A Versatile and Efficient Synthesis of Carbinolamine-Containing Pyrrolo[1,4]benzodiazepines via the Cyclization of *N*-(2-Aminobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetals: Total Synthesis of Prothracarcin

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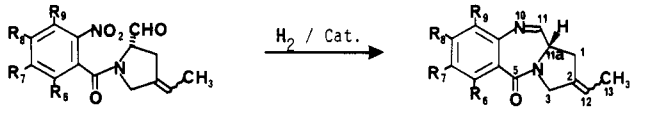
A versatile and efficient synthesis of carbinolamine-containing pyrrolo[1,4]benzodiazepines (or the corresponding imine forms) of types **2**, **7**, and **8** is described that involves mercuric chloride mediated cyclization of the corresponding *N*-(2-aminobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetals. This new synthesis has significant advantages over previously existing methods in that (a) catalytic hydrogenation is not involved in the cyclization process, thus allowing preservation of unsaturation in the product, (b) all steps are mild and take place in high yields, (c) the success of the reaction is apparently independent of substituent effects, (d) the reaction proceeds with retention of stereochemistry at the aldehyde-bearing carbon, and (e) it can be readily adapted for the convergent synthesis of a variety of analogues. In addition to the synthesis of some model carbinolamine-containing compounds, the overall utility of this procedure is demonstrated by the total synthesis of prothracarcin (**2d**), a natural product with antitumor activity from *Streptomyces umbrosus*. This allowed confirmation of the *E* configuration previously assigned to the C2-ethylidene side chain of prothracarcin.

There is presently an interest in both the synthetic aspects and the mechanism of the biological activity of the carbinolamine-containing pyrrolo[1,4]benzodiazepine group of antitumor antibiotics, members of which include anthramycin, tomaymycin the neothramycins A and B, sibiromycin, mazethramycin, chicamycin, prothracarcin, DC-81, and possibly dextrochrysin.[1] The antitumor activity of these compounds is thought to be associated with covalent binding to N2 of guanine within the minor groove of DNA,[2] and in the case of anthramycin, the precise structure of the drug–DNA adduct has been elucidated.[3] More recently, fluorescence studies have been carried out on the tomaymycin–DNA adduct[4] and investigations into the DNA sequence specificity of these compounds have been reported.[5] A rational approach to the development of clinically useful drugs in this series has been suggested,[6] and a few groups, including our own,[7,8] have embarked upon the investigation of synthetic methodologies for the preparation of rationally designed analogues for SAR studies.

The synthesis of compounds in this group is usually problematic, due to the lability of the N10–C11 carbinolamine functionality, which is typically incorporated at the last step of the synthetic sequence. Prior to 1984, there were two major synthetic routes in the literature, the carbinolamine-forming steps involving (a) hydride reduction of a cyclic dilactam[9] or (b) reductive cyclization of an acyclic nitro aldehyde.[10-12] The generality and scope of both these reactions were recently investigated in our laboratory.[7,8] In 1983, Kaneko and co-workers[13] reported an alternative approach (c) involving the aluminum–amalgam reduction of imino thioethers, and work carried out by other groups has led, more recently, to the development of two new techniques involving (d) the cyclization of amino acetals[14,15] and (e) the cyclization of N-protected amino aldehydes.[15] These routes were recently reviewed in more detail.[8]

Unfortunately, most of these synthetic methods suffer from limitations. For example, the success of route (a) is entirely dependent on the type and pattern of substituents in the aromatic ring,[7,16] and route (b), which involves hydrogenolysis results in low yields, can lead to loss of unsaturation in the product and is limited to certain sub-

Scheme I



1a-d 2a-d

a : R_6-R_9 = various substituents
b : R_6=R_9 = H; R_7 = OCH_3; R_8 = OBz
c : R_6=R_9 = H; R_7 = OCH_3; R_8 = OH
d : R_6-R_9 = H

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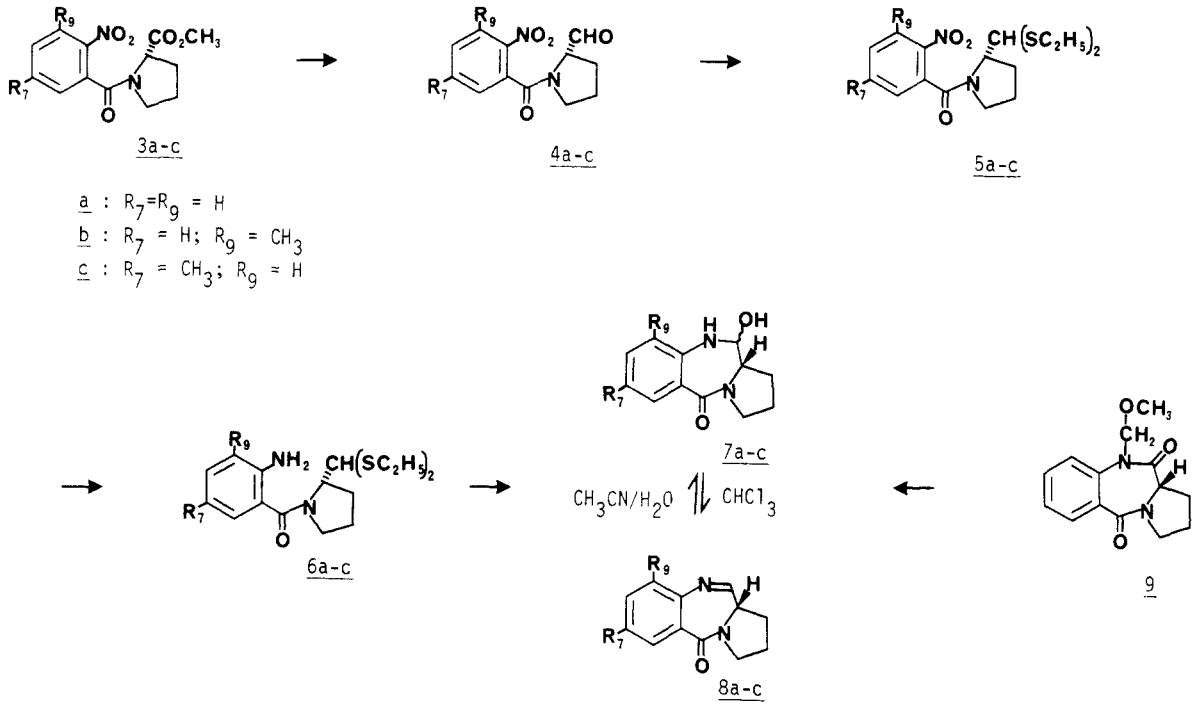
Scheme II



stituent types and patterns in the aromatic ring.[8] Route (c) provides reasonable overall yields although it requires at least four extra steps from the same dilactam used in route (a). Finally, exposure of an amino aldehyde (produced in situ) to low pH, as in route (d), can lead to racemization at the C11a position of the product[17] (vide infra). For example, one limitation of route (b) was recently encountered during an attempt to synthesize analogues of type **2a**, from nitro aldehyde precursors of type **1a** (Scheme I). Even though poisoned catalyst was used (5% Pd–$BaSO_4$), the exocyclic double bond was partially reduced after 5 min and prior to carbinolamine formation.[18] This was surprising, as Tozuka and co-workers have reported the total synthesis of tomaymycin (**2c**) and related analogues in high yield (~70%), using identical reduction conditions for **1b**.[11,12] However, variable catalyst activity could explain this anomaly.[8] Furthermore, we could not use route (a) because of the type of substituents in the aromatic ring, and racemization at the aldehyde-bearing carbon had been observed during attempts to cyclize amino dimethyl acetal precursors via route (d).[17] We were particularly concerned about racemization at C11a, as this could adversely affect the DNA-binding potential of the product.[6]

For these reasons we felt that it was necessary to develop a new cyclization technique that (1) was generally applicable and not dependent on the type or pattern of ring substituents, (2) proceeded in high yield, (3) involved nonhydrogenolytic conditions, thereby preserving unsaturation, and (4) retained stereochemical integrity at C11a of the product. The cyclization process described below meets all of these criteria and, in addition, can be adapted for convergent syntheses.

