyl ether N10 H or phenolic OH, exchangeable), 6.42 (d, *J* = 8.5 Hz, 11*S* carbinolamine Ar), 6.63 (d, *J* = 8.5 Hz, 11*S* carbinolamine Ar), 6.73 (d, *J* = 7.85 Hz, 11*S* methyl ether Ar), 6.95 (d, *J* = 7.89 Hz, 11*S* methyl ether Ar), 7.10 (d, *J* = 8.41 Hz, imine Ar), 7.25 (d, *J* = 8.41 Hz, imine Ar), 7.92 (d, *J* = 4.2 Hz, imine H11) [D_2O exchange caused only a loss of the broad singlets at δ 5.27 and 5.69]; MS (imine), *m/e* (relative intensity) 230 (M^+, 100), 215 (14), 201 (29), 185 (14), 174 (17), 160 (29), 149 (57); mp 75–78 °C (methyl ether form from methanol as a yellow amorphous solid). Anal. Calcd for $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1060. (Reduction time, 30 min; purified yield, 55%.)

Racemic (11*R*,11a*S*)- and (11*S*,11a*S*)-11-methoxy-9-methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-ones (23b) and the corresponding carbinolamine and imine forms: IR (mixture of imine and carbinolamine forms, Nujol) 3675–3020 (OH, NH), 1645 (broad, C=N), 1600 (C=O), 1578 (C=C), 1290, 1240, 1230, 1160, 1130, 1100, 1030, 970, 890, 770, 720; ^1H NMR (imine form, CD_3CN) 1.71–2.51 (m, 4 H), 2.30 (s, 3 H), 2.98–3.88 (m, 3 H), 6.73–7.50 (m, 2 H), 7.58–7.88 (m, 2 H, imine H11 doublet at δ 7.80, *J* = 4 Hz); ^1H NMR (mixture of imine and 11*R* and 11*S* methyl ethers and corrseponding enantiomers, CD_3CN) similar to imine spectrum above but with additional signals at 3.29 (s, 11*R* OCH_3), 3.40 (s, 11*S* OCH_3), 4.38 (d, *J* = 9 Hz, 11*S* H), and 4.61 (d, *J* = 6 Hz, 11*R* H) [ratio of 11*R*:11*S* = 1:1.4] [small amount of carbinolamine visible at δ 4.80 (d, *J* = 9 Hz)], [D_2O exchangeable signals at 5.0 (methyl ether 11*R* and 11*S* N10 H) and 5.75 (carbinolamine 11*R* and 11*S* N10 H)]; ^1H NMR (mixture of 11*R* and 11*S* carbinolamines and methyl ethers and corresponding enantiomers, 3:1 CD_3CN/D_2O) similar to imine spectrum except for the absence of the imine doublet at δ 7.8 and the presence of additional signals at 3.25 (s, 11*S* OCH_3), 3.40 (s, 11*R* OCH_3) 4.45 (d, *J* = 9 Hz, methyl ether 11*S* H), 4.69 (s, methyl ether 11*R* H), 4.87 (d, *J* = 9 Hz, carbinolamine 11*S* H11), 5.13 (s, carbinolamine 11*R* H); MS (imine), *m/e* (relative intensity) 214 (M^+, 90), 199 (10), 185 (20), 171 (5), 158 (12), 144 (9), 131 (5), 117 (29), 90 (41), 70 (100) (imine form as viscous pale yellow oil). Anal. Calcd for $C_{13}H_{14}N_2O$: 214.1106. Found: 214.1102. (Reduction time, 5 min; purified yield, 59%.)

Racemic (11*R*,11a*S*)- and (11*S*,11a*S*)-7-methyl-11-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (23c) and the corresponding carbinolamine and imine forms: IR (mixture of imine, carbinolamine, and methyl ether forms, Nujol) 3700–3015 (OH and NH), 1620, 1600 (broad, C=N, C=O), 1575 (C=C), 1240, 1061, 820, 780; ^{1}H NMR (mixture of imine, 11*R* and 11*S* carbinolamines and 11*R* and 11*S* methyl ethers and corresponding enantiomers, CD_3CN) 1.5–2.34 (m), 2.19, 2.25, and 2.37 (s for C7-CH_3), 3.11–3.90 (m), 3.27 (s, 11*R* OCH_3), 3.38 (s, 11*S* OCH_3), 4.38 (d, J = 9 Hz, 11*S* H), 4.52 (d, J = 6 Hz, 11*R* H) [ratio of 1:1.5], 4.75 (d, J = 9 Hz, carbinolamine, 11*S* H), 4.96 (d, J = 6Hz, carbinolamine, 11*R* H) [D_2O exchangeable signals at 5.23 (methyl ether 11*R* and 11*S* N10 H) and 5.82 (carbinolamine 11*R* and 11*S* N10 H)], 6.50–7.81 (m, Ar), 7.76 (d, J = 4 Hz, imine H11); MS (imine), m/e (relative intensity) 214 (M^+, 100), 198 (3), 185 (41), 171 (10), 158 (25), 144 (10), 131 (15), 117 (54), 104 (10), 89 (67), 77 (21), 70 (99); (imine form as viscous pale yellow oil). Anal. Calcd for $C_{13}H_{14}N_2O$: 214.1106. Found: 214.1098. (Reduction time, 15 min; purified yield, 16%.)

