A New Route to 7-Substituted Derivatives of *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-ethyl]benzoyl}-L-glutamic Acid [ALIMTA (LY231514, MTA)][1]

Edward C. Taylor* and Bin Liu

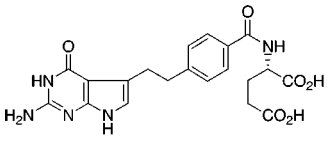
Department of Chemistry, Princeton University, Princeton, New Jersey 08655

etaylor@princeton.edu

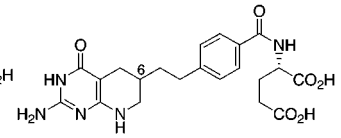
Received November 6, 2000

Alkylation of various primary amines with crotyl bromide, followed by DMAP-promoted acylation with methyl malonyl chloride to **4** and then manganic triacetate dihydrate/cupric acetate induced radical cyclization, gave 1-substituted-4-vinyl-3-carbomethoxy-2-pyrrolidinones (**5**). Thiation to the thiolactams **6** and guanidine cyclization then gave a series of 2-amino-3,4-dihydro-4-oxo-5-vinyl-7-substituted pyrrolo[2,3-*d*]pyrimidines (**7**). Palladium-catalyzed C−C coupling with diethyl 4-iodobenzoylglutamate led in one step via an unexpected redox reaction to the diethyl esters **9** of a series of 7-substituted derivatives of ALIMTA (LY231514, MTA), from which the target analogues **10** were readily prepared by saponification. Attempted deprotection at position 7 was successful in only one case (**9d**, R = $CH_2C_6H_3(OMe)_2$(-3′,4′), which resulted in a known pentultimate precursor (**9**, R = H) of ALIMTA. The 7-substituted derivatives **10** proved to be inactive in vitro as inhibitors of cell division.

During our extensive program involving the design and synthesis of inhibitors of folate-dependent enzymes as potential antitumor agents, we prepared *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl-)ethyl]benzoyl}-L-glutamic acid (ALIMTA, **1**).[2] This compound may be considered a structural analogue of DDATHF (**2a**)[3] and lometrexol (**2b**)[4] in which the ring junction position joining the ethano side-chain bridge to the bicyclic heterocyclic ring is sp^2 rather than sp^3. ALIMTA is a unique antifolate in that it has been shown



1: LY231514, MTA
ALIMTA™ (disodium salt)



2a: DDATHF (6R,S)
2b: lometrexol (6R)

to inhibit (following intracellular polyglutamylation) at least five of the major folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, aminoimidazole ribonucleotide formyltransferase, and C-1 tetrahydrofolate synthetase). Its cell growth inhibition spectrum thus contrasts sharply with those of DDATHF and lometrexol, which function as effective inhibitors only of glycinamide ribonucleotide formyltransferase.[5−7] ALIMTA is an extraordinarily effective antitumor agent that is now in Phase III clinical trials for lung cancer and in multiple additional trials, both as a single agent and in combination with other oncolytic agents. In the course of our extensive SAR studies on this new drug, we had earlier found that substitution at position 7 essentially eliminated cell growth inhibitory activity.[8] For example, the N-7 methyl derivative of **1** exhibited only minimal activity, and the N-7 phenylsulfonyl derivative was

(1) This compound was originally referred to as LY231514, and later as MTA (for MultiTargeted Antifolate). The disodium salt of this compound has recently been given the proprietary name ALIMTA (pemetrexed disodium).

(2) Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, R. G. *J. Med. Chem.* **1992**, *35*, 4450.

(3) Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1985**, *28*, 914.

(4) Taylor, E. C.; Moran, R. G.; Baldwin, S. W.; Shih, C. *J. Biol. Chem.* **1989**, *264*, 21047.

(5) Shih, C.; Chen, V. J.; Gossett, L. S.; Gates, S. B.; MacKellar, W. C.; Habeck, L. L. Shackelford, K. A.; Mendelsohn, L. G.; Soose, D. J.; Patel, V. F.; Andis, S. L.; Bewley, J. R.: Rayl, E. A.; Moroson, B. A.; Beardsley, G. P.; Kohler, W.; Ratnam, M.; Schultz, R. M. *Cancer Res.* **1997**, *57*, 1116.

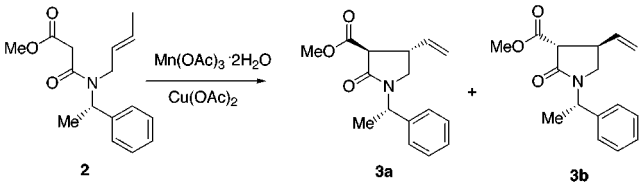
(6) (a) Taylor, E. C.; Kuhnt, D.; Shih, C. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W., Rokos, H. Eds.; Blackwell Science: Cambridge, MA, 1997; p 81. (b) Shih, C.; Beardsley, G. P.; Chen, V. J.; Ehlhardt, W. J.; MacKellar, W. C.; Mendelsohn, L. G.; Ratnam, M.; Schultz, R. M.; Taylor, E. C.; Worzalla, J. F. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W., Rokos, H. Eds.; Blackwell Science: Cambridge, MA, 1997; p 181. (c) Thornton, D. E.; John, W.; Loeher, P.; Eisenhauer, E. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W., Rokos, H. Eds.; Blackwell Science: Cambridge, MA, 1997; p 195. (d) Rinaldi, D. A.; Burris, H. A.; Dorr, F. A.; Woodworth, J. R.; Kuhn, J. G.; Eckardt, J. R.; Rodriguez, G.; Corso, S. W.; Fields, S. M.; Langley, C.; Clark, G.; Faries, D.; Lu, P.; Van Hoff, D. D. *J. Clin. Oncol.* **1995**, *13*, 2842. (e) Calvert, A. H.; Walling, J. M. *Br. J. Cancer* **1998**, *78* (Suppl), 35. (f) Hammond, L.; Baker, S. D.; Villalona-Calero, M.; Eckhardt, S. G.; Drengler, R.; Aylesworth, C.; Johnson, T.; Hidalgo, M.; Rodriguez, G.; Diab, S.; Monroe, P.; Thornton, D.; Johnson, R.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (g) Johnson, T.; Schwartz, G.; McCune, D.; Stephenson, J.; Aylesworth, C.; Hammond, L.; Monroe, P.; Thornton, D.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (h) John, W.; Clark, J.; Burris, H.; Picus, J.; Schulman, L.; Thornton, D.; Lochrer, P. *Proc. Am. Soc. Clin. Oncol.* **1997**, *16*, 292a−A1038. (i) Cripps, M. C.; Burnell, M.; Jolivet, J.; Lofters, W.; Fischer, B.; Panasci, L.; Iglesias, J.; Eisenhauer, E. *Eur. J. Cancer* **1997**, *33* (Suppl 8), S172−a768. (j) Rusthoven, J.; Eisenhauer, E.; Butts, C.; Gregg, R.; Dancey, J.; Fisher, B.; Iglesias, J. *Eur. J. Cancer* **1997**, *33* (Suppl 8), S231−a1045. (k) Thoedtmann, R.; Kemmerich, M.; Depenbrock, H.; Blatter, J.; Ohnmacht, U.; Rastetter, J.; Hanauske, A. R. *Eur. J. Cancer* **1997**, 33 (Suppl 8), S247−a1116.

(7) For a review and leading references, see: Taylor, E. C. *Adv. Exp. Med. Biol.* **1993**, *338*, 387.

(8) Taylor, E. C.; Shih, C.; Gossett, L. S.; Meldelsohn, L. G., unpublished observations.

10.1021/jo001580l CCC: $20.00
Published on Web 05/09/2001

Scheme 1

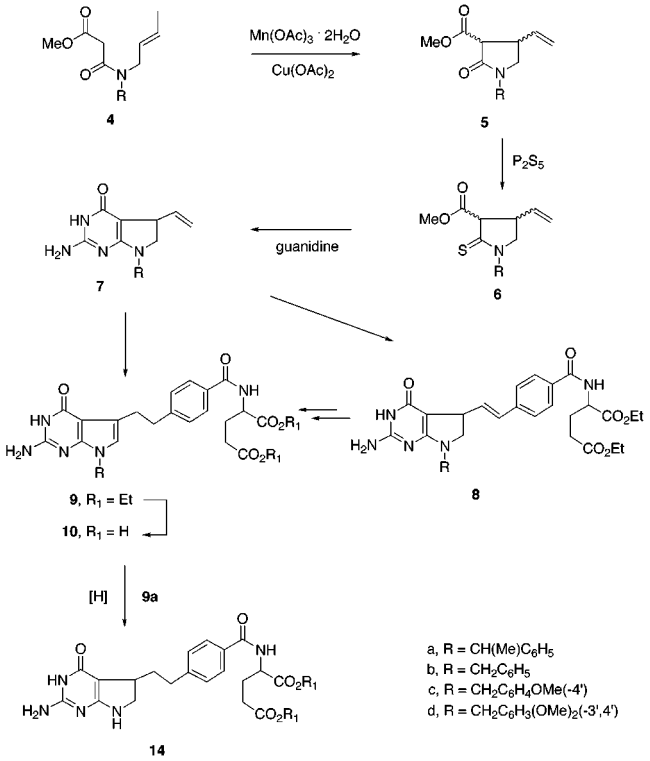


totally inactive. A recent patent from Takeda Chemical Industries, however, claims that a broad variety of 7-substituted derivatives of **1**, including the two derivatives above, are active antitumor agents.[9] To resolve this contradiction, we have prepared a number of 7-substituted derivatives by a new synthetic route and examined their cell growth inhibitory activity. In addition, we report on a number of surprisingly unsuccessful attempts to remove a number of standard nitrogen protecting groups from position 7, as well as a successful N-7 deprotection that exploits this new synthetic methodology for an alternative preparation of ALIMTA itself.

