butyllithium/cyclohexane (1.05 equiv) was added at -40 °C, and then to the dark-red solution at -65 °C methyl chloroformate (0.6 mL) was added. Warming to room temperature and the usual workup (see above) left an oil which was hydrolyzed with NaOH in EtOH/$H_2O$ (see for preparation of **51**) under reflux for 3.5 h. The product after acidification, taken up in TBME, was fractionated by fractional extraction[55] starting with small quantities of 2% sodium bicarbonate, proceeding in base strength up to 5% sodium carbonate. The fractions obtained crystalline after acidification were combined and extracted with $CHCl_3$/THF (3:1) to give acid **79** (0.35 g, 42.4% overall yield); recrystallization from toluene gave mp 197-197.5 °C: IR 3400-2950, 1690, 1625, 1475, 1280-1180 $cm^{-1}$, $^1H$ NMR (200 MHz) δ 3.865 (d, 2 H), 3.98 (s, 3 H), 5.15 (d, 1 H), 5.22 (s, 1 H), 6.15 (m, 1 H), 7.22-7.99 (total 5 H), 8.55 (s, 1 H); $^{13}C$ NMR (50 MHz) δ 171.6, 159.9, 136.65, 136.15, 135.25, 131.95, 130.9, 128.25, 126.3, 123.8, 116.95, 116.7, 103.05, 55.35, 37.2; nominal mass spectrum $m/z$ 243, 242 ($M^+$), 197, 167, 165, 153, 152; exact mass $m/z$ calcd for $C_{15}H_{14}O_3^+$ 242.0943, found 242.0998.

**Experiments on Regiochemistry of Allylation (Table I). Conditions.** (a) The sulfonamide (4 mmol) was deprotonated in THF with *n*-butyllithium/cyclohexane and then reduced in THF-liquid $NH_3$ with lithium metal, followed by quenching with 3-bromo-1-propene (0.8 mL) and then workup as described in the General Procedure (see above). The total crude product, isolated with $CH_2Cl_2$, was hydrolyzed by heating under reflux in ethanol (4 mL) and 3 N NaOH (3 mL) for 3 h, followed by removal of the ethanol, extraction with hexane, passage through a short column (1-1.5 g) of alumina, and distillation (flask to vial[56]) at 110 °C (Kugelrohr ot) (0.08 mmHg). The proportion of regioisomers **47** to **76** in the distilled product was determined in the $^1H$ NMR spectrum by integration of the doublets centered at δ 3.89 and 3.505, respectively.

(b) The same procedure was followed except for the use of NaH instead of *n*-BuLi and of Na metal instead of Li.

(c) Sodium hydride suspension (0.38 g) was washed free of oil with pentane and covered with anhydrous DMF (2.5 mL), the suspension cooled to -35 °C (acetonitrile-solid $CO_2$ bath), and the dihydrosulfonamide (4 mmol) and 3-bromo-1-propene (0.8 mL) added with stirring which was continued as the reaction mixture reached rt overnight, after which water was added and the product isolated with $CH_2Cl_2$. Thereafter hydrolysis was effected as in a.

(d) To anhydrous THF (8 mL) and anhydrous TMEDA (distilled from sodium, 1.38 mL, 2.5 equiv) was added *N*-benzylbenzamide indicator (4 mg) and to the solution at -20 °C was added dropwise with stirring *n*-butyllithium in cyclohexane to a blue color and then at -70 °C a total of 2.4 equiv of *n*-butyllithium in cyclohexane. The dihydro-*N*-alkylsulfonamide (4 mmol) was then added as a solid and stirring continued at -70 °C until it had all dissolved to give a red solution (1.5-2.5 h). Thereafter, 3-bromo-1-propene (0.95 mL) was added, the solution allowed to reach rt during 2-4 h, the THF removed in vacuo, the product taken up in $CH_2Cl_2$, and the TMEDA extracted with 2 M aqueous citric acid. Thereafter, the product was hydrolyzed and worked up as in a.

**Registry No.** **1**, 29083-07-6; **2**, 139633-35-5; **3**, 56875-61-7; **4**, 121429-55-8; **5**, 139633-36-6; **6**, 121429-56-9; **7**, 139633-37-7; **8**, 139633-38-8; **9**, 102153-62-8; **10**, 139633-39-9; **11**, 121429-58-1; **12**, 121429-59-2; **13**, 121429-72-9; **14**, 121429-60-5; **15**, 139633-40-2; **16**, 139633-41-3; **17**, 121429-63-8; **18**, 139633-42-4; **19**, 121429-62-7; **20**, 139633-43-5; **21**, 121429-73-0; **22**, 121429-74-1; **23**, 121429-75-2; **24**, 66413-57-8; **25**, 139633-44-6; **26**, 139633-45-7; **27**, 56875-56-0; **28**, 139633-46-8; **29**, 121429-57-0; **30**, 139633-47-9; **31**, 139633-48-0; **32**, 121429-61-6; **33**, 139633-49-1; **34**, 139633-50-4; **35**, 121429-64-9; **36**, 139633-51-5; **37**, 139655-47-3; **38**, 139633-52-6; **39**, 139633-53-7; **40**, 96362-60-6; **41**, 139633-54-8; **42**, 139633-55-9; **43**, 1634-09-9; **44**, 2825-01-6; **45**, 23076-74-6; **46**, 139633-56-0; **47**, 121429-80-9; **48**, 109250-93-3; **49**, 91903-17-2; **50**, 121429-81-0; **51**, 91903-16-1; **52**, 7147-68-4; **53**, 24293-49-0; **54**, 139633-57-1; **55**, 56875-59-3; **56**, 121429-65-0; **57**, 139633-58-2; **58**, 121429-66-1; **59**, 139633-80-0; **60**, 139633-82-2; **61**, 139633-84-4; 1,2-dihydro-**61**, 139633-59-3; **62**, 139633-78-6; **63**, 121429-76-3; **64**, 139633-76-4; **65**, 121429-78-5; **66**, 139633-60-6; **67**, 139633-61-7; **68**, 121429-77-4; **69**, 139633-62-8; **70**, 139633-63-9; **71**, 139633-64-0; **72**, 121429-69-4; **73**, 121429-70-7; **74**, 26386-94-7; **75**, 94134-18-6; **76**, 139633-65-1; **77**, 139633-66-2; **78**, 121429-82-1; **79**, 139633-67-3; **80**, 56875-60-6; **81**, 139633-68-4; **82**, 139633-69-5; **83**, 139633-70-8; **84**, 139633-71-9; **85**, 33295-54-4; **86**, 139633-74-2; **87**, 139633-72-0; $CH_2$=$CHCH_2Br$, 106-95-6; sodium 6-hydroxynaphthalene-2-sulfonate, 135-76-2.