Results and Discussion

The essential requirements of such a reaction sequence are reduction of a nitro group to an amino functionality under nonhydrogenolytic conditions and careful formation, protection, and deprotection of an aldehyde in a mild and nonracemizing environment. Preliminary experiments demonstrated that nitro aldehydes of type **4**, prepared by diisobutylaluminum hydride (Dibal) reduction[19] of the corresponding nitro esters of type **3**, form diethyl thioacetals of type **5** by stirring at room temperature with ethanethiol and trimethylsilyl chloride in chloroform[20] for 16–48 h. These stable intermediates could then be smoothly reduced by refluxing for 1–2 h with stannous chloride dihydrate in methanol,[21] to afford the corresponding amino diethyl thioacetals of type **6**, in nearly quantitative yield. Efficient deprotection with concomitant cyclization to the carbinolamines **7** was then effected by treatment at room temperature with mercuric chloride and calcium carbonate in acetonitrile/water[22] for 12–48 h (Scheme II). The products, however, were usually isolated in the imine form **8**, because of the workup procedure that involved extraction into chloroform.[23] The procedure was tested on three model nitro aldehydes **4a–c**, which afforded, over three steps, the cyclized imines **8a–c**, in overall yields of 53%, 72%, and 68%, respectively. In each case, apart from a trace amount of starting material, the final products were clean and consisted of single components as visualized by TLC. The fact that cyclization took place with both substituted and unsubstituted aromatic rings is significant, as other synthetic methods usually fail in one or the other case.[7,8,16] Furthermore, we were able to demonstrate, conclusively, preservation of stereochem-

(17) Evidence from this laboratory suggests that acid-catalyzed deprotection of amino acetals of this type can lead to racemization at the aldehyde-bearing carbon (unpublished data). In addition, Ito and coworkers[19] have shown that similar amino acetals undergo racemization at temperatures above 40 °C and/or on prolonged contact with silica gel. Mazzocchi and Schuda recently reported[14] the use of trimethylsilyl iodide to accomplish this deprotection but did not address the stereochemistry at C11a.

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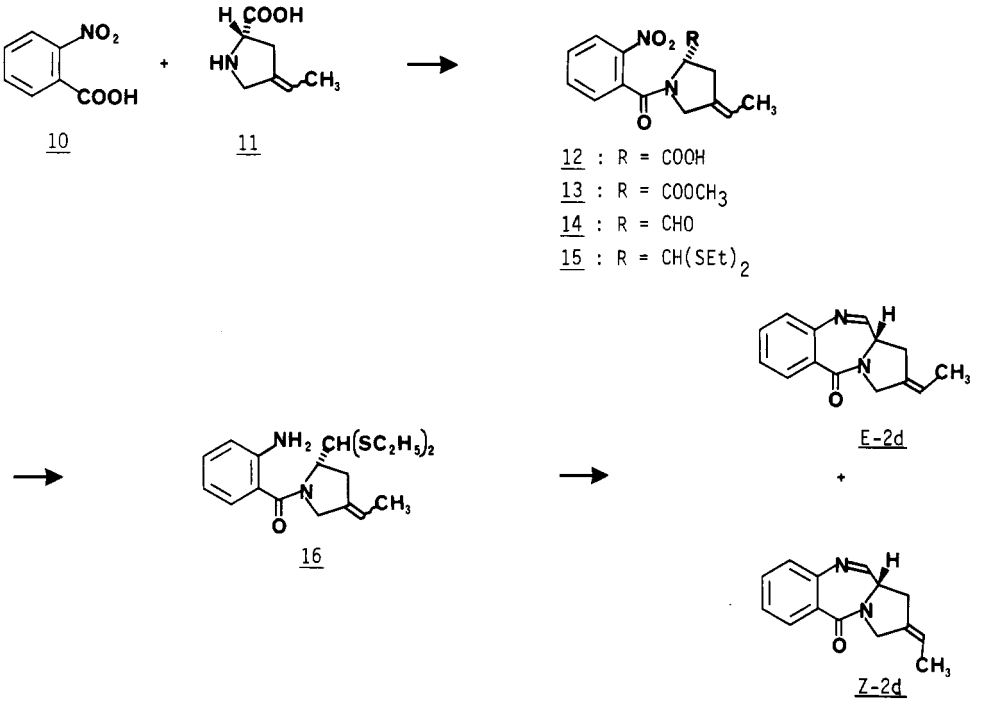
(23) Pyrrolo[1,4]benzodiazepines of this type may exist in either the carbinolamine, carbinolamine methyl ether or imine forms (or a mixture thereof), depending on the final workup and isolation procedure. For a detailed discussion of these interconversions, see ref 8.

Scheme III



istry at the aldehyde-bearing carbon during diethyl thioacetal formation and subsequent deprotection. The nitro aldehyde **4a**, prepared via Dibal reduction of the corresponding methyl ester **3a** and shown to have an optical rotation of $[\alpha]^{25}_D$ −146.9, was treated with ethanethiol and trimethylsilyl chloride in chloroform, to afford the nitro diethyl thioacetal **5a**, which had an optical rotation of $[\alpha]^{25}_D$ −209.8. Treatment of **5a** with $HgCl_2/CaCO_3/H_2O/CH_3CN$ regenerated the nitro aldehyde **4a** with an optical rotation of $[\alpha]^{25}_D$ −146.1, demonstrating that negligible racemization had occurred.

It is noteworthy that, during the course of this work, Mori and co-workers[24] reported that the imine form **8a** of the carbinolamine **7a** could be prepared in high yield (80%) via reduction of the *N*-methoxymethyl-protected dilactam **9** with $NaBH_4$ in CH_3OH at 0 °C, followed by silica gel chromatography. It was also suggested that this method may be of general synthetic utility for the preparation of carbinolamine-containing pyrrolo[1,4]benzodiazepines. Unfortunately, after the N-protected dilactam **9** was prepared, it failed, in our hands, to reduce to the carbinolamine **7a** or the corresponding imine **8a**, using either the reported conditions or a number of variations. However, Mazzocchi and Schuda recently reported[14] a multistep synthesis of **8a**, starting with a pyrrolobenzazepinedione ring system, obtained via a novel photostimulated ring expansion. The final carbinolamine-forming step involved trimethylsilyl iodide mediated deprotection of the corresponding amino acetal, although optical activity of the final product was not reported.