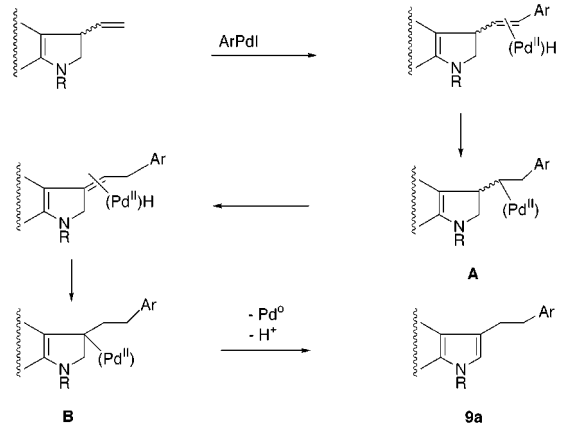
Orena has described a manganic triacetate dihydrate induced radical cyclization of methyl (*S*)-*N*-crotyl-*N*-(1-phenyleth-1-yl)malonamide (**2**) to yield a diastereomeric mixture of the 3-carbomethoxy-2-pyrrolidinones **3a,b** (Scheme 1).[10] Cyclization of a variety of N-substituted malonamides **4** under the above conditions to malonamides **5**,[11] followed by guanidine annulation of 2-amino-4(3*H*)-pyrimidinone rings unto the resulting 3-carbomethoxy-2-pyrrolidinones **7**, palladium-catalyzed Heck coupling with diethyl 4-iodobenzoylglutamate to **8**, appropriate manipulation of the oxidation states of the bridge and the fused pyrroline ring to give **9**, and final hydrolysis would provide a straightforward route to our target MTA analogues **10** bearing a variety of substituents on the pyrrole nitrogen (Scheme 2).

The pyrrolidinone **5a** was prepared as described by Orena through alkylation of racemic α-methylbenzylamine with crotyl bromide, followed by DMAP-promoted acylation with methyl malonyl chloride to give **4a**, and manganic triacetate dihydrate/cupric acetate hydrate induced radical cyclization.[10,12] Although the two diastereomers could be isolated by column chromatography, we employed the mixture of diastereomers for the next reaction, since the stereogenic centers at positions 3 and 4 would be destroyed in the eventual conversion of this proposed intermediate to a pyrrolopyrimidine. Pyrrolidinone **5a** was thiated with P_2S_5 in THF to give the thiolactam **6a**, which was then converted in fair yield with guanidine to the 5,6-dihydropyrrolo[2,3-*d*]pyrimidine **7a**. This appealing intermediate was then subjected to a standard Pd-catalyzed Heck reaction with diethyl 4-iodobenzoylglutamate. The coupling product was not, however, the anticipated vinyl-bridged pyrrolinopyrimidine **8a** but was the *ethano-bridged pyrrolopyrimidine* ***9a***. Since **7a** itself does not undergo an analogous double bond rearrangement under the reaction conditions (Pd(Oac)$_2$, CuI, (*o*-tolyl)$_3$P, Et$_3$N, DMF), it appears (see

Scheme 2



Scheme 3

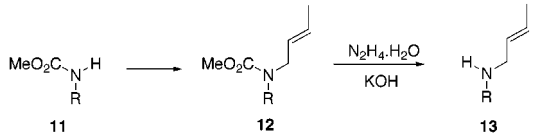


Scheme 3) that the Pd^{II} adduct initially formed in the above Heck reaction (**A**) must undergo *β*-hydride elimination from the pyrroline ring bridgehead position more rapidly than from the benzylic position. We suggest that the resulting PdH complex then re-adds to give **B** faster than it undergoes deprotonation. A second *β*-hydride elimination from **B** would then lead to the pyrrolopyrimidine **9a**. This unexpected double bond rearrangement obviated our anticipated need for reduction of the unsaturated bridge and subsequent oxidation of the pyrroline ring. Saponification of the glutamate esters with sodium hydroxide in aqueous THF then gave our first target compound **10a**.

Target compounds **10b** and **10c** were similarly prepared starting with the appropriate malonamides **4b** and **4c**. However, the precursor crotylamines **13b** and **13c** proved in our hands impossible to prepare by direct alkylation of benzylamine and *p*-methoxybenzylamine with crotyl bromide, since dialkylation inevitably occurred. As a consequence, the above benzylamines were

(9) Akimoto, H.; Ootsu, K. Eur. Pat. Appl. 91-300266 910115.
(10) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069.
(11) An alternative strategy for the preparation of *trans*-*N*-benzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (**5b**, vide infra) has recently been described that involves a palladium(0)-catalyzed cyclization of (*Z*)-[benzyl(malonyl)amino]-but-2-enyl acetate (Giambastiani, G.; Pacini, B.; Porcelloni, M.; Poli, G. *J. Org. Chem*. **1998**, *63*, 804).
(12) (a) Cossy, J.; Leblanc, C. *Tetrahedron Lett*. **1989**, *30*, 4531. (b) Cossy, J.; Bouzide, A.; Leblanc, C. *J. Org. Chem*. **2000**, *k*, 7257.

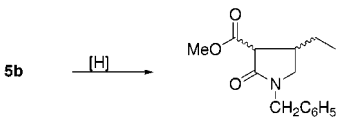
Scheme 4



b, R = $CH_2C_6H_5$
c, R = $CH_2C_6H_4OMe(-4')$
d, R = $CH_2C_6H_3(OMe)_2(-3',4')$
e, R = $CH_2CH_2C_6H_5$

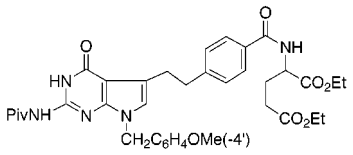
first acylated with methyl chloroformate,[13] and the resulting carbamates **11b** and **11c** were alkylated with crotyl bromide to give **12b** and **13c**, respectively. These compounds were then converted to the desired secondary amines with aqueous hydrazine and potassium hydroxide (Scheme 4).[14]

We then turned to removal of the above N-7 benzyl protecting groups in an effort to utilize compounds **9a**−**c** as intermediates for a possible alternative preparation of ALIMTA itself. To our surprise, all efforts to remove the α-methylbenzyl protecting group from **9a** proved fruitless, despite encouraging precedents.[15] Even under forcing reductive conditions, only a miniscule yield could be obtained of an impure deprotected derivative (**14**) in which the fused pyrrole 5,6-double bond had simultaneously been reduced.[16] Although reductive hydrogenolysis of an N-benzyl group can be easier than hydrogenolysis of an α-methylbenzyl protecting group,[17] efforts to deprotect **9b** were also unsuccessful. Hydrogenolysis using Pd−C in methanol at various temperatures and pressures failed to give straightforward debenzylation; only small amounts of the corresponding 5,6-dihydropyrrolopyrimidine still bearing the N-7 benzyl protecting group were obtained. Benzoyl peroxide in methylene chloride, either under reflux or in a sealed tube at 80 °C,[18] brought about extensive decomposition of the substrate, in contrast to encouraging literature precedents with indoles. We also attempted to remove the N-7 benzyl group from the precursor pyrrolidinone **5b**. Transfer hydrogenation with Pd−C and ammonium formate[19] resulted (unsurprisingly) in quantitative reduction of the vinyl side chain to give **15** but with no impact on the N-benzyl grouping. Similar results were obtained upon catalytic reduction with Pd−C in methanol under various temperatures and pressures.



15

Utilization of **9c** as a possible precursor to ALIMTA seemed attractive, since the literature is replete with various reductive and oxidative methods for removal of 4-methoxybenzyl groups from nitrogen.[20] Once again, however, we were completely frustrated in our attempts to deprotect **9c**. Catalytic reduction with 10% Pd−C under 50 psi of hydrogen resulted in partial reduction of the pyrrole ring, with retention of the 4-methoxybenzyl group, while no reaction whatsoever occurred upon transfer hydrogenation using Pd−C and ammonium formate. Acidic conditions (either with TFA alone or with TFA/sulfuric acid)[21,22] at room temperature or upon heating again had no impact on **9c**, which was recovered unchanged. Ceric ammonium nitrate (CAN) oxidation decomposed the substrate. Similar negative results were obtained with the 2-pivaloyl derivative **16**.