Racemic (11*S*,11a*S*)-6-methyl-11-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (23d) and the corresponding carbinolamine and imine forms: IR (mixture of carbinolamine and methyl ether forms, Nujol) 3650–3100 (OH), 3260 (NH), 1615 (C=O), 1595 (C=C), 1255, 1160, 1069, 720; ^{1}H NMR (imine and 11*S* methyl ether form and corresponding enantiomers, $CDCl_3$) 1.68–2.56 (m, 4 H), 2.43 (methyl ether C7-CH_3), 2.55 (imine C7-CH_3), 3.20–4.08 (m), 3.38 (s, 11*S* OCH_3), 4.35 (d, J = 9 Hz, 11*S* H), 6.43–7.47 (m), 7.78 (d, J = 5 Hz); ^{1}H NMR (mixture of imine, 11*S* carbinolamine, 11*S* methyl ether, and corresponding enantiomers, CD_3CN) 1.65–2.56 (m), 2.38 (s), 3.19–3.95 (m), 3.38 (s, 11*S* OCH_3), 4.35 (dd, J = 9, 2 Hz, methyl ether 11*S* H), 4.48 (br s, carbinolamine 11*S* N10 H), 4.73 (d, J = 9 Hz, carbinolamine 11*S* H), 5.14 (br s, methyl ether 11*S* N10H), 6.65–7.52 (m), 7.83 (d, J = 5 Hz, imine) [exchange with D_2O caused a loss of broad singlets at δ 4.48 and 5.14 and sharpened the doublets at δ 4.48 and 4.73, thus confirming the presence of both 11*S* carbinolamine and 11*S* methyl ether forms and the absence of any 11*R*,11a*S* forms]; ^{1}H NMR (11*S* methyl ether, CD_3CN) 1.68–2.50 (m, 4 H), 2.37 (s, 3 H), 3.0–3.93 (m, 3 H), 3.32 (s, 3 H, 11*S* OCH_3), 4.30 (dd, J = 9, 2 Hz), 5.10 (br s, 1 H methyl ether N10 H), 6.68–7.28 (m, 3 H) [exchange with D_2O caused a loss of the δ 5.10 singlet and a loss of fine coupling on the δ 4.30 doublet]; MS (imine), m/e (relative intensity) 214 (M^+, 70), 185 (16), 158 (22), 145 (7), 131 (8), 118 (28), 104 (4), 90 (37), 70 (100); (imine form as viscous pale yellow oil). Anal. Calcd for $C_{13}H_{14}N_2O$: 214.1106. Found: 214.1113. (Reduction time, 30 min; purified yield, 43%.)

Racemic (11*R*,11a*S*)- and (11*S*,11a*S*)-9,11-dimethoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-ones (23e) and the corresponding carbinolamine and imine forms: IR (methyl ether, Nujol) 3300 (NH), 1610 (C=O), 1570 (C=C), 1379, 1243, 1210, 1080, 749; ^{1}H NMR (11*S*,11a*S* methyl ether and corresponding enantiomer, CD_3CN) 1.65–2.32 (m, 4 H) 2.90–3.70 (m, 3 H), 3.35 (s, 3 H, 11*S* OCH_3), 3.80 (s, 3 H), 4.47 (d, J = 9 Hz, 11*S* H), 5.35 (br s, exchangeable N10 H), 6.55–7.53 (m, 3 H); ^{1}H NMR (mixture of 11*R*,11a*S* and 11*S*,11a*S* carbinolamines and corresponding enantiomers in CD_3CN/D_2O) 1.41–2.23 (m), 3.0–3.72 (m), 3.29 (stoichiometric amount of methanol), 3.82 (s), 4.88 (d, J = 9 Hz, carbinolamine 11*S* H), 5.13 (s, carbinolamine 11*S* H), 6.58–7.48 (m); MS (imine), m/e (relative intensity) 230 (M^+, 100), 215 (91), 199 (63), 187 (15), 171 (24), 160 (41), 146 (34), 133 (71), 117 (30), 106 (56), 95 (8), 92 (19), 83 (6), 76 (59), 70 (76), 63 (29); (imine form as viscous pale yellow oil). Anal. Calcd for $C_{13}H_{14}N_2O_2$: 230.1055. Found: 230.1059. (Reduction time, 30 min; purified yield, 41%.)