**Supplementary Material Available:** Experimental procedures and data for **3**, **24**, **27**, **38**, **40**, **9**, **80**, **82**, **1**, **2**, **5**, **8**, **10**, **25**, **28**, **29**, **30**, **39**, **41**, **42**, **53**, **57**, **81**, **84**, **11**, **16**, **26**, **32**, **33**, **34**, **18**, **20**, **35**, **59**, **61**, **64**, **70**, **67**, **60**, **65**, **46**, **48**, **50**, **74**, **68**, **75** and **51** and the $^1H$ or $^{13}C$ NMR spectra for 1-87 (97 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(55) Reference 39, p 145.
(56) Reference 39, p 202.

# Addition of Amino Amides to Vinyl Vicinal Tricarbonyls. Formation of Tricyclic 3-Azadethiacephams

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*Received October 16, 1991*

Amino amides react as trinucleophiles with vinyl vicinal tricarbonyl esters. Reaction of the primary amino group takes place at the β-position of the α,β-unsaturated ketone along with addition to the central carbonyl group. In a third-stage reaction, the amide residue adds to the iminium ion formed from the intermediate carbinolamine. The resulting product is a bicyclic or tricyclic (acylamino)pyrrolidone carboxylate. A novel tricyclic 3-azadethiacepham of biological interest has been prepared using this reaction.

## Introduction

In earlier work, we have reported the reactions of the polyelectrophilic vinyl vicinal tricarbonyl system with donor reagents having multiple nucleophilic capability. Thus, a primary amine attached to an auxiliary nucleophilic center undergoes addition in conjugate fashion to the reagent **1** along with attack at the central carbonyl group to generate an intermediate carbinolamine which then gives rise to the iminium ion **2**. The auxiliary nucleophile then adds to **2** to form the bicyclic product as

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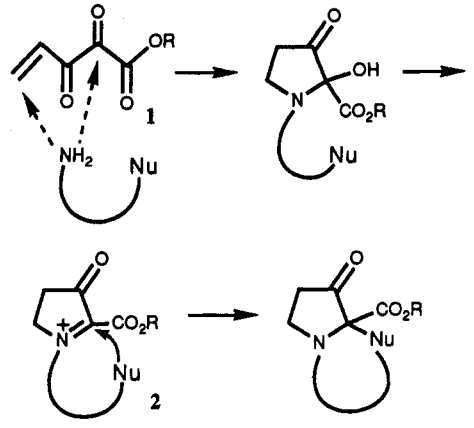
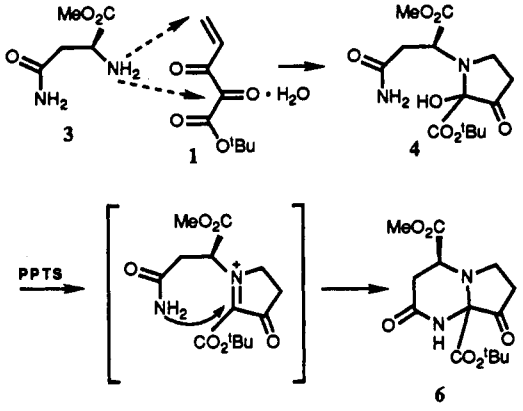



Figure 1.

Scheme I




shown (Figure 1).[1] The donor species have included indole residues,[2] activated aromatic rings,[3] enol ethers and other nucleophilic residues.[4]

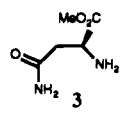
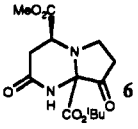
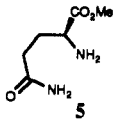
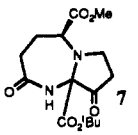
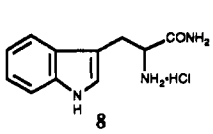
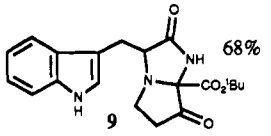
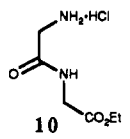
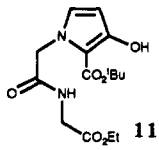
In the present work, we have extended the range of these auxiliary nucleophiles to include amide NH or lactam NH groups attached by tethers of varying length and composition to the primary amine. This process, in which the amide group acts as a "third-stage" nucleophile, constitutes a facile route to novel bicyclic and tricyclic systems incorporating lactam residues.