16

Neither the pyrrolidinone intermediate **5c** nor the 5,6-dihydropyrrolo[2,3-*d*]pyrimidine **7c** was affected by TFA, and both decomposed when treated with CAN. As was the case with precursor **5b**, the 4-methoxybenzyl pyrrolidinone **5c** was also recovered unchanged upon treatment with TFA, and it decomposed when treated with ceric ammonium nitrate. The pyrrolinopyrimidine **7c** was also inert to TFA and also decomposed when treated with CAN.

Since it was clear at this point that deprotection of the N-7 benzyl derivatives **9a**−**c** or their respective pyrrolidinone precursors was not promising, we looked at the possibility that the methodology utilized for the initial preparation of the vinyl pyrrolidinones **5a**−**c** might be applicable to the preparation of an N-unsubstituted derivative. Thus, crotylamine hydrochloride was prepared by the reported method involving silver iodide promoted alkylation of lithium bis(trimethylsilyl)amine with crotyl bromide followed by desilylation with dry HCl in ether.[23] In a one-pot procedure, crotylamine was obtained from its hydrochloride by treatment with triethylamine in ethyl acetate; addition of methyl malonyl chloride and DMAP then gave **4** (R = H). Unfortunately, no reaction took place when this material was treated with manganic triacetate dihydrate in the presence of cupric acetate; unchanged starting material was recovered.

We thus had to consider the introduction of a nitrogen protecting group that might be more readily removed than the recalcitrant N-7 benzyl derivatives explored above. A BOM protecting group was first examined. Crotylamine was acylated with methyl chloroformate to

(13) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett*. **1978**, 1051.

(14) (a) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem*. **1984**, *49*, 300. (b) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem*. **1992**, *57*, 4404.

(15) (a) Marx, E.; El Bouz, M.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett*. **1992**, *30*, 4307. (b) Haviari, G.; Célérier, J. P.; Petit, H.; Lhommet, G.; Gardette, D.; Gramain, J. C. *Tetrahedron Lett*. **1992**, *30*, 4311.

(16) This compound has been prepared by a different strategy: Barnett, C. J.; Wilson, T. M. *Heterocycles* **1993**, *35*, 925.

(17) See: Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994; p 221.

(18) Nakatsuka, S.-i.; Asano, O.; Goto, T. *Heterocycles* **1986**, *24*, 2791.

(19) (a) Ram, S.; Spicer, L. D. *Synth. Commun*. **1987**, *17*, 415. (b) Botta, M.; Summa, V.; Saladino, R.; Nicoletti, R. *Synth. Commun*. **1991**, *21*, 2181. (c) Kiguchi, T.; Kuninobu, N.; Takahashi, Y.; Yoshida, Y.; Naito, T.; Ninomiya, I. *Synthesis* **1989**, 778.

(20) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999.

(21) (a) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc*. **1991**, *113*, 8791. (b) Smith, A. B., III; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc*. **1992**, *114*, 8008.

(22) Jones, M. I.; Froussios, C.; Evans, D. A. *J. Chem. Soc., Chem. Commun*. **1976**, 472.

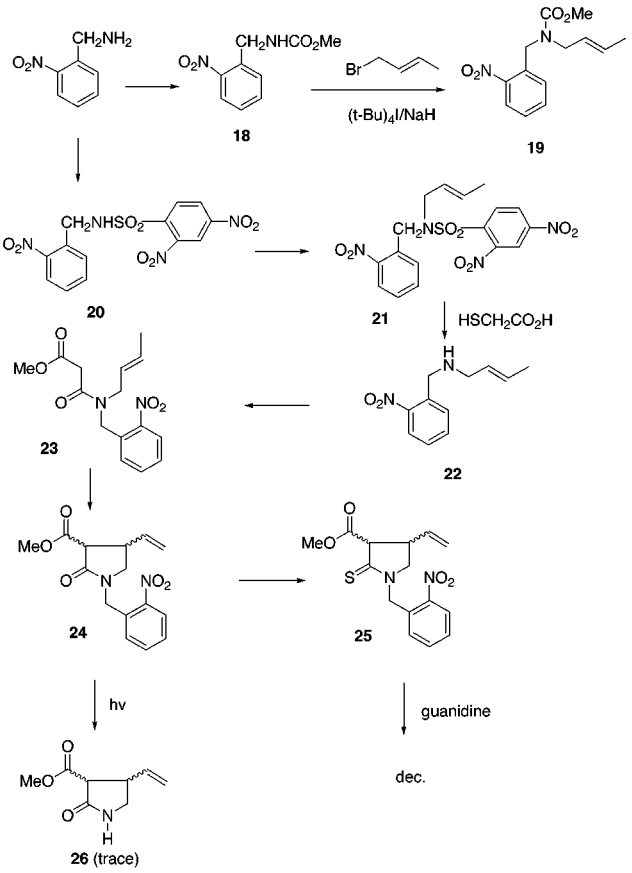
(23) (a) Murai, T.; Yamamoto, M.; Kato, S. *J. Chem. Soc., Chem. Commun*. **1990**, 789. (b) Bestmann, H. J.; Wøolfel, G. *Chem. Ber*. **1984**, *117*, 1250.

give methyl *N*-crotylcarbamate (**17a**). Attempted alkylation with BOM chloride in the presence of sodium hydride gave an impure product that rapidly disentegrated in the presence of KOH and hydrazine. With the intention of introducing a carbamate that might be cleaved under gentler conditions, crotylamine was acylated with BOC anhydride to give *tert*-butyl *N*-crotylcarbamate (**17b**), but attempted alkylation with BOM chloride at room temperature with NaH in THF again was not a clean reaction, and subsequent attempts to remove the *tert*-butoxycarbonyl group with acid again led to extensive decomposition, with only a trace of completely deprotected crotylamine being recovered.

We next investigated the possible utility of a 2-nitrobenzyl protecting group, whose removal from nitrogen by photolysis has been widely exploited. 2-Nitrobenzylbromide was converted to 2-nitrobenzylamine with hexamethylenetetramine followed by HCl as previously described.[24] Acylation with methyl chloroformate proceeded uneventfully to give **18**, but alkylation with crotyl bromide under Finkelstein conditions (tetrabutylammonium iodide and NaH) gave a low yield of **19** that rapidly decomposed upon attempts to remove the carbamate functionality with hydrazine and KOH. Since we suspected that both the low yield in the alkylation step and the failure of the carbamate cleavage step were due to the acidity of the benzyl protons, we were intrigued by the possibility of utilizing the 2,4-dinitrobenzenesulfonamide intermediate **20** for the alkylation step with crotyl bromide, since alkylation could presumably be carried out under much milder conditions, and a mild procedure for removal of the 2,4-dinitrobenzenesulfonyl group has recently been described.[25] Thus, treatment of 2-nitrobenzylamine with 2,4-dinitrobenzenesulfonyl chloride gave **20**, which was smoothly alkylated to **21** with crotyl chloride using potassium carbonate in DMF. The desired secondary amine **22** was then easily obtained by treatment of **21** with thioacetic acid in the presence of triethylamine. DMAP-catalyzed acylation with methyl malonyl chloride yielded **23**, which underwent radical cyclization in high yield to **24** upon treatment with manganic triacetate and cupric acetate in acetic acid. Thiation with P_2S_5 in THF then gave the thioamide **25**. Unfortunately, this intermediate instantly decomposed when exposed to guanidine, probably again as a consequence of the acidity of the *o*-nitrobenzyl protons. An attempt to remove the *o*-nitrobenzyl protecting group from the pyrrolidinone **24** by photolysis in MeOH met with some success under very dilute conditions, but preparative quantities of the deprotected pyrrolidinone **26** could never be obtained (Scheme 5).

We next considered a 4-nitrophenethyl protecting group, since there are encouraging reports of its use with a deoxyguanosine derivative.[26] However, since deprotection is achieved with DBU, and the preparation of the necessary intermediate crotylamine requires base cleavage of an intermediate carbamate (see Scheme 3), we chose to prepare the pyrrolinone **28** using phenethylamine and to introduce the nitro group at a later step in the synthesis. Thus, phenethylamine was acylated

Scheme 5



with methyl chloroformate, and the resulting carbamate **11e** was alkylated without incident with crotyl bromide and sodium hydride to give **12e**. Cleavage to the secondary amine **13e** was achieved as before with KOH and hydrazine. Acylation with methyl malonyl chloride proceeded in good yield to give **27**, which was successfully cyclized to the pyrrolidinone **28** with manganic triacetate dihydrate/cupric acetate. Heck coupling of **28** with methyl 4-iodobenzoate gave **29** with no accompanying double bond rearrangement as was observed earlier in the conversion of **7** to **9**. It appears that annulation of the pyrimidinone ring is a requisite for this unexpected Pd-promoted rearrangement reaction. Nitration of **29** with TFAA/ammonium nitrate yielded a mixture of 2- and 4-mononitrated derivatives (**30a,b**), but attempted deprotection with DBU then returned unchanged starting material. Deprotonation of the 3-carbomethoxy-2-pyrrolidinone ring apparently blocks the reverse Michael deprotection pathway (Scheme 6)