As a demonstration of the utility of the diethyl thioacetal procedure, particularly with respect to the ability to preserve unsaturation in the final product, it was applied to the total synthesis of prothracarcin (**2d**), a carbinolamine-containing pyrrolo[1,4]benzodiazepine with antitumor activity, isolated from *Streptomyces umbrosis* in 1982.[25] It is structurally similar to tomaymycin,[11] possessing an identically substituted pyrrolidine ring but lacking substitution in the aromatic ring. However, Shimizu and co-workers[25] did not cite definitive evidence for their assignment of the *E* configuration to the C2-ethylidene side chain.

Table I. Comparison of Diagnostic ^{1}H NMR Data (δ) for the Synthetic Prothracarcin, the Synthetic Unnatural *Z* Isomer, and the Natural Product[25a]

	synthetic[a]		
	E	*Z*[c]	natural[b,25]
13-CH_3	1.75 (d)[d]	1.70 (d)[e]	1.75
H1's	2.98 (d)[f]	α-2.90 (d),[g] β-3.09 (d)[g,h] (AB q)	2.97
H11a	3.92 (q)[i]	3.82–3.87 (m)	3.91
H3's	4.18–4.4 (m)[j]	4.17 (d),[k] 4.39 (d)[k] (AB q)	4.28
H12	5.53–5.67 (m)	5.53–5.67 (m)	5.61
H11	7.78 (d)[l]	7.78 (d)[m]	7.78

[a] $CDCl_3$ at 360 MHz. [b] Signal multiplicities and instrument frequency not reported. [c] Slight contamination with *E* isomer. [d] J = 6.9 Hz. [e] J = 6.2 Hz. [f] J = 5.2 Hz. [g] J = 16 Hz. [h] Fine coupling of approximately 4 Hz into C11a confirms the β configuration of this proton. [i] J = 5.8 Hz. [j] This signal appears as a doublet (4.28, J = 9.1 Hz) in an NMR of a mixture of *E* and *Z* isomers. [k] J = 16.1 Hz. [l] J = 4.4 Hz. [m] J = 3.7 Hz.

The synthesis began by coupling 2-nitrobenzoic acid (**10**) to a mixture (1:1.6) of (*E*)- and (*Z*)-(2*S*)-4-ethylidenepyrrolidine-2-carboxylic acids (**11**), prepared via a modification of the method of Tozuka,[11] to afford a mixture of *E* and *Z* nitro acids **12** (Scheme III). Continuation through intermediates **13–16**, using the reactions described above, then afforded a mixture of prothracarcin (**2d**) and the unnatural *Z* isomer (1:1.6), which was separated by thin-layer chromatography on silica gel, with benzene/acetone (3:2) as eluant. The chemical shift of the ethylidine methyl group for the lower R_f component was identical (δ 1.75) with that reported by Shimizu[25] for the natural product (Table I). Furthermore, the H1 and H3 protons for this component were identical in their ^{1}H NMR coupling patterns to the equivalent protons in tomaymycin, the *E* configuration of which has been established from X-ray data.[26] On this basis, we were able to assign the

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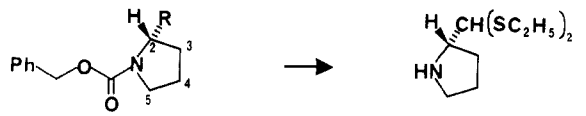
Scheme IV



17 : R = CO_2CH_3
18 : R = CHO
19 : R = $CH(SEt)_2$

20

E configuration to the lower R_f synthetic component and thus to the natural product, thereby confirming the original assignment of Shimizu.[25] This similarity in the configuration of the ethylidene-substituted pyrrolidine rings would tend to suggest a common biosynthetic precursor for both prothracarcin and tomaymycin.[27]

The synthetic isomer of higher R_f was assigned the *Z* configuration as the ethylidene methyl group had a lower chemical shift (δ 1.70), and the H1 and H3 signals appeared as AB quartets instead of the doublets (J = 10 Hz) observed for tomaymycin and prothracarcin. Additional evidence for the above assignments was obtained through comparison of our ^{1}H NMR data with spectra provided by Mazzocchi and Schuda, who had previously synthesized a mixture of prothracarcin and the corresponding unnatural *Z* isomer, by an alternative route.[14,28] These workers had assigned the *E* configuration to that component of their synthetic mixture that matched the natural product, on the basis of ^{13}C chemical shift predictions. Attempts in this laboratory to obtain further supporting evidence through NOE difference experiments were unhelpful, as although a strong NOE effect was observed between the ethylidine methyl and vinylic protons for both *E* and *Z* isomers, neither the H1 or H3 protons of either isomer showed an NOE effect into the corresponding ethylidine methyl groups.

Although mass spectral and infrared data were also consistent with those reported by Shimizu, the optical rotation of our purified *E* isomer [$[\alpha]^{33}_D$ +213.0 (*c* 0.395, EtOAc[29])] was significantly higher than that reported for the natural product [$[\alpha]^{22}_D$ +17.1 (*c* 0.1, EtOAc)]. One explanation for this anomaly is that racemization may have occurred during isolation of the natural product. However, the isolation conditions reported[25] appear to be mild and do not involve the use of silica gel or extremes of pH or temperature.

Of further interest is the potential of this route to be adapted for a convergent approach to the synthesis of a series of analogues. For example, (2*S*)-pyrrolidine-2-carboxaldehyde diethyl thioacetal (**20**) was prepared in bulk, via deprotection of the *N*-Cbz derivative **19**, derived from intermediates **17** and **18**[19] (Scheme IV). After coupling to a 2-nitrobenzoyl derivative, an efficient conversion to a carbinolamine-containing product may then be achieved in two high-yielding steps. For example, **20** was coupled to the nitro acid **10**, to afford **5a** (92% yield), which had an optical activity ($[\alpha]^{25}_D$ −204.5) similar to that of the material prepared by linear synthesis ($[\alpha]^{25}_D$ −209.8). Continuation of the synthesis through **6a** afforded the final product **8a** in 69% overall yield from **20**. The 4-keto derivative of **19** has also been prepared and will be utilized for the convergent synthesis of novel pyrrolo[1,4]benzodiazepines with side chains at the C2 position.

In conclusion, we report a new synthetic procedure for the preparation of carbinolamine-containing pyrrolo[1,4]benzodiazepines, involving mercuric chloride mediated cyclization of amino diethyl thioacetals. This method has significant advantages over existing techniques, particularly with respect to the insensitivity toward substituent types and patterns in the aromatic ring, the retention of stereochemistry at the aldehyde-bearing carbon, the preservation of unsaturation in the final product, the high yields obtained, and the adaptability to a convergent approach. This methodology has allowed us to synthesize the antitumor antibiotic prothracarcin and confirm the *E* configuration of the C2-ethylidene side chain.

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 (^{1}H NMR) spectra, unless otherwise stated, were recorded on a Varian Associates Model EM-390 spectrometer. A few spectra were recorded on Nicolet NT-200 (200 MHz) or NT-360 (360 MHz) spectrometers 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 (Hz), and spin multiplicities are described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), or AB q (AB quartet). Low-resolution mass spectral (MS) data were obtained by using electron ionization (EI) on a Du Pont 21-491 spectrometer coupled to an Incos data system. High-resolution MS data were obtained on a Du Pont 21-110B spectrometer using EI and the same data system. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter and are reported in the text for solutions in $CHCl_3$ unless otherwise stated. Flash chromatography, when necessary, was performed according to the method of Still[30] using Sigma chromatographic grade 230–240 mesh silica gel (No. S-0507). Reversed-phase analytical HPLC (RP-HPLC) and preparative medium-pressure HPLC (MP-HPLC) were carried out using PRP-1 (No. 79426, #202, Hamilton, Reno, NV) and RP-8 (Lobar LiChroprep, size B (310-25) 40–63 μm, EM Reagents) columns, respectively. All solvents were dried and distilled prior to use.