Carbinolamine adducts derived from straight-chain amino amides yield bicyclic products and those from amino lactams give tricyclic compounds. Of particular interest are tricyclic β-lactam-containing derivatives which are formed readily and stereospecifically using this method.

## Results and Discussion

**Amino Amides.** The addition of amino amides to the vinyl tricarbonyl reagent, VTC (1, R = *t*-Bu), in $CH_2Cl_2$/MeOH at room temperature takes place smoothly to give the hydroxypyrrolidinone carboxylates which, in turn, can be converted to a bicyclic system with pyridinium *p*-toluenesulfonate (PPTS) through the intermediate iminium ion. Scheme I illustrates the conversion of **3** to **6**

Table I. Bicyclic and Pyrrole Adducts from the Addition of Amino Amides to VTC (1)

| amino amide[a] | product | yield[b] |
|---|---|---|
|  3 |  6 | 81% |
|  5 |  7 | 33% |
|  8 |  9 | 68% |
|  10 |  11 | 38% |

[a] The corresponding Cbz-protected amino amide was hydrogenated (Pd/C catalyst) to the amino amide shown and used directly. The HCl salts were added in the presence of $Et_3N$ (1 equiv). [b] Based on the protected amine starting material.

through the carbinolamine **4**. The best results were achieved using the methyl ester of L-asparagine (**3**) and L-glutamine (**5**) (Table I). Glycinamide gave many side products, while tryptophanamide **8** gave the bicyclic product **9** in good yield. Secondary amides formed by monoacetylation of 1,3-diaminopropane and ethylenediamine gave mixtures including a substantial amount of hydroxypyrrole[5] and very little cyclized material. Likewise, with small peptide units such as the ethyl ester of glycylglycine **10**, we observed only formation of pyrrole **11** rather than the bicyclic product.

The addition product **6** from L-asparagine (**3**) was identified as a single isomer of unknown stereochemistry at the bridgehead carbon (Table I). The bicyclic adduct **7** from L-glutamine (**5**), on the other hand, produced two diastereomers in roughly equal proportions. There has been considerable interest in fused ring systems corresponding to **6**, **7**, and **9** in connection with a wide range of biological activity including antihypertensive, antipyretic, and analgesic properties.[6-8]

**Tryptophanamide.** In earlier work, we showed that the addition of tryptamine (**12**) to VTC (**1**, R = *t*-Bu) takes place by a 3-fold nucleophilic addition whereby the primary amino group initially adds to the α,β-unsaturated ketone and the central carbonyl to form a carbinolamine which is then converted to the iminium salt. A third-stage addition then takes place in which the indole ring acts as a donor to form the tetracyclic system **15** (Scheme II).[2]

(1) In the absence of these third-stage nucleophiles, pyrrole formation is usually the alternative reaction outcome.

(2) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371-372.

(3) Wasserman, H. H.; Amici, R. M. *J. Org. Chem.* **1989**, *54*, 5843-5844.

(4) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701-1702.

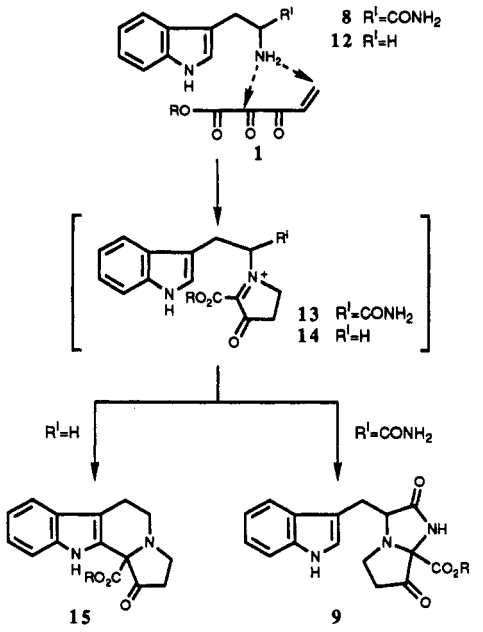
(5) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721-1724.

(6) Preston, P. N., Ed. *Condensed Imidazoles* (Weissberger, A., Taylor, E. C., Eds.); The Chemistry of Heterocyclic Compounds 46; John Wiley and Sons: New York, 1986; pp 15-41.

(7) Bicyclic Six- and Five-membered Rings. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1990; Vol. 49, pp 255-257.

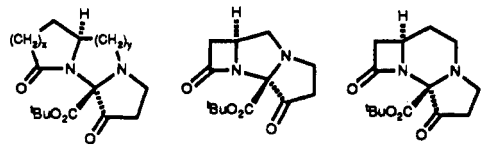
(8) Fryer, R. I., Ed. *Bicyclic Diazepines. Diazepines with an Additional Ring* (Taylor, E. C., Weissberger, A. Eds.); The Chemistry of Heterocyclic Compounds 50; John Wiley and Sons: New York, 1991; pp 100-103, 148-150.