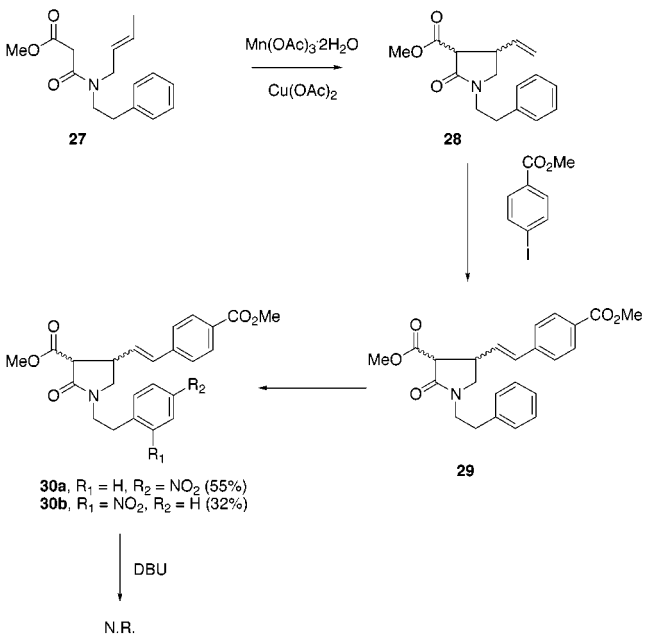
The above mixture of 2- and 4-mononitro derivatives was separated by column chromatography, and the predominant 4-nitro derivative **30a** was thiated with P_2S_5 in THF to give the thiolactam **31**. Methylation with methyl iodide/potassium carbonate then gave the methylthiopyrroline **32**, which no longer contained the acidic α-methine proton positioned between the carbomethoxy and pyrrolidinone carbonyl group. To our surprise, however, treatment of this substrate with DBU resulted in conversion to the pyrrole **33** in excellent yield. No reaction whatsoever took place upon subsequent treatment of **33** with an excess of DBU. To make the pyrrole ring a potentially better leaving group for the reverse Michael deprotection route, the methylthio substituent was oxidized to the methylsulfonyl derivative **34** with

(24) Ong-Lee, A.; Sylvester, L.; Wasley, J. W. F. *J. Heterocycl. Chem*. **1983**, *20*, 1565.

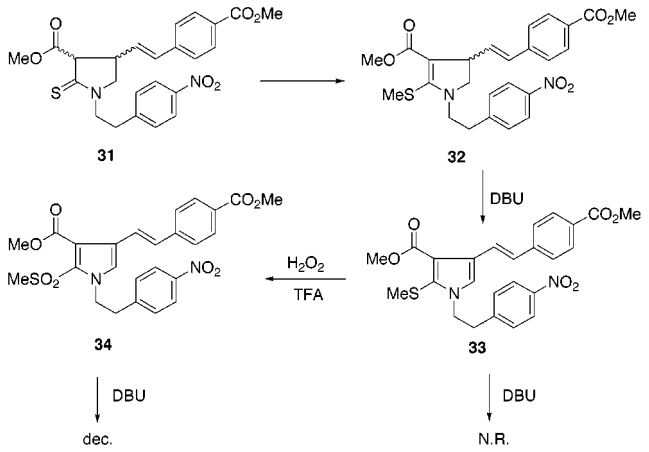
(25) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett*. **1997**, *38*, 5831.

(26) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett*. **1982**, *23*, 2257.

Scheme 6



Scheme 7



hydrogen peroxide in TFA, but treatment of **34** with DBU resulted only in rapid decomposition (Scheme 7).

We finally turned to the 3,4-dimethoxybenzyl protecting group that had been successfully employed (in contrast to benzyl or 4-methoxybenzyl groups) for the protection/deprotection of a pyrrole NH group.[22] The requisite urethane **11d** (obtained in 94% yield by acylation of 3,4-dimethoxybenzylamine with methyl chloroformate) was alkylated with crotyl bromide to give **12d** in 95% yield in a procedure analogous to that employed for the preparation of **12b,c**. Cleavage of urethane **12d** with hydrazine hydrate/KOH gave the crotylamine **13d** in 90% yield, and subsequent acylation with methyl malonyl chloride gave **4d** in 87% yield. Manganic triacetate dihydrate/cupric acetate oxidation to the 4-vinyl-2-pyrrolidinone **5d**, thiation to **6d**, guanidine cyclization to **7d**, and palladium diacetate mediated Heck coupling/rearrangement to **9d** were carried out as described above for the conversions of **4a**−**c** through to **9a**−**c**. Compound **9** (R = H), a known precursor of ALIMTA (**1**)[27] was finally obtained by deprotection of **9d** (29.5% yield) with H_2SO_4/TFA at room temperature[22] (rapid decomposition took place at higher temperatures).

(27) Taylor, E. C.; Liu, B. *Tetrahedron Lett.* **1999**, *40*, 4023.

It is thus apparent that what appeared initially to be an attractive alternative synthetic approach to the pyrrolopyrimidine oncolytic agent ALIMTA (**1**), starting from the readily accessible N-protected pyrrolidinones **5a**−**c**, **24**, and **30**, faltered at the projected deprotection steps. However, the general strategy outlined in Scheme 2 was eventually vindicated by successful deprotection of the 7-(3′,4′-dimethoxybenzyl) derivative **9d** to **9** (R = H), which has been previously converted by saponification to **1**.[27]

In confirmation of our earlier studies[8] and in contradiction to the Takeda claims,[9] we have found that compounds **10a**−**c** are essentially devoid of cell growth inhibitory activity and conclude that 7-substituted derivatives of ALIMTA, which *are* easily prepared by the above novel strategy, are not themselves of interest as antitumor agents. We are currently exploring synthetic applications of the intriguing double bond rearrangement reaction that takes place under Heck-coupling conditions, as exemplified by the conversions of **8a**−**d** to **9a**−**d**.

Experimental Section

General. All commercial reagents were used without further purification. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Methylene chloride, *N*,*N*-dimethylformamide (DMF), and triethylamine were distilled from calcium hydride. ^{1}H and ^{13}C NMR data were obtained with a Varian INOVA-500 MHz, GE QE−300 MHz or JEOL-270 MHz instrument. IR spectra were obtained on a Nicolet FT-IR instrument. Melting points are uncorrected. High resolution mass spectral data were determined at Princeton University on AEI MS-920 and Kratos MS50TC spectrometers. Elemental analyses and FABMS analyses were provided by Eli Lilly and Co., Indianapolis, Indiana.

Methyl *N*-Benzylcarbamate (11b). The following representative procedure was used for the preparation of all of the carbamates described herein. To a solution of 10.7 g (100 mmol) of benzylamine in 150 mL of acetone were added 42.0 g (304 mmol) of potassium carbonate followed by 37.8 g (400 mmol) of methyl chloroformate. After stirring at reflux overnight, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residual solid was washed with water followed by petroleum ether and then dried under vacuum to afford 14.4 g (87% yield) of **11b** as a white solid: IR (KBr) 3373, 1692, 1532, 1275, 1246, 1202, 739, 704, 611 cm^{-1}; ^{1}H ($CDCl_3$) δ 7.37−7.26 (5 H, m), 5.05 (1 H, br s), 4.37 (2 H, d, J = 5.1 Hz), 3.71 (3 H, s).

Methyl *N*-(4′-Methoxybenzyl)carbamate (11c). Isolated in 94% yield as a white solid: IR (KBr) 3323, 1692, 1515, 1512, 1273, 1256, 1033, 810, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (2 H, d, J = 7.8 Hz), 6.86 (2 H, d, J = 8.4 Hz), 4.99 (1 H, br s), 4.29 (2 H, d, J = 5.1 Hz), 3.79 (3 H, s), 3.68 (3 H, s).

Methyl *N*-(3′,4′-Dimethoxybenzyl)carbamate (11d). Isolated in 94% yield as a light yellow solid: IR (KBr) 3331, 2962, 2838, 1692, 1594, 1539, 1517, 1457, 1262, 1138, 1024, 993, 886, 807, 766, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (3 H, m), 5.13 (1 H, br s), 4.30 (2 H, d, J = 4.6 Hz), 3.87 (6 H, s), 3.70 (3 H, s)

Methyl *N*-Phenethylcarbamate (11e). Isolated in 88% yield as a yellow oil: IR (neat) 3335, 3060, 3022, 2941, 1699, 1456, 1257, 1194, 1144, 1031, 1000, 901, 769, 745, 695, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33−7.18 (5 H, m), 4.69 (1 H, br s), 3.06 (3 H, s), 3.45 (2 H, m), 2.85 (2 H, t, J = 6.5 Hz); EIMS m/z 179(M^+), 164, 147, 132, 119, 104, 91, 88, 77.

Methyl *N*-(2′-Nitrobenzyl)carbamate (18). Isolated in 85% yield as a light yellow solid: IR (KBr) 3337, 3194, 2950, 1705, 1610, 1520, 1455, 1348, 1259, 1077, 860, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.03 (1 H, d, J = 8.5 Hz), 7.62 (2 H, m), 7.47−7.41 (1 H, m), 5.64 (1 H, br s), 4.60 (2 H, d, J = 6.8 Hz), 3.65 (3 H, s); EIMS m/z 211 (MH^+), 179, 164, 148, 136, 135, 133, 118, 108, 105, 104, 103, 92, 91, 79, 77, 76.