I. General Synthetic Procedures. (2*S*)-*N*-(2-Nitrobenzoyl)prolines. These were prepared according to the method of Thurston and Langley.[8]

Methyl (2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxylates. DMF (2 drops) was added to a stirred suspension of the *N*-(2-nitrobenzoyl)proline (37.84 mM, 1 equiv) and oxalyl chloride (45.41 mM, 1.2 equiv) in dry benzene (100 mL) and the stirring continued for a further 3 h. Dry methanol (100 mL) was added and the resulting mixture stirred for a further 1 h. The solvent was removed by evaporation in vacuo and the residue dissolved in ethyl acetate (100 mL), which was extracted with saturated $NaHCO_3$ solution (2 × 50 mL) and brine (2 × 25 mL), dried ($MgSO_4$), and evaporated in vacuo to afford the methyl ester.

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes. (i-Bu)$_2$AlH solution (38.72 mL of a 1 M solution in hexane, 38.72 mM, 2.02 equiv) was added dropwise over a period of 30 min to a vigorously stirred solution of the methyl (2*S*)-*N*-(2-nitrobenzoyl)pyrrolidine-2-carboxylate (19 mM, 1 equiv) in anhydrous toluene (150 mL), under dry argon at approximately −78 °C (dry ice/acetone bath). After the mixture was stirred for an additional 30 min, excess reagent was decomposed by careful addition of methanol (50 mL) followed by 5% HCl (150 mL). The resulting mixture was allowed to warm to 0 °C and the organic layer removed. The aqueous layer was extracted with ethyl acetate (4 × 60 mL), the organic layers were combined, washed with brine (2 × 50 mL), and dried ($MgSO_4$), and the solvent was evaporated in vacuo (below 40 °C) to afford the crude aldehyde, which was usually used directly in the next step.

(26) Arora, S. K. *J. Antibiot.* **1981**, *34*, 462.
(27) Hurley, L. H. *Acc. Chem. Res.* **1980**, *13*, 263.
(28) Schuda, A. D. Ph.D. Thesis, University of Maryland, 1984.
(29) The optical rotation of isomer (*E*)-**2d** in chloroform was $[\alpha]^{23}_D$ +241.5 (*c* 0.4).
(30) Clark Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetals. Ethanethiol (3.95 mM, 2.2 equiv) was added to a stirred solution of the nitro aldehyde (1.8 mM, 1 equiv) in dry $CHCl_3$ (3 mL) under a nitrogen atmosphere. The mixture was stirred for a further 30 min, followed by the addition of trimethylsilyl chloride (4.5 mM, 2.5 equiv). After a further 16–24 h of stirring under nitrogen, or when TLC indicated that reaction was complete, the reaction mixture was carefully neutralized with saturated $NaHCO_3$ solution and then extracted with water (3 × 10 mL). The combined aqueous phase was back-extracted with $CHCl_3$ (10 mL) and the combined organic phase dried ($MgSO_4$) and evaporated in vacuo to afford the diethyl thioacetal, which was purified by flash chromatography on silica gel.

(2*S*)-*N*-(2-Aminobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetals. A solution of the nitro diethyl thioacetal (0.82 mM, 1 equiv) and stannous chloride dihydrate (4.1 mM, 5 equiv) in methanol (3 mL) was refluxed for 1.5 h, or until TLC indicated that reaction was complete. The reaction mixture was carefully adjusted to pH 8 with saturated $NaHCO_3$ solution and then extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford the crude amino diethyl thioacetal, which was usually carried through directly to the next step.[31]

(11a*S*)-1,2,3,11a-Tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-ones. A solution of the amino diethyl thioacetal (0.50 mM, 1 equiv), mercuric chloride (1.12 mM, 2.2 equiv), and calcium carbonate (1.26 mM, 2.5 equiv) in 5 mL of CH_3CN/H_2O (4:1) was stirred at room temperature for 12–48 h, or until TLC indicated that reaction was complete. The reaction mixture was diluted with ethyl acetate (15 mL) and centrifuged at 10000 rpm for 5 min and the supernatant decanted and extracted with saturated $NaHCO_3$ solution (2 × 10 mL) and brine (2 × 10 mL). The combined aqueous phase was back-extracted with ethyl acetate (2 × 10 mL) and the combined organic phase dried ($MgSO_4$), filtered through a short pad of Celite, and evaporated in vacuo to afford the imine, usually as a yellow oil, which in most cases was further purified by reversed-phase MP-HPLC using an aqueous solvent system. The appropriate carbinolamine-containing fractions were then extracted with $CHCl_3$ to afford, after drying ($MgSO_4$) and evaporation, the pure imine form.[23]

II. Model Compounds. (2*S*)-*N*-(2-Nitrobenzoyl)prolines. (2*S*)-*N*-(2-Nitrobenzoyl)proline, (2*S*)-*N*-(3-methyl-2-nitrobenzoyl)proline, and (2*S*)-*N*-(5-methyl-2-nitrobenzoyl)proline have been previously reported.[8]

Methyl (2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxylate (3a): IR (neat) 1740, 1645 (C=O), 1575 (C=C), 1480, 1422, 1530 and 1350 (NO_2), 1243, 1200, 1173, 1045, 855, 790, 752, 745, 702; ^1H NMR (200 MHz, $CDCl_3$) δ 1.86–2.47 (m, 4 H), 3.18–3.47 (m, 2 H), 3.57 and 3.81 (s, 3 H, minor and major rotamers of $COOCH_3$, 1:3), 4.76 (dd, *J* = 8 and 4.4 Hz), 7.34–7.82 (m, 3 H), 8.18 (d, *J* = 8.5 Hz, 1 H); MS, *m/e* (relative intensity) 278 (M^+, 2), 219 (62), 150 (100), 134 (7), 128 (7), 120 (5), 104 (15), 92 (7), 76 (24); pale yellow oil; 95% yield; TLC, hexane/EtOAc 1:4. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.10; H, 5.05; N, 9.92.

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes. (2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**4a**), *N*-(3-methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**4b**), and *N*-(5-methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**4c**) have been previously reported.[8] Racemic nitro aldehydes **4b** and **4c** were prepared via bis(triphenylphosphine)copper borohydride reduction of the corresponding carboxylic acids. **4a**, previously prepared by pyridinium chlorochromate oxidation of the corresponding nitro alcohol [$[\alpha]^{25}_D$ −121.4 (*c* 0.049, $CHCl_3$)], was resynthesized for this work, via Dibal reduction of the methyl ester **3a**: 89% yield; TLC, hexane/EtOAc 1:4; $[\alpha]^{36}_D$ −146.9 (*c* 0.049, $CHCl_3$).