**Scheme II**



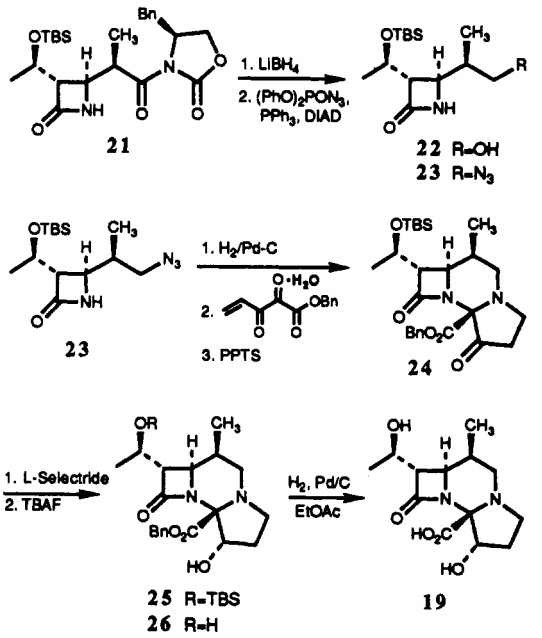

We were particularly interested in the nature of the third stage nucleophilic attack in the case of tryptophanamide. It can be seen that reaction of **8** with the VTC reagent would lead, after the first steps, to the iminium ion **13**. As illustrated in Scheme II, this salt would have two additional donor sites capable of addition to the electrophilic center: (a) the indole ring, as in the tryptamine case, or (b) the primary amide residue, as observed in the present work using amino amides. A priori, we had no way of predicting which pathway would supervene. In the event, we found that when the reactant **8** (hydrochloride salt) was stirred with vinyl tricarbonyl reagents in $CH_2Cl_2$ in the presence of triethylamine, the reaction led exclusively to **9** in which the amide group competed favorably with the indole ring in the attack on the intermediate iminium ion (yield: $R$ = *t*-Bu, 68%; R = Me, 59%).

**Amino Lactams.** We have previously reported that amino lactams undergo ready addition to **1** to form novel heterotricyclic systems.[9] This three-stage nucleophilic addition reaction takes place readily with β-, γ-, and δ-lactams yielding products corresponding to the general structure **16**. Among these tricyclic adducts, there is particular interest in the novel β-lactam derivatives **17** and **18**.

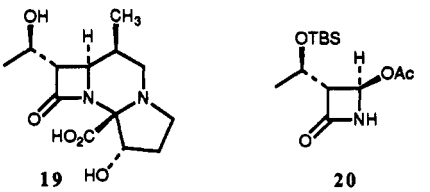



An X-ray crystallographic analysis of tricyclic β-lactam **17** showed that the carboxylate group has a β-orientation.[9] The β-disposition of the carboxylate residue is particularly desirable in these tricyclic compounds from the standpoint of potential biological activity, as reported in earlier papers.[10-13]

**Scheme III**




In studying the generality of this cyclization, we sought to prepare a 4–6–5 fused ring system **19** containing the 3-(1-hydroxyethyl) group as an analogue of known biologically-active fused-ring β-lactams.[14] Starting with β-lactam **20**,[15] a precursor of thienamycin, we prepared **21**




under Reformatsky conditions as reported by Ito and Terashima (70%).[16] Treatment of this β-lactam oxazolidinone with $LiBH_4$ provided alcohol **22** (79%) which was then transformed to the azide **23** (95%) using diphenylphosphoryl azide.[17] Hydrogenation of the azide, followed by addition to VTC and cyclization using PPTS provided the tricyclic product **24** (71%). The ketone **24** was selectively reduced with L-Selectride, presumably by hydride addition to the convex face of the cyclic system, to provide the alcohol **25** (93%). Removal of the TBS group with TBAF (84%) yielded the diol ester **26** which was then subjected to hydrogenolysis giving the β-lactam derivative **19** (92%).

(9) Wasserman, H. H.; Henke, S. L.; Luce, P.; Nakanishi, E.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 5821–5822.
(10) Cohen, N. C. *J. Med. Chem.* **1983**, *26*, 259–264.
(11) Nakao, Y. In **Recent Advances in the Chemistry of β-Lactam Antibiotics**; Bentley, P. H., Southgate, R., Eds.; The Royal Society of Chemistry: London, 1989; pp 119–138.
(12) (a) Christenson, J.; Georgopapadakou, N.; Keith, D.; Luk, K.-C.; Madison, V.; Mook, R.; Pruess, D.; Roberts, J.; Rossman, P.; Wei, C.-C.; Weigele, M.; West, K. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bentley, P. H., Southgate, R., Eds.; The Royal Society of Chemistry: London, 1989; pp 33–48. (b) Keith, D. D.; Tengi, J.; Rossman, P.; Todaro, L.; Weigele, M. *Tetrahedron* **1983**, *39*, 2445–2458.
(13) For other biologically active azadethiocepham, cephem, and penam analogues, see: (a) Azadethiocephem: Gleason, J. G.; Bryan, D. B.; Holden, K. G. *Tetrahedron Lett.* **1980**, *21*, 3947–3950. (b) Azadethiocepham: Branch, C. L.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1077–1095. (c) Azadethiocepham and cephem: Pfaendler, H. R.; Strasser, R. *Leibigs Ann. Chem.* **1987**, 911–919. (d) Azadethiopenam: Huffman, W. F.; Holden, K. G.; Buckley, T. F.; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352–2353.
(14) For other biologically active tricyclic analogues, see: Branch, C. L.; Finch, S. C.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1491–1498. Lammert, S. R.; Kukolja, S. *J. Am. Chem. Soc.* **1975**, *97*, 5583–5584.
(15) A sample of **20** was generously provided by Lederle Laboratories.
(16) Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1987**, *28*, 6625–6628.
(17) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.
(18) Testing was done at Hoffman-LaRoche, Inc., Nutley, NJ.