Methyl *N*-Crotylcarbamate (17a). To a mixture of 2.8 g (26 mmol) of crotylamine hydrochloride and 12.6 g (91 mmol) of potassium carbonate in 100 mL of acetone was added 7.4 g (6.1 mL, 78 mmol) of methyl chloroformate at room temperature. The resulting mixture was stirred at reflux overnight. The mixture was filtered, concentrated, and dried under vacuum at 0 °C to give 2.78 g (83% yield) of **17a** as a yellow oil that was used without further purification in the next step: IR (neat) 3338, 3013, 2952, 1705, 1532, 1450, 1361, 1259, 1194, 1162, 1115, 1069, 1037, 968, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70−5.56 (1 H, m), 5.52−5.35 (1 H, m), 4.68 (1 H, br s), 3.79−3.62 (5 H, m), 1.67 (3 H, d, J = 5.1 Hz); EIMS m/z 129 (M^+), 114, 97, 88, 82, 70, 68.

Methyl *N*-Crotyl-*N*-benzylcarbamate (12b). To a solution containing 15.9 g (100 mmol) of 85% pure crotyl bromide, 4.18 g (174 mmol) of sodium hydride, and 1.6 g (4.34 mmol) of tetrabutylammonium iodide in 350 mL of dry THF at 0 °C was added a solution of 14.4 g (87 mmol) of methyl *N*-benzyl carbamate (**11b**) in 100 mL of dry THF via a cannula. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature overnight. Some suspended solid was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residual solid was dissolved in 150 mL of ethyl acetate, and the solution was washed with brine (2 × 30 mL). After drying over sodium sulfate, the solvent was evaporated under reduced pressure to give 17.7 g (93%) of **12b** as a light yellow oil: IR (neat) 3064, 3028, 2954, 2920, 2858, 1705, 1471, 1455, 1437, 1407, 1234, 1132, 1101, 969, 946, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.23 (5 H, m), 5.70−5.30 (2 H, m), 4.44 (2 H, s), 3.98−3.76 (5 H, br m), 1.68 (3 H, d, J = 5.9 Hz); EIMS m/z 219 (M^+), 204, 176, 164, 160, 132, 128, 121, 104, 96, 92, 91, 85; HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1246.

The following *N*-crotyl carbamates were prepared similarly.

Methyl *N*-Crotyl-*N*-(4′-methoxybenzyl)carbamate (12c). Isolated in 99.0% as a light yellow oil: IR (neat) 3002, 2955, 2857, 1701, 1612, 1512, 1472, 1405, 1302, 1230, 1175, 1132, 1036, 969, 840, 813, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (2 H, d, J = 22 Hz), 6.84 (2 H, d, J = 8.5 Hz), 5.53 (1 H, br s), 5.38 (1 H, br s), 4.37 (2 H, s), 3.78 (3 H, s), 3.73 (3 H, s), 3.68 (2 H, s), 1.68 (2 H, d, J = 6.5 Hz); EIMS m/z 249(M^+), 194, 162, 151, 141, 128, 121, 91, 77; HRMS calcd for $C_{14}H_{19}NO_3$ 249.1377, found 249.1372.

Methyl *N*-Crotyl-*N*-(3′,4′-dimethoxybenzyl)carbamate (12d). Isolated in 95% yield as a yellow oil: IR (neat) 3001, 2955, 2836, 1701, 1592, 1516, 1466, 1405, 1262, 1232, 1140, 1029, 969, 807, 767, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88−6.75 (3 H, m), 5.60−6.50 (1 H, m), 5.50−5.30 (1 H, m), 4.41 (2 H, s), 3.90 (6 H, s), 3.70 (3 H, s), 1.72 (3 H, d, J = 6.5 Hz); EIMS m/z 279 (M^+), 248, 224, 192, 181, 167, 151, 141, 128, 107, 91, 77; HRMS calcd for $C_{15}H_{21}NO_4$ 279.1470, found 279.1481.

Methyl *N*-Crotyl-*N*-phenethylcarbamate (12e). Isolated in 88% yield as a yellow oil: IR (neat) 3019, 2938, 1702, 1470, 1400, 1296, 1232, 1116, 1092, 965, 768, 739, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.29 (2 H, m), 7.24−7.22 (3 H, m), 5.58 (1 H, m), 5.41 (1 H, m), 3.79 (2 H, m), 3.71 (3 H, s), 3.44 (2 H, m), 2.85 (2 H, m), 1.71 (3 H, d, J = 6.0 Hz); EIMS m/z 233(M^+), 142, 105, 91, 88, 77; HRMS calcd for $C_{14}H_{19}NO_2$ 233.1435, found 233.1431.

Methyl *N*-Crotyl-*N*-(2′-nitrobenzyl)carbamate (19). Isolated in 20% yield as a yellow oil: IR (neat) 3100, 2948, 2852, 1705, 1257, 1468, 1405, 1312, 1242, 1190, 1130, 961, 859, 769, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (1H, m), 7.63 (1H, m), 7.45−7.29 (2H, m), 5.66−5.44 (2H, m), 4.82 (2H, s), 4.02−3.70 (5H, m), 1.68 and 1.56 (3H, two doublets, J = 6.0 and J = 5.0 Hz).

***tert*-Butyl *N*-Crotylcarbamate (17b).** To a suspension of 7.34 g (68 mmol) of crotylamine hydrochloride in 100 mL of methylene chloride were added 12 g (16.5 mL, 119 mmol) of trimethylamine and 22.3 g (102 mmol) of di-*tert*-butyl carbonate in 30 mL of methylene chloride at room temperature. The resulting mixture was stirred at room temperature for 30 min and then heated to 40 °C for 1.5 h. The mixture was filtered, and solvent was evaporated under vacuum. The residue was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to afford 11.2 g (96%) of **17b** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 5.68−5.61 (1 H, m), 5.52−5.41 (1 H, m), 4.58 (1 H, br s), 3.70 (2 H, s), 1.71 (3 H, d, J = 6.5 Hz), 1.48 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 155.94, 127.80, 127.71, 79.29, 42.70, 28.56, 17.76; EIMS m/z 171(M^+), 140, 111, 101, 83, 70, 68.

***N*-(2′-Nitrobenzyl)-2,4-dinitrobenzenesulfonamide (20).** To a solution of 4.0 g (26.3 mmol) of 2-nitrobenzylamine and 8.0 mL (99 mmol) of pyridine in 150 mL of methylene chloride was added 7.20 g (27.0 mmol) of 2,4-dinitrobenzenesulfonyl chloride in 200 mL of methylene chloride, and the resulting orange-colored mixture was stirred at room temperature overnight. The mixture was washed with 200 mL of 0.2 N HCl followed by 200 mL of water. The organic layer was separated, dried with sodium sulfate, and concentrated under vacuum to give 8.1 g (81% yield) of **20** as a light yellow solid that was used for the next step without further purification. A small amount of highly pure **20** was obtained by chromatography (silica gel, hexane/methylene chloride/ethyl acetate 10:15:1): IR (KBr) 3358, 3108, 1608, 1539, 1417, 1346, 1309, 1172, 1097, 1049, 89 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.18 (1 H, br s), 8.90 (1 H, d, J = 2.0 Hz), 8.60 (1 H, dd, J = 8.5 and 2.0 Hz), 8.21 (1 H, d, J = 8.5 Hz), 8.03 (1 H, d, J = 8.0 Hz), 7.72 (1 H, t, J = 7.5 Hz), 7.64 (1 H, d, J = 7.5 Hz), 7.55 (1 H, t, J = 7.5 Hz), 4.78 (2 H, s); ^{13}C NMR (DMSO) δ 149.71, 147.65, 147.48, 137.58, 133.86, 132.25, 131.35, 130.07, 128.94, 127.28, 124.79, 120.12, 42.28; EIMS m/z 383 (MH^+), 381, 352, 348, 231, 151, 135, 134, 133, 105, 104, 103, 93, 92, 91, 79, 78, 77.

***N*-Crotyl-*N*-(2′-nitrobenzyl)-2,4-dinitrobenzenesulfonamide (21).** The following procedure is representative for the preparation of *N*-crotylsulfonamides. To a mixture of 7.8 g (20.4 mmol) of *N*-(2′-nitrobenzyl)-2,4-dinitrobenzenesulfonamide (**20**) and 10.1 g (73 mmol) of potassium carbonate in 150 mL of DMF was added 5.1 g (32.0 mmol) of 85% pure crotyl bromide at room temperature. The resulting dark orange mixture was stirred for 1 h. The mixture was poured into 300 mL of methylene chloride, washed with concentrated aqueous $NaHCO_3$ (2 × 150 mL) and water (150 mL), dried with Na_2SO_4, and concentrated to give 6.98 g (79%) of crude **21** that was used for the next step without further purification. A small amount of **21** was purified by column chromatography (silica gel, methylene chloride/hexane 1:1) to afford a light yellow solid as a mixture of *cis* and *trans* isomers: IR (KBr) 3095, 2909, 1667, 1603, 1528, 1349, 1165, 918, 791, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.51 (1 H, d, J = 1.5 Hz), 8.46 (1 H, dd, J = 8.5 and 2.0 Hz), 8.20 (1 H, t, J = 8.5 Hz), 7.99 (1 H, t, J = 8.0 Hz), 7.72−7.63 (2 H, m), 7.46 (1 H, t, J = 7.5 Hz), 5.66−5.45 (1 H, m), 5.25−5.20 (1 H, m), 4.90 (2 H, s), 4.03 and 3.91 (2 H, two doublets, J = 7.5 and J = 6.5 Hz), 1.56 and 1.39 (3 H, two doublets, J = 5.0 and J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.03, 149.98, 148.85, 139.08, 133.91, 133.37, 132.90, 131.51, 130.02, 129.01, 126.34, 125.30, 123.84, 122.78, 120.11, 51.12, 47.85, 17.86; EIMS m/z 436 (M^+), 419, 381, 300, 254, 231, 205, 151, 138, 136, 120, 106, 92, 78.