(2*S*)-*N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (5a): IR (neat) 2960, 2920, 2865, 1632 (C=O), 1570 (C=C), 1480, 1418, 1522 and 1345 (NO_2), 1310, 1260, 1205, 1153, 968, 845, 785, 760, 735, 698; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.5 Hz, 6 H), 1.54–2.43 (m, 4 H), 2.58–2.98 (m, 4 H), 3.16–3.41 (m, 2 H), 4.55–4.78 (m, 1 H), 4.81 (d, *J* = 3.5 Hz, 1 H), 7.25–7.82 (m, 3 H), 8.13 (d, *J* = 8 Hz, 1 H); MS, *m/e* (relative intensity) 354 (M^+, 20), 325 (21), 293 (1), 219 (34), 200 (4), 189 (18), 150 (100), 143 (4), 135 (50), 120 (71), 104 (7), 97 (2), 92 (13), 83 (44), 78 (12), 76 (10); pale yellow oil; $[\alpha]^{33}_D$ −209.8 (*c* 0.041, $CHCl_3$); 70% yield; TLC, acetone/$CHCl_3$ 1:19. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2$: 354.1072. Found: 354.1083.

***N*-(3-Methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (5b):** IR (neat) 2960, 2920, 2860, 1630 (C=O), 1575 (C=C), 1425, 1400, 1522 and 1355 (NO_2), 1260, 1178, 1030, 968, 850, 825, 780, 738; ^1H NMR ($CDCl_3$) δ 1.16–1.47 (t, *J* = 8 Hz, 6 H), 1.53–2.37 (m, 4 H), 2.15 and 2.44 (s, 3 H, minor and major aromatic methyl rotamers), 2.57–2.94 (q, *J* = 8 Hz, 4 H), 3.31–3.58 (m, 2 H), 4.48–4.73 (m, 1 H), 4.80 (d, *J* = 4 Hz, 1 H), 7.25–7.67 (m, 3 H); MS, *m/e* (relative intensity) 368 (M^+, 8), 339 (5), 307 (5), 277 (4), 245 (2), 233 (82), 203 (6), 164 (100), 148 (8), 135 (49), 118 (13), 107 (13), 90 (25); pale yellow oil; 98% yield; TLC, acetone/$CHCl_3$ 1:19. Anal. Calcd for $C_{17}H_{24}N_2O_3S_2$: 368.1228. Found: 368.1220.

***N*-(5-Methyl-2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (5c):** IR (neat) 2960, 2920, 2860, 1635 (C=O), 1585 (C=C), 1420, 1518 and 1346 (NO_2), 1310, 1260, 1187, 965, 840, 823, 755; ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.5 Hz, 6 H), 1.47–2.35 (m, 4 H), 2.39 (s, 3 H), 2.52–2.90 (m, 4 H), 2.98–3.39 (m, 2 H), 4.49–4.75 (m, 1 H), 4.79 (d, *J* = 3.5 Hz, 1 H), 7.13–7.45 (m, 2 H), 8.03 (d, *J* = 8 Hz, 1 H); MS, *m/e* (relative intensity) 368 (M^+, 30), 339 (19), 307 (43), 277 (14), 261 (3), 233 (100), 214 (5), 203 (19), 200 (22), 187 (19), 174 (14), 164 (95), 148 (43), 135 (78), 118 (51), 114 (27), 107 (46), 97 (11), 89 (57), 70 (41), 65 (54); pale yellow oil; 89% yield; TLC, acetone/$CHCl_3$ 1:19. Anal. Calcd for $C_{17}H_{24}N_2O_3S_2$: 368.1228. Found: 368.1238.

(2*S*)-*N*-(2-Aminobenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (6a): IR (neat) 3440 and 3340 (NH_2), 2960, 2920, 2860, 1610 (C=O), 1580 (C=C), 1487, 1445, 1408, 1310, 1260, 1203, 1151, 965, 860, 748; ^1H NMR ($CDCl_3$) δ 1.09–1.48 (m, 6 H), 1.53–2.48 (m, 4 H), 2.50–2.92 (m, 4 H), 3.38–3.78 (m, 2 H), 4.47–4.98 (m, 3 H), 6.56–6.82 (m, 2 H), 7.03–7.37 (m, 2 H); MS, *m/e* (relative intensity) 324 (M^+, 7), 295 (1), 200 (4), 189 (32), 120 (100), 97 (2), 92 (22), 83 (7), 65 (12); pale yellow oil; $[\alpha]^{22}_D$ −207.7 (*c* 0.2672, $CHCl_3$); 93% yield; TLC, EtOAc. Anal. Calcd for $C_{16}H_{24}N_2OS_2$: 324.1330. Found: 324.1337.

***N*-(2-Amino-3-methylbenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (6b):** IR (neat) 3450 and 3350 (NH_2), 2950, 2915, 2860, 1608 (C=O), 1560 (C=C), 1400, 1258, 1180, 1150, 1118, 1072, 750; ^1H NMR ($CDCl_3$) δ 1.10–1.45 (m, 6 H), 1.48–2.40 (m, 4 H), 2.15 (s, 3 H), 2.48–3.0 (m, 4 H), 3.34–3.80 (m, 2 H), 4.24 (d, *J* = 4.5 Hz, 1 H), 4.38–5.0 (m, 3 H), 6.65 (t, *J* = 7.5 Hz, 1 H), 7.0–7.24 (m, 2 H); MS, *m/e* (relative intensity) 338 (M^+, 4), 309 (3), 279 (3), 215 (2), 203 (44), 187 (1), 167 (10), 149 (27), 134 (100), 106 (15), 91 (2); yellow oil; 90% yield; TLC, EtOAc. Anal. Calcd for $C_{17}H_{26}N_2OS_2$: 338.1487. Found: 338.1496.

***N*-(2-Amino-5-methylbenzoyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (6c):** IR (neat) 3438 and 3340 (NH_2), 3220, 2960, 2920, 2860, 1620, (C=O), 1580 (C=C), 1495, 1415, 1332, 1300, 1260, 1185, 1153, 1120, 1048, 968, 812; ^1H NMR ($CDCl_3$) δ 1.08–1.48 (m, 6 H), 1.51–2.30 (m, 4 H), 2.19 (s, 3 H), 2.47–2.90 (m, 4 H), 3.35–3.72 (m, 2 H), 4.46–4.91 (m, 4 H), 6.59 (d, *J* = 7.5 Hz, 1 H), 6.84–7.10 (m, 3 H); MS, *m/e* (relative intensity) 338 (M^+, 11), 309 (8), 278 (3), 215 (13), 203 (95), 187 (5), 134 (100), 106 (61), 91 (5), 83 (45), 79 (34), 77 (26), 70 (13); yellow oil; 96% yield; TLC, EtOAc. Anal. Calcd for $C_{17}H_{26}N_2OS_2$: 338.1487. Found: 338.1493.

(11a*S*)-1,2,3,11a-Tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one (8a): IR (neat) 3310 (carbinolamine form), 2970, 2875, 1610 (C=O), 1570, 1480, 1450, 1412, 1240, 1160, 1105, 1020, 878, 867, 834; ^1H NMR ($CDCl_3$) δ 1.6–2.48 (m, 4 H), 3.28–3.90 (m, 3 H), 7.10–7.62 (m, 3 H), 7.72 (d, *J* = 4.6 Hz, 1 H), 8.0 (d, *J* = 6 Hz, 1 H, fine coupling of 1 Hz) (CD_3OD shake caused a loss of the C11 imine signal at δ 7.72 and the appearance of a doublet (δ 4.38, *J* = 9 Hz) and singlet (δ 4.51) for the C11 protons of the 11*R* and 11*S* methyl ether forms); MS, *m/e* (relative intensity) 200 (M^+, 17), 189 (2), 171 (11), 145 (2), 130 (2), 120 (19), 103 (22), 76 (20), 74 (16), 70 (45), 59 (100), 50 (14), 45 (45); pale yellow oil;

(31) All of the amino diethyl thioacetals described here, slowly turned black on exposure to the atmosphere. For this reason, freshly prepared amino dithioacetals were usually purified by flash chromatography and used directly in the next step. Stability was observed for at least several days, if stored below 0 °C under a N_2 atmosphere.