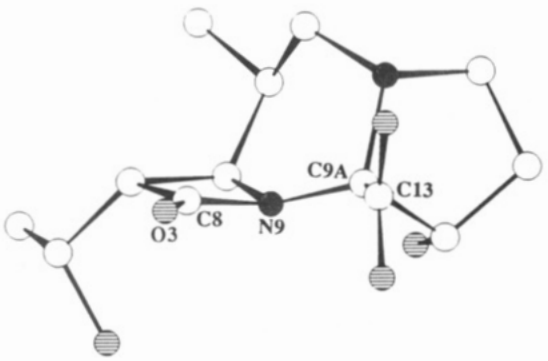



Figure 2.

The X-ray crystal structure of compound **19** is represented by the UPLOT drawing in Figure 2. In previous studies on the structure–activity relationships of β-lactam antibiotics, activity has been correlated with the torsional angle of the carboxylate relative to the lactam ring as well as with the distance between the carboxylate carbon and the β-lactam oxygen.[10,12a] The torsional angle C13–C9A–N9–C8 of β-lactam **19** is 26.8° and the distance between the carboxylate carbon C13 and the oxygen of the β-lactam O3 is 3.01 Å. These values are close to the values obtained for cephalosporins which have torsional angles between 30 and 60° and carboxylate carbon to lactam oxygen distances of 3.2–3.3 Å.[10,12a] In comparison, the unsubstituted tricyclic β-lactam **17** possesses a torsional angle of 9.35° and a distance between the carboxylate carbon and oxygen of the β-lactam of 3.13 Å. It is interesting to note that despite the favorable disposition of the carboxylate in compound **19**, the compound was found to be inactive in concentrations up to 64 mg/μL in standard screening tests against a variety of microorganisms.[18]

In summary, the addition of amino amides to vinyl vicinal tricarbonyl esters provides a facile route to bicyclic and tricyclic compounds incorporating lactam residues. In one application, this novel method has been used to prepare tricyclic β-lactams of biological interest.

## Experimental Section

**General Methods.** Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250 MHz. Ultraviolet spectra were recorded on a Varian Cary 219 spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. The infrared spectra were recorded on a Perkin-Elmer 1420 or Nicolet 5SX (FT) spectrometer. Mass spectra were obtained on a Hewlett-Packard GC5840Q/MS 5985 system or Hewlett-Packard 5989A instrument. High-resolution mass spectra were obtained at Yale University on a Kratos MS80RFA instrument.

**Procedure A. Addition of Amino Amides to the VTC Reagent. 4-Carbomethoxy-8a-carbo-*tert*-butoxy-2,8-dioxoperhydropyrrolo[1,2-*a*]pyrimidine (6).** A dry 100-mL round-bottomed flask was charged with VTC (1, R = *t*-Bu) (96.1 mg, 0.475 mmol) in dry $CH_2Cl_2$ (34 mL), and the clear solution was cooled to 0 °C. The methyl ester of L-asparagine (**3**) (63.1 mg, 0.432 mmol), obtained by hydrogenation of the Cbz-protected amine, in 8 mL of MeOH was added to the VTC solution dropwise over 10 min. The reaction was stirred for 1.5 h at approximately 0 °C, the solvent was removed in vacuo, and the resulting clear oil was dissolved in 35 mL of $CH_2Cl_2$. PPTS (108.6 mg, 0.432 mmol) in 8 mL of $CH_2Cl_2$ was added to the reaction mixture, and the resulting clear solution was stirred at room temperature for 30 min. The reaction was quenched by the addition of 10 mL of saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ layers were washed with brine, dried over $Na_2SO_4$, filtered, concentrated, and purified by column chromatography (silica gel, 1:1 EtOAc/hexanes). A clear oil was obtained (109.2 mg, 81%): IR ($CHCl_3$) 3400, 1785, 1750, 1685, 1160 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 6.42 (br s, 1 H), 4.09 (d of d, $J$ = 11.7, 5.1 Hz, 1 H), 3.81 (s, 3 H), 3.44 (d of t, $J$ = 8.8, 2.2 Hz, 1 H), 3.11 (d of d, $J$ = 16.0, 7.1 Hz, 1 H), 2.81 (d of d, $J$ = 18.0, 12.0 Hz, 1 H), 2.60 (d of d, $J$ = 18.0, 5.1 Hz, 1 H), 2.87–2.60 (m, 2 H), 1.47 (s, 9 H); MS $m/e$ (relative intensity) 259 (33.9), 241 (16.4), 211 (100.0), 129 (83.3); HRMS (CI) calcd for $C_{14}H_{21}N_2O_6$ (M + H) 313.1400, found 313.1382.