***N*-Crotylbenzylamine (13b).** The following procedure is representative for the preparation of the N-substituted crotylamines. To a mixture of 8.76 g (40 mmol) of methyl *N*-benzyl-*N*-(2-buten-1-yl)carbamate (**12b**) and 33.6 g (600 mmol) of potassium hydroxide in 280 mL of ethylene glycol was added 10.0 g (200 mmol) of hydrazine monohydrate at room temperature. The resulting mixture was heated to 110 °C for overnight. After the mixture cooled to room temperature, 400 mL of ethyl ether was added, and the mixture was washed with water (4 × 100 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc and then EtOAc/MeOH 4:1) to give 5.54 g (86%) of **13b** as a mixture of *cis* and *trans* isomers as a light yellow oil: IR (neat) 2932, 1581, 1450, 961, 848, 740, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.38 (4 H, m), 7.32−7.30 (1 H, m), 5.72−5.59 (2 H, m), 3.86 and 3.84 (2 H, two singlets), 3.36 and 3.26 (2 H, two doublets, J = 6.5 and J = 5.0 Hz), 2.08 (1 H, br s), 1.76 and 1.67 (3 H, two doublets, J = 5.0 and J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 140.20, 129.30, 128.56, 128.42, 127.92, 127.13, 53.30, 51.16, 45.41; EIMS m/z 161 (M^+), 160, 146, 132, 120, 106, 91, 77, 70, 65; HRMS calcd for $C_{11}H_{15}N$ 161.1204, found 161.1201.

***N*-Crotyl-(4′-methoxybenzyl)amine (13c).** Isolated in 88% as a light yellow oil: IR (neat) 3312, 3002, 2913, 2834, 1612, 1512, 1456, 1301, 1247, 1175, 1105, 1037, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (2 H, d, $J = 8.0$ Hz), 6.90 (2 H, d, $J = 8.5$ Hz), 5.69−5.54 (2 H, m), 3.83 (3 H, s), 3.76 (2 H, s), 3.24 (2 H, d, $J = 5.0$ Hz), 1.74 (3 H, d, $J = 5.5$ Hz), 1.39 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 159.33, 133.30, 130.28, 130.08, 128.05, 114.48, 55.96, 53.46, 51,80, 18.55; EIMS *m/z* 191(M^+), 190, 162, 137, 136, 135, 122, 91, 77, 70, 55; HRMS calcd for $C_{12}H_{17}NO$: 191.1310, found 191.1315. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.05; H, 8.84; N, 7.32.

***N*-Crotyl-(3′,4′-dimethoxybenzyl)amine (13d).** Isolated in 90% yield as a light yellow oil: IR (neat) 3303, 2967, 2836, 1592, 1516, 1465, 1376, 1241, 1157, 1140, 1029, 969, 809, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (1 H, d, $J = 7.5$ Hz), 6.88−6.79 (2 H, m), 5.67−5.52 (2 H, m), 3.90 (3 H, s), 3.87 (3 H, s), 3.74 (2 H, s), 3.22 (2 H, d, $J = 5.0$ Hz), 2.72 (1 H, br s), 1.71 (3 H, d, $J = 5.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 149.69, 148.82, 132.90, 129.42, 128.87, 121.18, 112.28, 111.67, 56.61, 56.60, 53.49, 51.50, 18.53; EIMS *m/z* 221 (M^+), 220, 206, 190, 178, 166, 151, 137, 121, 107, 95, 91, 84, 77, 70; HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1412.

***N*-Crotylphenethylamine (30).** Isolated in 76% yield as a light yellow oil: IR (neat) 3321, 3058, 3022, 2915, 2808, 1495, 1449, 1119, 970, 743, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.30 (2 H, m), 7.25−7.22 (3 H, m), 5.64−5.47 (2 H, m), 3.32 and 3.21 (2 H, d, $J = 6.5$ and 6.0 Hz), 2.93−2.88 (2 H, m), 2.86−2.82 (2 H, m), 1.71 and 1.66 (3 H, d, $J = 5.5$ Hz), 1.14 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 140.26, 129.59, 128.81, 128.54, 127.30, 126.20, 51.79, 50.72, 36.58, 17.87; EIMS *m/z* 176(MH^+), 175-(M^+), 174, 147, 134, 120, 105, 104, 102, 91, 89, 81. *N*-Crotylphenethylamine could also be prepared in 51% yield from *N*-crotyl-*N*-phenethyl-2,4-dinitrobenzenesulfonamide as described below for the preparation of **22**.

***N*-Crotyl-(2′-nitrobenzyl)amine (22).** To a solution of 4.2 g (9.6 mmol) of *N*-crotyl-*N*-(2-nitrobenzyl)-2,4-dinitrobenzenesulfonamide and 2.12 g (21 mmol) of triethylamine in 50 mL of methylene chloride was added 1.15 g (12.5 mmol) of thioacetic acid at room temperature. After the dark brown solution was stirred for 20 min, it was poured into 250 mL of diethyl ether, washed with a saturated solution of K_2CO_3 (2 × 100 mL), dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 7:3) to give 1.47 g (74%) of **22** as a mixture of *cis* and *trans* isomers: IR (neat) 3346, 3066, 3018, 2908, 2854, 1527, 1444, 1347, 1109, 964, 855, 787, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (1 H, d, $J = 8.0$ Hz), 7.63−7.56 (2 H, m), 7.40 (1 H, t, $J = 7.5$ Hz), 5.65−5.49 (2 H, m), 4.02 and 4.01 (2 H, two singlets), 3.31 and 3.20 (2 H, two doublets, $J = 6.5$ and $J = 6.0$ Hz); 1.68 and 1.62 (3 H, two doublets $J = 6.0$ and $J = 7.0$ Hz), 1.67 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 149.31, 135.92, 133.27, 131.50, 129.36, 128.58, 128.06, 128.02, 127.91, 126.86, 124.86, 51.42, 50.36, 50.17, 34.70, 17.94, 13.20; EIMS *m/z* 206 (M^+), 205, 189, 158, 151, 144, 136, 135, 134, 118, 105, 91, 78; HRMS calcd for $C_{11}H_{14}N_2O_2$ 206.1055, found 206.1050.

Methyl *N*-Crotyl-*N*-(α-methylbenzyl)malonylamide (4a). The following procedure is representative for the preparation of the malonylamides used in this study. To a mixture of 4.1 g (23.4 mmol) of *N*-crotyl-α-methylbenzylamine, 0.32 g (2.6 mmol) of DMAP, and 2.9 g (4.0 mL, 28.7 mmol) of triethylamine in 65 mL of dry ethyl acetate was added at 0 °C 4.1 g (29 mmol) of 97% pure methyl malonyl chloride in 25 mL of dry ethyl acetate. After stirring at 0 °C for 1 h and at room temperature for 2 h, the reaction mixture was poured into 150 mL of ethyl acetate and washed with 100 mL of 2.0 N HCl solution and then with 100 mL of 10% aqueous Na_2CO_3. The organic layer was separated, dried over Na_2SO_4, and concentrated to afford crude **4a** The product was purified by column chromatography (silica gel, EtOAc) to give 5.66 g (88%) of **4a** as a light yellow oil that was a mixture of *cis* and *trans* isomers: IR (neat) 3024, 2953, 1746, 1641, 1437, 1335, 1256, 1204, 1161, 1027, 970, 782, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.26 (5 H, m), 6.08 (1 H, q, $J = 7.5$ Hz), 5.52−5.41 (1 H, m), 5.21−5.03 (1 H, m), 3.77 (3 H, s), 3.66−3.45 (4 H, m), 1.66−1.60 (3 H, m), 1.54 (3 H, d, $J = 7.0$ Hz).