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Registry No. **3** (R = H), 72435-93-9; (*S*)-**6** (R = H), 94811-92-4; **7b** (R = H), 100230-77-1; **14** (R = H), 72435-94-0; **15** (R = H), 100230-73-7; (*L*)-**16** (R = H), 100230-74-8; (*L*)-**17** (R = H), 100230-75-9; **19** (R = H), 100230-76-0; **21** (R = H), 100296-62-6; (±)-**22a**, 100230-82-8; (*L*)-**22a** (acid chloride), 100230-98-6; (±)-**22b**, 100243-62-7; (*L*)-**22b** (acid chloride), 100230-99-7; (±)-**22c**, 100230-83-9; (*L*)-**22c** (acid chloride), 100231-00-3; (±)-**22d**, 100230-84-0; (*L*)-**22d** (acid chloride), 100231-01-4; (±)-**22e**, 100243-63-8; (*L*)-**22e** (acid chloride), 100231-02-5; (±)-**23Aa** (R′ = H), 100243-64-9; (±)-**23Aa** (R′ = CH_3), 100296-63-7; (±)-**23Ab** (R′ = H), 100231-04-7; (±)-**23Ab** (R′ = CH_3), 100230-86-2; (±)-**23Ac** (R′ = H), 100231-06-9; (±)-**23Ac** (R′ = CH_3), 100230-89-5; (±)-**23Ad** (R′ = H), 100231-08-1; (±)-**23Ad** (R′ = CH_3), 100230-92-0; (±)-**23Ae** (R′ = H), 100243-65-0; (±)-**23Ae** (R′ = CH_3), 100230-95-3; (±)-**23Ba** (R′ = H), 100231-03-6; (±)-**23Ba** (R′ = CH_3), 100296-64-8; (±)-**23Bb** (R′ = H), 100231-05-8; (±)-**23Bb** (R′ = CH_3), 100230-87-3; (±)-**23Bc** (R′ = H), 100231-07-0; (±)-**23Bc** (R′ = CH_3), 100230-90-8; (±)-**23Bd** (R′ = H), 100231-09-2; (±)-**23Bd** (R′ = CH_3), 100230-93-1; (±)-**23Be** (R′ = H), 100231-10-5; (±)-**23Be** (R′ = CH_3), 100230-96-4; (±)-**24a**, 100230-85-1; (±)-**24b**, 100230-88-4; (±)-**24c**, 100230-91-9; (±)-**24d**, 100230-94-2; (±)-**24e**, 100230-97-5; **27a**, 100296-65-9; **27b**, 100231-11-6; **27c**, 100231-12-7; **27d**, 100231-13-8; **27e**, 100231-14-9; 2-$O_2NC_6H_4COCl$, 610-14-0; 2-nitro-3-(phenylmethoxy)-4-methylbenzoic acid, 6623-31-0; 2-nitro-3-methylbenzoic acid, 5437-38-7; 2-nitro-5-methylbenzoic acid, 3113-72-2; 2-nitro-6-methylbenzoic acid, 13506-76-8; 3-methoxy-2-nitrobenzoic acid, 4920-80-3; 2-nitro-3-methylbenzoyl chloride, 50424-93-6; 2-nitro-5-methylbenzoyl chloride, 38818-49-4; 2-nitro-6-methylbenzoyl chloride, 66232-57-3; 3-methoxy-2-nitrobenzoyl chloride, 15865-57-3; (2*S*)-proline, 147-85-3; 3-(phenylmethoxy)-4-methyl-2-nitrobenzoyl chloride, 7536-35-8; (2*S*)-pyrrolidinemethanol, 23356-96-9; (2*S*)-*N*-[3-(benzyloxy)-4-methyl-2-nitrobenzoyl]proline, 18944-44-0; (2*S*)-*N*-(3-methyl-2-nitrobenzoyl)proline, 100230-78-2; (2*S*)-*N*-(5-methyl-2-nitrobenzoyl)proline, 100230-79-3; (2*S*)-*N*-(6-methyl-2-nitrobenzoyl)proline, 100230-80-6; (2*S*)-*N*-(3-methoxy-2-nitrobenzoyl)proline, 100230-81-7.