**5-Carbomethoxy-9a-carbo-*tert*-butoxy-2,9-dioxoperhydropyrrolo[1,2-*a*]diazepine (7).** Procedure A was used with the following changes: Equimolar amounts of L-glutamine methyl ester (80.1 mg, 0.5 mmol), VTC (1, R = *t*-Bu) (101 mg, 0.5 mmol), and PPTS (126 mg, 0.5 mmol) were used. The solution of amino amide and VTC was stirred at 0 °C for 30 min and then at room temperature for 30 min. The crude material was purified by column chromatography on silica gel using 2:1 to 1:1 hexanes/EtOAc to yield the two diasteromers, 24.4 mg and 25.8 mg. Lower $R_f$ diastereomer: IR ($CHCl_3$) 3380, 3030, 3010, 2980, 2960, 1790, 1760, 1675, 1390, 1170 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 6.07 (br s, 1 H), 3.85–3.64 (m, 2 H), 3.73 (s, 3 H), 3.31 (d of t, $J$ = 8.6, 3.5 Hz, 1 H), 2.98–2.46 (m, 4 H), 2.35–2.03 (m, 2 H), 1.47 (s, 9 H); MS $m/e$ (relative intensity) 226 (10.8), 225 (100.0), 182 (4.6), 156 (4.1), 129 (3.8); HRMS (CI) calcd for $C_{15}H_{23}N_2O_6$ (M + H) 327.1557, found 327.1546. Higher $R_f$ diastereomer: IR ($CHCl_3$) 3400, 3040, 3020, 3000, 2970, 1800, 1770, 1685, 1395, 1270, 1170, 1150 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 6.28 (br s, 1 H), 3.86 (t, $J$ = 5.1 Hz, 1 H), 3.80 (s, 3 H), 3.59–3.49 (m, 1 H), 3.19 (d of d, $J$ = 16.8, 8.4 Hz, 1 H), 2.84–2.69 (m, 3 H), 2.58–2.44 (m, 1 H), 2.24–1.95 (m, 2 H), 1.49 (s, 9 H); MS $m/e$ (relative intensity) 226 (11.3), 225 (100.0), 182 (5.2), 156 (4.4); HRMS (CI) calcd for $C_{15}H_{23}N_2O_6$ (M + H) 327.1557, found 327.1551.

**(3-Indolyl)[3-(7a-carbo-*tert*-butoxy-2,7-dioxoperhydropyrrolo[1,2-*a*]imidazolyl)]methane (9).** A 250-mL round-bottomed flask equipped with a magnetic stirbar and septum was dried under nitrogen and charged with VTC (1, R = *t*-Bu) (261 mg, 1.29 mmol) and tryptophanamide hydrochloride (309 mg, 1.29 mmol). Dry methylene chloride (100 mL) was then added. The resulting suspension was cooled to 0 °C, triethylamine (180 mL, 1.29 mmol) was added dropwise, and the solution was stirred at 0 °C for 1 h. The reaction mixture was then stirred at room temperature for 50 min, and pyridinium *p*-toluenesulfonate in 30 mL of methylene chloride was added. After 10 min, the solution was quenched by the addition of saturated $NaHCO_3$ solution, and the layers were partitioned and separated. The methylene chloride layer was washed with saturated $NaHCO_3$ solution. The aqueous layers were combined and extracted three times with methylene chloride. The methylene chloride layers were combined, dried over $Na_2SO_4$, and concentrated to yield a yellow oil. Purification by column chromatography (silica gel, 8:1 to 4:1 $CH_2Cl_2$/EtOAc) yielded a white solid (326 mg, 68%): IR ($CHCl_3$) 3512, 3460, 1760, 1732, 1694, 1195, 1135 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 8.43 (br s, 1 H), 7.57 (d, $J$ = 7.7 Hz, 1 H), 7.37 (d, $J$ = 7.9 Hz, 1 H), 7.24–7.09 (m, 3 H), 5.75 (br s, 1 H), 4.04 (d of d, $J$ = 11.1, 5.7 Hz, 1 H), 3.35–2.46 (m, 6 H), 1.51 (s, 9 H); MS $m/e$ (relative intensity) 370 (0.7, $M^+$ + 1), 369 (2.7, $M^+$), 268 (100.0), 223 (48), 130 (22), 57 (21.8); HRMS (CI) calcd for $C_{20}H_{24}N_3O_4$ 370.1768 (M + H), found 370.1758.

***N*-[1-(2-Carbo-*tert*-butoxy-3-hydroxypyrrolyl)]acetylglycine, Ethyl Ester (11).** A 100-mL round-bottomed flask was charged with glycylglycine ethyl ester hydrochloride (98 mg, 0.5 mmol) and VTC (1, R = *t*-Bu) (101 mg, 0.5 mmol) in dry methylene chloride (50 mL). The suspension was cooled to 0 °C, $Et_3N$ was added, and the mixture was allowed to warm to room temperature over 1 h. Silica gel (0.5 g) was added to the clear solution, and after 2 days an additional 0.5 g of silica gel was added and stirred for 2 more days, after which the suspension was filtered and the filtrate concentrated to a yellow oil. Purification by column chromatography (silica gel, 3:1 to 1:1 hexanes/EtOAc) provided 62 mg of white solid (38%): mp 97 °C; IR ($CHCl_3$) 3420, 1740, 1680, 1645, 1560, 1530, 1460, 1390, 1370, 1335, 1155, 1100 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 6.62 (d, 1 H, $J$ = 2.9 Hz), 6.03–5.90 (br s, 1 H), 5.89 (d, 1 H, $J$ = 3.0 Hz), 4.76 (s, 2 H ), 4.18 (q, 2 H, $J$ = 14.3, 7.1 Hz), 4.00 (d, 2 H, $J$ = 5.3 Hz), 1.64 (br s,

1 H), 1.56 (s, 9 H), 1.26 (t, 3 H, $J$ = 7.1 Hz); MS $m/e$ (relative intensity) 326 (5.1), 271 (12.5), 270 (100.0), 252 (26.3), 206 (47.8), 178 (48.7). Anal. Calcd for $C_{15}H_{22}N_2O_6$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.25; H, 6.83; N, 8.60.