Methyl *N*-Crotyl-*N*-benzylmalonylamide (4b). Isolated in 77% yield as a light yellow oil that was a mixture of isomers: IR (neat) 3028, 3005, 2953, 2920, 1751, 1652, 1473, 1326, 1262, 1202, 1160, 1027, 1013, 970, 952, 731, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.29 (4 H, m), 7.25−7.22 (1 H, m), 5.75−5.59 (1 H, m), 5.51−5.34 (1 H, m), 4.66 and 4.55 (2 H, two singlets), 3.82 and 3.77 (3 H, two singlets), 4.12−3.51 (4 H, m), 1.77−1.73 and 1.63−1.59 (3 H, m); ^{13}C NMR($CDCl_3$) δ 168.41, 166.46, 137.25, 136.38, 129.81, 129.26, 129.16, 128.77, 128.31, 127.91, 127.58, 126.63, 126.52, 125.35, 125.10, 52.63, 50.66, 49.38, 48.37, 47.71, 44.60, 41.42, 41.24, 17.84; EIMS *m/e* 261 (M^+), 230, 206, 170, 162, 145, 120, 106, 96, 91, 77, 70, 65, 55; HRMS calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1363. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.75; N, 7.34; N, 5.30.

Methyl *N*-Crotyl-*N*-(4′-methoxybenzyl)malonylamide (4c). Isolated in 82% yield as a light yellow oil that was a mixture of *cis* and *trans* isomers: IR (neat) 2999, 2960, 1749, 1652, 1513, 1437, 1248, 1175, 1032, 971, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 and 7.08 (2 H, two doublets, $J = 9.0$ and $J = 9.0$ Hz), 6.87 and 6.83 (2 H, two doublets, $J = 8.5$ and $J = 9.0$ Hz), 5.70−5.51 (1 H, m), 5.43−5.25 (1 H, m), 4.52 and 4.41 (2 H, two singlets), 4.04−3.69 (5 H, m), 3.49 and 3.46 (2 H, two singlets), 1.70−1.66 and 1.57−1.53 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 168.40 and 168.30, 166.3, 159.40 and 159.10, 129.71, 129.10, 127.86, 125.42 and 125.20, 114.5 and 114.1, 55.48 and 55.42, 52.56, 50.15, 49.10, 47.74 and 47.38, 41.39 and 41.42, 17.87 and 17.70; EIMS *m/z* 291(M^+), 263, 162, 136, 121, 91, 70; HRMS calcd for $C_{16}H_{21}N_1O_4$ 291.1470, found 291.1462. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.14; H, 7.36; N, 4.85.

Methyl *N*-Crotyl-*N*-(3′,4′-dimethoxybenzyl)malonylamide (4d). Isolated in 87% yield as a mixture of isomers, a light yellow oil: IR (neat) 3001, 2954, 2837, 1742, 1649, 1517, 1441, 1417, 1324, 1261, 1238, 1208, 1155, 1140, 1027, 970, 920, 809, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88−6.70 (3 H, m), 5.72−5.56 (1 H, m), 5.47−5.30 (1 H, m), 4.55 and 4.40 (2 H, two singlets), 3.89−3.88 (7 H, m), 3.77−3.74 (4 H, m), 3.54−3.49 (2 H, m), 1.74−1.69 and 1.61−1.53 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 168.95 and 168.84, 166.96 and 166.78, 150.20 and 149.95, 149.29 and 149.12, 130.35 and 130.25, 129.59, 125.73, 121.18 and 119.25, 112.85, 111.60, 56.62 (two carbons), 53.13, 51.06, 49.07, 48.63, 48.16, 41.85 and 41.70, 18.45 and 18.37; EIMS *m/z* 321 (M^+), 290, 266, 222, 192, 166, 151, 139, 132, 124, 107, 101, 87, 77, 70; HRMS calcd for $C_{17}H_{23}N_1O_5$ 321.1576, found 321.1555.

Methyl *N*-Crotyl-*N*-(2′-nitrobenzyl)malonylamide (23). Isolated in 82% yield as a light yellow oil that was a mixture of isomers: IR (neat) 3004, 2945, 1733, 1653, 1525, 1437, 1337, 1198, 1160, 1009, 961, 860, 785, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 and 8.04 (1 H, two doublets, $J = 8.0$ and $J = 8.0$ Hz), 7.70 and 7.63 (1 H, two triplets, $J = 6.5$ and $J = 6.5$ Hz), 7.56−7.50 (1 H, m), 7.44−7.39 (1 H, m), 5.73−5.52 (1 H, m), 5.45−5.27 (1 H, m); 4.9 and 4.89 (2 H, two singlets), 3.96 and 3.84 (2 H, two br singlets), 3.80 and 3.69 (3 H, two singlets), 3.60 and 3.40 (2 H, m), 1.71−1.66 and 1.57−1.50 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 168.46 and 167.77, 166.92 and 166.80, 148.57 and 147.98, 134.41, 134.00, 132.95, 130.46, 129.80, 129.33, 128.84, 128.77, 128.08, 127.84, 125.91, 125.16, 124.75, 124.61, 124.43, 52.72 and 52.63, 50.78, 48.57 and 48.25, 46.51, 46.40, 45.85, 41.12, 40.97, 17.77, 12.99; EIMS *m/z* 307 (MH^+), 291, 289, 175, 262, 233, 205, 189, 170, 151, 128, 119, 105, 95, 89, 70. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.95; N, 5.94; H, 9.03.

Methyl *N*-Crotyl-*N*-phenethylmalonylamide (27). Isolated in 83% yield as a light yellow oil that was a mixture of isomers: IR (neat) 3019, 2943, 1742, 1644, 1435, 1325, 1261, 1197, 1156, 1011, 971, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.27 (2 H, m), 7.24 (2 H, d, $J = 6.0$ Hz), 7.17 (1 H, d, $J = 7.0$ Hz), 5.74−5.54 (1 H, m), 5.49−5.29 (1 H, m), 4.11 and 3.98 (1 H, two doublets, $J = 7.0$ and 6.0 Hz), 3.78 and 3.74 (3 H, two singlets), 3.68−3.67 (1 H, m), 3.58−3.56 (1 H, m), 3.49−3.46 (2 H, m), 3.25 and 3.23 (1 H, two singlets), 2.92−2.84 (2 H, m), 1.73−1.70 and 1.65−1.63 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 168.35, 166.03, 165.80, 139.34, 138.18, 129.30, 129.04, 128.89,

128.64, 127.04, 126.49, 125.85, 125.45, 52.55, 51.17, 49.30, 48.49, 47.43, 46.19, 41.38, 40.86, 35.13, 34.07, 17.88, 17.77; EIMS *m/z* 275(M^+), 274, 244, 202, 185, 184, 174, 148, 130, 105, 104, 101, 91, 84, 77; HRMS calcd for $C_{16}H_{21}NO_3$ 275.1517, found 275.1515.

Methyl *N*-Crotylmalonylamide (4, R = H). To a suspension of 2.68 g (25 mmol) of crotylamine hydrochloride and 0.39 g (3.2 mmol) of DMAP in a mixture of 60 mL of dry EtOAc and 6.24 g (8.6 mL, 62 mmol) of dry triethylamine was added a solution of 3.96 g (3.1 mL, 29 mmol) of methyl malonyl chloride in 20 mL of dry EtOAc at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 4 h. The mixture was poured into 150 mL of EtOAc and washed with 100 mL of 2 N HCl followed by 100 mL of 10% aqueous Na_2CO_3. The organic layer was separated, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to afford 1.34 g (31% yield) of **4** (R = H) as a white solid: IR (KBr) 3289, 3077, 2949, 1745, 1644, 1559, 1436, 1280, 1155, 1024, 979, 850, 722, 614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (1 H, br s), 5.69−5.62 (1 H, m), 5.55−5.43 (1 H, m), 3.94 and 3.84 (2 H, two triplets for cis and trans isomers), 3.75 (3 H, s), 3.33 (2 H, s), 1.69 (3 H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.24, 164.70, 128.82, 126.53, 52.63, 41.68, 41.06, 17.89; EIMS *m/z* 171 (M^+) 156, 142, 111, 96, 83, 70; HRMS calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0884. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.20; H, 7.49; N, 8.26.

1-(α-Methylbenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (5a). The following procedure is representative for the preparation of the 4-vinyl-2-pyrrolidinones reported below. To a well degassed mixture of 4.82 g (18.0 mmol) of manganese(III) acetate dihydrate and 1.8 g (9.0 mmol) of copper(II) acetate monohydrate in 70 mL of acetic acid was added a well degassed solution of 2.48 g (9.0 mmol) of methyl *N*-crotyl-*N*-(α-methylbenzyl)malonylamide (**4a**) in 20 mL of acetic acid. The resulting mixture was stirred at room temperature for 18 h. The sky-blue mixture was poured into 300 mL of ethyl ether and washed with 50 mL of 10% aqueous sodium thiosulfate solution. The organic layer was separated, and the aqueous layer was extracted with 100 mL of ethyl ether. The combined organic solution was washed with saturated aqueous Na_2CO_3, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 70:30) to afford 2.38 g (97%) of **5a** as a mixture of two diastereomers. Although the two diastereomers can be separated by column chromatography, the mixture of diastereomers was used for next step: IR (neat) mixture of two diastereomers 3064, 3029, 2976, 2952, 1741, 1695, 1426, 1257, 1206, 1166, 701 cm^{-1}; (a) R_f = 0.40; ^1H NMR ($CDCl_3$) δ 7.38−7.30 (5 H, m), 5.70−5.61 (1 H, ddd, J = 17.0, 10.5 and 7.5 Hz), 5.51 (1 H, q, J = 7.0 Hz), 5.11 (1 H, d, J = 17.0 Hz), 5.07 (1 H, d, J = 10.5 Hz), 3.82 (3 H, s), 3.56−3.52 (1 H, m), 3.39−3.30 (2 H, m), 2.75−2.71 (1 H, m), 1.57 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.46, 169.21, 140.21, 136.96, 129.36, 128.47, 127.88, 117.93, 55.43, 53.35, 50.41, 46.65, 41.09, 16.85; (b) R_f = 0.34; ^1H NMR ($CDCl_3$) δ 7.40−7.30 (5 H, m), 5.83−5.76 (1 H, m), 5.50 (1 H, q, J = 7.0 Hz), 5.17 (1 H, dm, J = 17.0 Hz), 5.14 (1 H, dm, J = 10.0 Hz), 3.82 (3 H, s), 3.41−3.39 (1 H, m), 3.29 (1 H, quintet, J = 8.5 Hz), 3.22 (1 H, dd, J = 9.5 Hz), 3.11−3.07 (1 H, m), 1.56 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.49, 169.28, 140.26, 136.95, 129.37, 128.36, 127.66, 118.08, 55.37, 53.36, 50.22, 46.74, 41.23, 16.86.