$[\alpha]^{22}_D$ +676.3 (*c* 0.1072, $CHCl_3$) [lit.[10] $[\alpha]^{22}_D$ +319 (*c* 0.147, $CHCl_3$)]; 81% yield; TLC, EtOAc. Anal. Calcd for $C_{12}H_{12}N_2O$: 200.0950. Found: 200.0947.

Racemic 1,2,3,11a-Tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]-benzodiazepin-5-ones 8b,c. 1,2,3,11a-Tetrahydro-7-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**8c**) and 1,2,3,11a-tetrahydro-9-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**8b**) have been previously reported.[8] By the cyclization procedure reported here, they were obtained in yields of 84% and 77%, respectively.

III. Prothracarcin Synthesis. (2*S*)-(*E*,*Z*)-*N*-(2-Nitrobenzoyl)-4-ethylidene-2-pyrrolidinecarboxylic acids (12): IR (neat) 3680–2300, 1720 and 1625 (C=O), 1590, 1480, 1430, 1515 and 1335 (NO_2), 1300, 1170, 1070, 1020, 952, 848, 780, 752, 735, 690; ^{1}H NMR ($CHCl_3$) δ 1.44 (d) and 1.62 (d) (*J* = 7 Hz, 6 H, *E* and *Z* isomers, respectively; ratio 1:1.6), 2.65–3.20 (m, 4 H), 3.60–4.39 (m, 4 H), 4.89–5.13 (m, 2 H), 5.18–5.67 (m, 2 H), 7.29–7.98 (m, 6 H), 8.10–8.35 (m, 2 H), 10.50 (s, 1 H); MS, *m*/*e* (relative intensity) 290 (M^+, 2), 245 (8), 242 (21), 220 (8), 210 (19), 205 (8), 197 (13), 179 (12), 167 (63), 154 (12), 150 (98), 140 (44), 137 (85), 123 (63), 119 (100), 109 (35), 104 (44), 83 (47), 65 (81); brown amorphous solid; 58% yield; TLC, EtOAc/methanol 19:1. Anal. Calcd for $C_{14}H_{14}N_2O_5$: 290.0903. Found: 290.0908.

Methyl (2*S*)-(*E*,*Z*)-*N*-(2-Nitrobenzoyl)-4-ethylidene-pyrrolidine-2-carboxylate (13): IR (neat) 3120–2760, 1730 and 1630 (C=O), 1562 (C=C), 1471, 1405, 1515 and 1335 (NO_2), 1295, 1255, 1190, 1165, 1070, 1020, 970, 915, 848, 780, 752, 732, 693; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.3 Hz) and 1.56–1.74 (m, 6 H) (*E* and *Z* isomers, respectively; ratio 1:1.6) 2.56–2.85 (m, 2 H), 2.88–3.17 (m, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.91–4.35 (m, 4 H), 4.90–5.10 (m, 2 H), 5.24–5.67 (m, 2 H), 7.25–7.87 (m, 6 H), 8.13–8.28 (m, 2 H); MS, *m*/*e* (relative intensity) 305 (M^+ + 1, 13), 304 (M^+, 11), 287 (19), 257 (5), 245 (90), 150 (100), 134 (31), 121 (26), 104 (48), 94 (65), 76 (55), 67 (40), 59 (17), 51 (48) [chemical ionization, M^+ + 1 observed at *m*/*e* 305 (100%)]; pale yellow oil; 89% yield; TLC, EtOAc/hexane 3:2. Anal. Calcd for $C_{15}H_{16}N_2O_5$: 304.1059. Found: 304.1064.

(2*S*)-(*E*,*Z*)-*N*-(2-Nitrobenzoyl)-4-ethylidenepyrrolidine-2-carboxaldehyde (14): IR (neat) 3640–2760, 1725 and 1625 (C=O), 1565 (C=C), 1473, 1410, 1512 and 1333 (NO_2), 1192, 1165, 1067, 1022, 845, 780, 750, 690; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (d, *J* = 6.3 Hz) and 1.55–1.74 (m, 6 H) (*E* and *Z* isomers, respectively; ratio 1:1.6), 2.53–3.17 (m, 4 H), 3.83–4.73 (m, 4 H), 4.79–5.08 (m, 2 H), 7.23–7.86 (m, 6 H), 8.14–8.27 (m, 2 H), 9.76 (d, *J* = 1.5 Hz, 1 H) and 9.79 (d, *J* = 1.5 Hz, 1 H) (minor rotamers at δ 9.37 and 9.38, respectively; *J* = 1.5 Hz); MS, *m*/*e* (relative intensity) 274 (M^+, 3), 245 (100), 231 (17), 199 (6), 154 (75), 150 (85), 134 (36), 121 (26), 104 (48), 94 (51), 76 (48), 67 (39), 51 (43), 41 (35); pale yellow oil; 90% yield; TLC, EtOAc/hexane 3:2. Anal. Calcd for $C_{14}H_{14}N_2O_4$: 274.0953. Found: 274.0964.

(2*S*)-(*E*,*Z*)-*N*-(2-Nitrobenzoyl)-4-ethylidenepyrrolidine-2-carboxaldehyde Diethyl Thioacetal (15): IR (neat) 2945, 2900, 2845, 1622 (C=O), 1565 (C=C), 1470, 1400, 1510 and 1330 (NO_2), 1255, 1070, 965, 845, 780, 725, 690; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14–1.42 (m, 12 H), 1.43–1.50 (m) and 1.59–1.74 (m, 6 H) (*E* and *Z* isomers, respectively; ratio 1:1.6), 2.62–2.95 (m, 12 H), 3.67–3.82 (m, 2 H), 3.93–4.05 (m, 2 H) 4.59 (d, *J* = 3.8 Hz, 1 H), 4.67 (d, *J* = 3.8 Hz, 1 H), 4.84–5.01 (m, 2 H), 5.18–5.34 (m, 1 H), 5.35–5.5 (m, 1 H), 7.43–7.57 (m, 2 H), 7.58–7.67 (m, 2 H), 7.68–7.81 (m, 2 H), 8.14–8.27 (m, 2 H); MS, *m*/*e* (relative intensity) 380 (M^+, 15), 351 (21), 319 (15), 289 (4), 257 (24), 245 (100), 215 (11), 169 (13), 150 (93), 135 (74), 120 (33), 104 (25), 94 (13), 76 (27), 51 (38); pale yellow oil; $[\alpha]^{23}_D$ −104.4 (*c* 0.2232, $CHCl_3$); 86% yield; TLC, EtOAc/hexane 2:3. Anal. Calcd for $C_{18}H_{24}N_2O_3S_2$: 380.1228. Found: 380.1240.