**3-[1-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]]-4-[2-(1-hydroxy-2-methylethyl)]azetidin-2-one (22).** $LiBH_4$ (9.0 mL, 2M in THF) was added dropwise over 5 min to a solution of the starting material (2.07 g, 4.50 mmol) in 100 mL of dry THF at −30 °C. After 5 h at −10 to 0 °C, the solution was maintained at −25 °C overnight. The reaction was diluted with EtOAc and quenched with 0.2 N HCl (aqueous). The organic layer was separated, washed with brine, dried over $Na_2SO_4$, filtered, concentrated, and purified by column chromatography on silica gel using 10:1 $CH_2Cl_2$/acetone to yield a white solid (1.02 g, 79%): IR ($CHCl_3$) 3416, 3020, 2959, 2931, 1755, 1257 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.19 (br s, 1 H), 4.19–4.10 (m, 1 H), 3.58 (d of d, $J$ = 4.4, 11.8 Hz, 1 H), 3.47 (d of d, $J$ = 8.5, 11.7 Hz, 1 H), 3.28 (d of d, $J$ = 1.7, 8.9 Hz, 1 H), 3.18 (d of d, $J$ = 1.6, 9.2 Hz, 1 H), 1.94–1.80 (br m, 1 H), 1.35 (d, $J$ = 6.0 Hz, 3 H), 0.92 (s, 9 H), 0.88 (d under previous peak, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H); MS $m/e$ (relative intensity) 230 (100.0), 200 (12.0), 186 (15.3); HRMS (CI) calcd for $C_{14}H_{30}NO_3Si$ 288.1996 (M + H), found 288.2015.

**3-[1-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]]-4-[2-(1-azido-2-methylethyl)]azetidin-2-one (23).** A solution of alcohol **22** (426 mg, 1.48 mmol, 1.0 equiv) and triphenylphosphine (467 mg, 1.78 mmol, 1.2 equiv) in dry THF (12 mL) was cooled to 0 °C. Diisopropylazodicarboxylate (350 μL, 1.78 mmol, 1.2 equiv) and then diphenylphosphoryl azide (384 μL, 1.78 mmol, 1.2 equiv) were added to the solution. After 2 min, a white precipitate formed and the solution was allowed to warm to room temperature after a total of 10 min. The solvent was removed in vacuo, and the remaining yellow oil was chromatographed on silica gel using 8:1 hexanes/acetone to yield a white solid, weight 441 mg (95%): IR ($CHCl_3$) 3410, 2960, 2930, 2855, 2105, 1758, 1258, 840 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 5.80 (br s, 1 H), 4.22–4.13 (m, 1 H), 3.56 (d of d, $J$ = 6.6, 2.2 Hz, 1 H), 3.43 (d of d, $J$ = 12.2, 5.1 Hz, 1 H), 3.26 (d of d, $J$ = 12.2, 6.5 Hz, 1 H), 2.89–2.84 (m, 1 H), 1.98–1.85 (m, 1 H), 1.25 (d, $J$ = 6.2 Hz, 3 H), 1.06 (d, $J$ = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H ), 0.09 (s, 3 H); HRMS (CI) calcd for $C_{14}H_{29}N_4O_2Si$ 313.2062 (M + H), found 313.2069.

**7-[1-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]]-6-methyl-9a-carbobenzoxy-1,8-dioxoazetidino[1,2-*c*]perhydropyrrolo[1,2-*a*]pyrimidine (24).** Procedure A was used with the following changes: The benzyl ester of VTC (239 mg, 1.01 mmol) and the azide **23** (264 mg, 0.845 mmol) were stirred at 0 °C for 15 min, and the mixture was maintained at −25 °C overnight. The solvents were then removed, and the resultant white foam was diluted with $CH_2Cl_2$. PPTS (212 mg, 0.845 mmol) was added, and the solution was held at reflux for 15 min. Purification by column chromatography (silica gel, 4:1 hexanes/EtOAc) provided a clear oil, 292 mg (71%): IR ($CHCl_3$) 2960, 2930, 2850, 1785, 1760, 1255 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40–7.29 (m, 5 H), 5.25 (d, $J$ = 2.0 Hz, 2 H), 4.22–4.14 (m, 1 H), 3.71 (d of d, $J$ = 7.5, 2.4 Hz, 1 H), 3.34–3.27 (m, 1 H), 3.22–3.12 (m, 2 H), 2.96 (d of d, $J$ = 6.7, 13.9 Hz, 1 H), 2.80 (d of d, $J$ = 8.2, 13.9 Hz, 1 H), 2.69–2.33 (m, 3 H), 1.20 (d, $J$ = 6.2 Hz, 3 H), 1.05 (d, $J$ = 7.0 Hz, 3 H), 0.86 (s, 9 H), 0.07 (s, 6 H); MS $m/e$ (relative intensity) 458 (31.7), 429 (53.2), 367 (100.0), 351 (46.1); HRMS (CI) calcd for $C_{26}H_{39}N_2O_5Si$ 487.2630 (M + H), found 487.2629.

**7-[1-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]]-1-hydroxy-6-methyl-9a-carbobenzoxy-1,8-oxoazetidino[1,2-*c*]perhydropyrrolo[1,2-*a*]pyrimidine (25).** L-Selectride (468 μL, 1.0M in THF, 1.2 equiv) was added dropwise to a solution of tricyclic compound **24** (190 mg, 0.390 mmol, 1.0 equiv) in 12 mL of dry THF cooled to −78 °C. After 10 min, the solution was quenched with saturated $NH_4Cl$ solution, diluted with EtOAc, and allowed to warm to room temperature. The EtOAc layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to yield a yellow oil. The oil was purified by column chromatography on silica gel using 4:1–2:1 hexanes/EtOAc: yield, 177 mg of clear oil (93%); IR 3600, 2960, 2930, 2860, 1750, 1460, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40–7.33 (m, 5 H), 5.21 (d of d, $J$ = 17.0, 12.3 Hz, 2 H), 4.78–4.76 (m, 1 H), 4.22 (d of d, $J$ = 6.2, 4.5 Hz, 1 H), 3.97 (d of d, $J$ = 8.4, 2.5 Hz, 1 H), 3.33–3.21 (m, 1 H), 3.13 (d of d, $J$ = 4.3, 2.6 Hz, 1 H), 3.06–2.97 (m, 1 H), 2.87 (d, $J$ = 1.5 Hz, 1 H), 2.83 (s, 1 H), 2.59–2.43 (m, 1 H), 2.05–1.88 (m, 3 H), 1.20 (d, $J$ = 6.2 Hz, 3 H), 0.94 (d, $J$ = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); MS $m/z$ 431 (5.8), 355 (7.3), 354 (24.2), 353 (100.0), 195 (26.7), 153 (25.3); HRMS (CI) calcd for $C_{26}H_{41}N_2O_5Si$ 489.2786 (M + H), found 489.2785.

**7-[1-(1-Hydroxyethyl)]-1-hydroxy-6-methyl-9a-carbobenzoxy-8-oxoazetidino[1,2-*c*]perhydropyrrolo[1,2-*a*]pyrimidine (26).** Tetrabutylammonium fluoride (0.39 mL, 1.0M in THF) was added to a solution of the tricyclic alcohol **25** (96 mg, 0.196 mmol, 1 equiv) in 10 mL of dry THF. The mixture was stirred at room temperature for 4 h, and then EtOAc and $H_2O$ was added. The EtOAc layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to yield a clear oil. The oil was chromatographed on silica gel using 2:1–4:1 EtOAc/hexanes yielding 62 mg of white solid (84%): IR ($CHCl_3$) 3400 (br), 2960, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.41–7.30 (m, 5 H), 5.20 (s, 2 H), 4.82–4.75 (m, 1 H), 4.32–4.22 (m, 1 H), 4.02–4.10 (m, 2 H), 3.41–3.40 (br d, 1 H), 3.39–3.25 (m, 1 H), 3.15 (t, $J$ = 3.1 Hz, 1 H), 3.07–2.98 (m, 1 H), 2.86–2.80 (m, 2 H), 2.65–2.45 (m, 1 H), 2.00–1.88 (m, 2 H), 1.22 (d, $J$ = 6.5 Hz, 3 H), 0.93 (d, $J$ = 6.9 Hz, 3 H); MS $m/z$ 240 (15.7), 239 (100.0), 195 (95.2), 153 (46.1); HRMS (CI) calcd for $C_{20}H_{27}N_2O_5$ 375.1921 (M + H), found 375.1927.

**7-[1-(1-Hydroxyethyl)]-1-hydroxy-6-methyl-9a-carboxy-8-oxoazetidino[1,2-*c*]perhydropyrrolo[1,2-*a*]pyrimidine (19).** Ester cleavage was achieved by hydrogenation of the benzyl ester tricycle **26** (44 mg, 0.12 mmol) in EtOAc at 50 psi with an excess of 10% Pd/C. When the reaction was complete, the solids were collected by suction filtration through a pad of Celite. The solids were washed with EtOAc and then triturated with MeOH. The MeOH extracts were then concentrated in vacuo to yield a white solid, 30 mg (99%). Recrystallization from cool MeOH yielded flat, triangular crystals which became opaque upon drying. The crystals turned orange at 140 °C and then melted from 140.5 to 141.5 °C: IR (KBr) 3400 (br), 2970, 1750, 1660, 1465, 1370 $cm^{-1}$; $^1H$ NMR (Na salt in $D_2O$) $\delta$ 4.58–4.56 (m, 1 H), 4.08–3.97 (m, 1 H), 3.81 (d of d, $J$ = 7.8, 2.4 Hz, 1 H), 3.15 (d of d, $J$ = 5.8, 2.5 Hz, 1 H), 3.10–2.98 (m, 1 H), 2.87–2.66 (m, 2 H), 2.60–2.35 (m, 2 H), 1.92–1.72 (m, 2 H), 1.12 (d, $J$ = 6.5 Hz, 3 H), 0.84 (d, $J$ = 6.8 Hz, 3 H), MS $m/z$ (20 eV) 240 (5.8), 98 (100.0); HRMS (FAB) calcd for $C_{13}H_{20}N_2O_5$ 285.1451, found 285.1444. Anal. Calcd for diol + 1.5 $H_2O$: C, 50.15; H, 7.44; N, 9.00. Found: C, 50.12; H, 7.41; N, 9.07.

**Acknowledgment.** This research was supported by Grants GM31350-08 and GM07874-26 from the NIH. Biological testing was kindly provided by Hoffman-La-Roche, Inc. S.L.H. gratefully acknowledges support received from a Dox Fellowship.

**Supplementary Material Available:** Proton NMR spectra of new compounds **6**, **7**, **9**, **22–26**, and X-ray crystallographic data for compound **19** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.