(2*S*)-(*E*,*Z*)-*N*-(2-Aminobenzoyl)-2-ethylidine-pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (16): IR (neat) 3440 and 3339 (NH_2), 3220, 2950, 2905, 2855, 1605 (C=O), 1575 (C=C), 1485, 1440, 1400, 1308, 1255, 1203, 1150, 1048, 1007, 967, 853, 740, 645; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–1.44 (m, 12 H), 1.45–1.55 (m) and 1.58–1.71 (m, 6 H) (*Z* and *E* isomers, respectively; 1:1.3), 2.55–2.90 (m, 12 H), 3.84–4.08 (m, 2 H), 4.21–4.45 (m, 4 H), 4.46–4.72 (m, 4 H), 4.81–5.03 (m, 2 H), 5.20–5.48 (m, 2 H), 6.64–6.78 (m, 4 H), 7.09–7.30 (m, 4 H); MS, *m*/*e* (relative intensity) 350 (M^+, 23), 289 (4), 259 (2), 227 (8), 215 (100), 168 (8), 147 (6), 140 (6), 135 (21), 120 (94), 108 (11), 96 (43), 92 (47), 65 (19); pale yellow oil; 98% yield; TLC, EtOAc. Anal. Calcd for $C_{18}H_{26}N_2OS_2$: 350.1487. Found: 350.1496.

(11a*S*)-(*E*,*Z*)-2-Ethylidene-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (2d, Prothracarcin): IR (Nujol) 2900, 2833, 1620 (C=O), 1573 (C=C), 1450, 1370, 1255, 1150, 1011, 780, 750, 715; MS, *m*/*e* (relative intensity) 226 (M^+, 100), 211 (19), 197 (35), 183 (19), 173 (13), 167 (17), 156 (6), 149 (47), 132 (14), 119 (9), 113 (12), 103 (21), 96 (20), 76 (23); 69% yield; RP-MPLC, CH_3OH/H_2O 7:3. Anal. Calcd for $C_{14}H_{14}N_2O$: 226.1106. Found: 226.1110. The *E* and *Z* isomers were separated by preparative TLC (Baker Si250F, #7001-3; silica gel, 250 μM, 254 nM fluorescent indicator, 10 × 20 cm), using benzene/acetone (3:2) as eluant, to afford the pure *E* isomer and the *Z* isomer slightly contaminated with *E*. *E* Isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.75 (d, *J* = 6.9 Hz, 3 H), 2.98 (d, *J* = 5.2 Hz, 2 H), 3.92 (q, *J* = 5.8 Hz, 1 H), 4.18–4.40 (m, 2 H), 5.53–5.67 (m, 1 H), 7.34 (t, *J* = 7.0 Hz, 2 H), 7.53 (t, *J* = 6.9 Hz, 1 H), 7.78 (d, *J* = 4.4 Hz, 1 H), 8.04 (d, *J* = 5.6 Hz, 1 H; fine coupling of 2 Hz); $[\alpha]^{33}_D$ +213.0 (*c* 0.395, EtOAc).[29] *Z* Isomer: ^{1}H NMR (360 MHz, $CHCl_3$) δ 1.70 (d, *J* = 6.2 Hz, 3 H), 2.90 (d, of AB q, *J* = 16.0 Hz, 1 H) and 3.09 (d of AB q, *J* = 16 Hz, 1 H), 3.82–3.87 (m, 1 H), 4.17 (d, of AB q, *J* = 16.1 Hz, 1 H) and 4.39 (d, of AB q, *J* = 16.1 Hz, 1 H), 5.53–5.67 (m, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.53 (t, *J* = 7.3 Hz, 1 H), 7.78 (d, *J* = 3.7 Hz, 1 H), 8.04 (d, *J* = 5.6 Hz, 1 H; fine coupling of 2 Hz).

IV. Convergent Synthesis. The ester **17**, aldehyde **18**, and diethyl thioacetal **19** reported below were prepared by the methods described in General Synthetic Procedures.

Methyl (2*S*)-*N*-(Benzoxycarbonyl)pyrrolidine-2-carboxylate (17): IR (neat) 3160–2740, 1748 and 1700 (C=O), 1588 (C=C), 1495, 1408, 1350, 1278, 1195, 1168, 1115, 1083, 1030, 1000, 950, 912, 875, 825, 762, 740, 692, 600; ^{1}H NMR ($CDCl_3$) δ 1.68–2.45 (m, 4 H), 3.34–3.84 (m, 5 H, rotameric $COOCH_3$; signals at δ3.76 and 3.59, ratio 1:1.45), 4.25–4.51 (m, 1 H), 5.09 and 5.13 (s, 2 H, rotameric $PhCH_2O$ signals), 7.35 and 7.38 (s, 5 H, rotameric aromatic signals); MS, *m*/*e* (relative intensity) 263 (M^+, 23), 204 (100), 160 (81), 128 (21), 91 (93), 77 (6), 68 (6), 65 (21); pale yellow oil; $[\alpha]^{24}_D$ −58.7 (*c* 0.2038, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ −57.3 (*c* 1.0, CH_3OH)]; 98% yield; TLC, EtOAc/hexane 2:3. Anal. Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1169.

(2*S*)-*N*-(Benzoxycarbonyl)pyrrolidine-2-carboxaldehyde (18): IR (neat) 3680–3160 (hydrate), 3120–2740, 1730 and 1690 (C=O), 1588 (C=C), 1494, 1442, 1410, 1350, 1200, 1168, 1109, 1094, 1023, 980, 910, 763, 735, 690; ^{1}H NMR ($CDCl_3$) δ 1.60–2.24 (m, 4 H), 3.25–3.81 (m, 2 H), 3.90–4.50 (m, 1 H), 5.12 (s, 2 H), 7.32 (s, 5 H), 9.49 and 9.57 (s, 1 H, rotameric *CH*O) [contaminant dimeric aldehyde, δ 4.50 (s)]; MS, *m*/*e* (relative intensity) 233 (M^+, 1), 204 (100), 160 (86), 128 (9), 114 (19), 108 (16), 91 (91), 77 (18), 65 (32); colorless oil; $[\alpha]^{24}_D$ −74.42 (*c* 0.1384, $CHCl_3$) [lit.[19] $[\alpha]^{21}_D$ −40.8 (*c* 1.90, CH_3OH)]; 75% yield, TLC, EtOAc/hexane 2:3. Anal. Calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1061.

(2*S*)-*N*-(Benzoxycarbonyl)pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (19): IR (neat) 3120–2780, 1690 (C=O), 1585 (C=C), 1495, 1440, 1403, 1350, 1325, 1280, 1260, 1189, 1170, 1100, 1027, 1003, 969, 914, 863, 760, 745, 690; ^{1}H NMR ($CDCl_3$) δ 0.95–1.44 (m, 6 H), 1.53–2.25 (m, 4 H), 2.30–2.90 (m, 4 H), 3.26–3.83 (m, 2 H), 4.10–4.41 (m, 1 H), 3.64 (d, *J* = 3 Hz, 1 H), 5.15 (br s, 2 H), 7.38 (s, 5 H); MS, *m*/*e* (relative intensity) 339 (M^+, 11), 204 (94), 160 (85), 142 (6), 135 (18), 126 (5), 114 (6), 107 (9), 91 (100), 70 (9), 65 (14); colorless oil; $[\alpha]^{24}_D$ −50.9 (*c* 0.2104, $CHCl_3$); 79% yield; TLC, EtOAc/hexane 1:4. Anal. Calcd for $C_{17}H_{25}NO_2S_2$: 339.1327. Found: 339.1336.

(2*S*)-Pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (20). A solution of 2,3-dimethylbutene (0.5 mL, 4.2 mM, 4.2 equiv) and trimethylsilyl iodide (0.5 mL, 3.54 mM, 2.4 equiv) in dry dichloromethane (15 mL) was stirred under argon for 30 min. A solution of **19** (0.5 g, 1.47 mM, 1 equiv) in dichloromethane (5 mL) was added dropwise over 5 min and the mixture stirred for approximately 30 min or until reaction was complete as indicated by TLC (ethyl acetate/hexane, 1:9). After quenching with methanol (10 mL) and evaporation at 35 °C in vacuo, the resulting oil was dissolved in ether (25 mL) and extracted with 0.5 N HCl (3 × 25 mL). The combined aqueous phase, after adjusting to pH 8 with 2 N NaOH, was back-extracted with ether (4 × 20 mL), and the combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford **20** (0.29 g): IR (neat) 3420 (NH),

3040–2700, 1660, 1440, 1400, 1370, 1335, 1255, 1070, 1105, 1048, 968, 920, 750; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 6 H), 1.52–2.32 (m, 4 H), 2.55–3.18 (m, 6 H), 3.20–3.51 (m, 1 H), 3.81 (d, J = 8 Hz, 1 H); MS, m/e (relative intensity) 205 (M^+, 6), 176 (2), 160 (32), 144 (36), 135 (30), 130 (24), 114 (20), 107 (13), 97 (13), 91 (12), 86 (23), 83 (51), 82 (51), 75 (13), 70 (100); pale yellow oil; $[\alpha]^{23}_D$ -31.8 (c 0.434, $CHCl_3$); 96% yield; TLC, $CHCl_3$ saturated with NH_4OH. Anal. Calcd for $C_9H_{19}NS_2$: 205.0959. Found: 205.0954.

Convergent Coupling Method. The 2-nitrobenzoyl chloride (4.2 mM, 1 equiv, prepared from the corresponding 2-nitrobenzoic acid and oxalyl chloride[8]) was taken up in THF (20 mL) and added dropwise to an ice-cold solution of **20** (4.2 mM, 1 equiv) and triethylamine (8.4 mM, 2 equiv) in THF (30 mL). After addition was completed, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. The mixture was then filtered and evaporated in vacuo, to give an oil that was dissolved in EtOAc (20 mL) and extracted with 0.5 M HCl (4 × 20 mL), saturated $NaHCO_3$ solution (4 × 20 mL), and brine (2 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo to afford the coupled product. By this method, **5a** was countersynthesized in 92% yield; $[\alpha]^{25}_D$ -204.4 (c 0.1712, $CHCl_3$).

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Registry No. (*E*)-**2d**, 81542-99-6; (*Z*)-**2d**, 105120-29-4; **3a**, 105089-64-3; **4a**, 72435-94-0; **4b**, 100243-62-7; **4c**, 100230-83-9; **5a**, 105089-65-4; **5b**, 105089-68-7; **5c**, 105089-72-3; **6a**, 105089-66-5; **6b**, 105089-69-8; **6c**, 105089-73-4; **7a**, 105120-27-2; **7a** (11*S* methyl ester), 100230-77-1; **7a** (11*R* methyl ester), 105120-28-3; **7b**, 105089-70-1; **7c**, 105089-74-5; **8a**, 72435-89-3; **8b**, 100231-11-6; **8c**, 100231-12-7; **10**, 552-16-9; (*E*)-**11**, 105089-75-6; (*Z*)-**11**, 105089-76-7; (*E*)-**12**, 105089-77-8; (*Z*)-**12**, 105089-78-9; (*E*)-**13**, 105089-79-0; (*Z*)-**13**, 105089-80-3; (*E*)-**14**, 105089-81-4; (*Z*)-**14**, 105089-82-5; (*E*)-**15**, 105089-83-6; (*Z*)-**15**, 105089-84-7; (*E*)-**16**, 105089-85-8; (*Z*)-**16**, 105089-86-9; **17**, 5211-23-4; **17** (acid), 1148-11-4; **18**, 71461-30-8; **19**, 105089-87-0; **20**, 105089-88-1; *N*-(2-nitrobenzoyl)proline, 18877-33-3; (±)-*N*-(3-methyl-2-nitrobenzoyl)proline, 105089-67-6; (±)-*N*-(5-methyl-2-nitrobenzoyl)proline, 105089-71-2; 2-nitrobenzoyl chloride, 610-14-0.

Reactions of an *o*-Quinone Monoimide with 1,3,5-Trimethoxybenzene, 2-Methoxythiophene, 2-Methoxyfuran, and 1-Methyl-, 2-Methyl-, and 1,2-Dimethylindoles

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The *o*-quinone monoimide **1** reacts with the electron-rich aromatic reagents 1,3,5-trimethoxybenzene, 2-methoxythiophene, and 1-methyl-, 2-methyl-, and 1,2-dimethylindoles to give the *N*-2,4-dichloro-6-hydroxyphenyl derivatives of *N*-(2,4,6-trimethoxyphenyl)-, *N*-(5-methoxy-2-thienyl)-, *N*-(1-methyl-1*H*-indol-3-yl)-, *N*-(2-methyl-1*H*-indol-3-yl)-, and *N*-(1,2-dimethyl-1*H*-1-indol-3-yl)-4-nitrobenzamides, compounds **8**, **10**, and **19a–c**, respectively. Treatment of **1** with 2-methoxyfuran forms the 2-benzoxazolyl-2-propenoate **14**.

In previous papers we reported that the *o*-quinone monoimide **1** underwent cycloadditions with electron-rich alkenes to form 2,3-dihydro-1,4-benzoxazines **2** (Scheme I).[1,2] More recently we observed that **1** when treated with sulfoxides, diazoalkanes, and triphenylphosphine gave sulfoximines **3**, imines **4**, and the benzoxazole **5**[3] (Scheme I). A rationalization for the latter reactions has the electron-rich sulfur, carbon, and phosphorus atoms of the above reagents bonding to the electron-deficient nitrogen atom of **1** to form the phenoxide ion intermediate **6**. Addition of the phenoxide ion of **6** to the carbonyl carbon forms intermediate **7**, which is the precursor to compounds **3–5**.[3]

An earlier observation that **1** combined with benzofuran to give a cycloadduct, furo[3,2-*b*][1,4]benzoxazine, prompted us to treat **1** with other aromatic substrates, namely, 1-methyl-, 2-methyl-, and 1,2-dimethylindoles, 1,3,5-trimethoxybenzene, 2-methylthiophene, and 2-methoxyfuran. In contrast to benzofuran the products are phenols save in the case of 2-methoxyfuran. An intermediate analogous to **6** is presumed to form in each reaction.

Treatment of **1** with 1,3,5-trimethoxybenzene in methylene chloride gave **8** in 86% yield (Scheme II). Proof of structure rested on an X-ray crystallographic examination of a single crystal of **8**. One plausible mechanistic route to **8** involves attack on the nitrogen of **1** by the electron-rich 1,3,5-trimethoxybenzene to give **9**. Alternatively, a one electron transfer process may take place to give a radical cation and radical anion which can collapse to **9**. Loss of a proton from the benzenium ion moiety of **9** produced **8** (Scheme II). The reaction may be regarded overall as an electrophilic substitution of 1,3,5-trimethoxybenzene by the novel electrophile **1**. No reaction of **1** occurred with anisole under comparable experimental conditions.

2-Methoxythiophene undergoes the same reaction with **1** or with the benzoquinone monoimide **11** to give the

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