1-Benzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (5b). Isolated as a mixture of two diastereomers as a light yellow oil in 94% yield: IR (neat) 3071, 3032, 2953, 1740, 1698, 1652, 1436, 1256, 1168, 1003, 924, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.21 (5 H, m), 5.74−5.68 (1 H, m), 5.11 (1 H, d, J = 16.5 Hz), 5.06 (1 H, d, J = 10.0 Hz), 4.44 (2 H, s), 3.76 (3 H, s), 3.43−3.39 (1 H, m), 3.36−3.34 (2 H, m), 3.02−2.99 (1 H, m); ^{13}C ($CDCl_3$) δ 169.60, 168.78, 136.09, 135.68, 128.62, 127.96, 127.61, 117.14, 54.10, 52.47, 49.78, 46.66, 40.29; EIMS *m/z* 259 (M^+), 228, 206, 201, 200, 199, 172, 170, 162, 146, 136, 132, 119, 118, 117, 108, 106, 104, 92, 91, 81, 77, 65, 53; HRMS calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1196.

1-(4′-Methoxybenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (5c). Isolated in 92% yield as a mixture of two diastereomers as a light yellow oil: IR (neat) 3071, 3006, 2954, 1740, 1696, 1514, 1437, 1248, 1175, 1032, 924, 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (2 H, d, J = 9.0 Hz), 6.85 (2 H, d, J = 8.5 Hz), 5.75−5.68 (1 H, ddd, J = 17.0, 10.0 and 3.5 Hz), 5.11 (1 H, d, J = 17.5 Hz), 5.08 (1 H, d, J = 10.5 Hz), 4.39 (2 H, AB, J = 7.0 Hz), 3.80 (3 H, s), 3.79 (3 H, s), 3.77−3.70 (1 H, m), 3.43−3.33 (2 H, m), 3.01−2.98 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 169.99, 168.98, 159.42, 136.44, 129.74, 128.03, 117.51, 114.33, 55.47, 54.56, 52.90, 50.05, 46.52, 40.53; EIMS *m/z* 289 (M^+), 230, 202, 176, 162, 149, 136, 121, 77, 55; HRMS calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1310. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.72; N, 4.87.

1-(3′,4′-Diethoxybenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (5d). Isolated in 86% yield as a mixture of isomers as a light yellow oil: IR (neat) 3081, 3009, 2954, 2838, 1741, 1694, 1593, 1516, 1437, 1358, 1262, 1157, 1140, 1027, 923, 854, 813, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85−6.76 (3 H, m), 5.74−5.67 (1 H, ddd, J = 17.5, 10.5 and 3.5 Hz), 5.14 (1 H, d, J = 17.5 Hz), 5.08 (1 H, d, J = 10.5 Hz), 4.29 (2 H, s), 3.86 (3 H, s), 3.85 (3 H, s), 3.79 (3 H, s), 3.56−3.42 (1 H, m), 3.38−3.32 (2 H, m), 3.04−2.99 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 170.01, 169.08, 149.49, 148.87, 136.47, 128.50, 120.79, 117.49, 111.37, 111.24, 56.11, 56.09, 54.53, 52.90, 50.12, 46.90, 40.49; EIMS *m/z* 319 (M^+), 304, 288, 260, 232, 206, 192, 179, 166, 151, 136, 121, 127, 91, 77, 67; HRMS calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1426.

1-(2′-Nitrobenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (24). Isolated as a mixture of isomers in 93% yield as a yellow oil: IR (neat) 3079, 2955, 1739, 1699, 1653, 1528, 1436, 1343, 1253, 1169, 1046, 1005, 857, 791, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (1 H, d, J = 8.0 Hz), 7.62 (1 H, t, J = 8.0 Hz), 7.47 (2 H, d, J = 8.0 Hz), 5.82−5.75 (1 H, ddd, J = 17.0, 10.0 and 7.0 Hz), 5.19 (1 H, d, J = 17.0 Hz), 5.16 (1 H, d, J = 10.0 Hz), 4.94 (1 H, d, J = 16.0 Hz), 4.73 (1 H, d, J = 16.0 Hz), 3.83 (3 H, s), 3.63−3.57 (1 H, m), 3.43−3.39 (2 H, m), 3.16 (1 H, dd, J = 9.5 and 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.00, 169.91, 148.82, 136.18, 134.12, 131.60, 129.91, 128.84, 125.26, 117.84, 54.10, 53.04, 51.18, 43.89, 40.68; EIMS *m/z* 305 (MH^+), 289, 274, 273, 258, 170, 138, 136, 135, 119, 108, 95, 91, 79, 78; HRMS calcd for $C_{15}H_{17}N_2O_5$ 305.1137, found 305.1148.

1-Phenethyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (28). Isolated as a mixture of isomers in 87% yield as a yellow oil: IR (neat) 3094, 3057, 3023, 2951, 1740, 1690, 1485, 1429, 1318, 1207, 1163, 1007, 918, 752, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.30 (2 H, m), 7.25−7.21 (3 H, m), 5.71 (1 H, ddd, J = 17.0, 10.5 and 7.5 Hz), 5.14 (1 H, d, J = 17.0 Hz), 5.10 (1 H, d, J = 10.5 Hz), 3.79 (3 H, s), 3.56 (2 H, t, J = 7.5 Hz), 3.40 (1 H, t, J = 9.0 Hz), 3.33 (1 H, t, J = 8.0 Hz), 3.26 (1 H, d, J = 8.5 Hz), 3.02 (1 H, dd, J = 9.0 and 7.5 Hz), 2.87 (2 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 169.92, 168.92, 138.58, 136.50, 128.84, 128.75, 126.74, 117.35, 54.45, 52.75, 51.38, 44.60, 40.60, 33.83; EIMS *m/z* 273(M^+), 242, 214, 182, 151, 150, 132, 122, 121, 105, 104, 91, 77, 67; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1315, found 273.1350.

3-Methoxycarbonyl-4-vinyl-2-pyrrolidinone (26). A solution of 15 mg (0.049 mmol) of 1-(2′-nitrobenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (**24**) in 15 mL of methanol (3.0×10^{-6} M) was degassed thoroughly and then irradiated with a mercury vapor lamp in a quartz tube for 1.5 h. After evaporation of the methanol, the product was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2 1:1) to give 1.1 mg (14%) of **26** as a yellow oil: ^1H NMR ($CDCl_3$) δ 6.22 (1 H, br s), 5.87 (1 H, ddd, J = 17.0, 10.0 and 7.0 Hz), 5.23 (1 H, d, J = 17.0 Hz), 5.17 (1 H, d, J = 10.0 Hz), 3.80 (3 H, s), 3.61 (1 H, q, J = 8.5 Hz), 3.57 (1 H, t, J = 8.0 Hz), 3.30 (1 H, d, J = 8.5 Hz), 3.20 (1 H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 168.21, 153.47, 136.26, 117.76, 53.45, 52.99, 45.85, 43.38; EIMS *m/z* 169 (M^+), 138, 137, 113, 111, 110, 97, 82, 81, 80; HRMS calcd for $C_8H_{11}NO_3$ 169.0739, found 169.0734.

1-Benzyl-3-methoxycarbonyl-4-ethyl-2-pyrrolidinone (15). Method A. To a mixture of 0.259 g (1.0 mmol) of 1-benzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (**5b**) and

0.39 g of 10% Pd/C in 20 mL of methanol was added 0.64 g (10.0 mmol) of ammonium formate in one portion. The resulting mixture was stirred at reflux overnight. The mixture was cooled to room temperature and passed through a Celite pad. The methanol was evaporated, and 50 mL of ethyl acetate was added. The solution was washed with water (3 × 30 mL), dried with Na_2SO_4, concentrated, and dried under vacuum to give 0.256 g (98% yield) of **15** as a colorless oil: IR (neat) 3059, 3031, 2953, 1741, 1696, 1493, 1435, 1349, 1263, 1168, 916, 733, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.24 (5 H, m), 4.48 (2 H, s), 3.81 (3 H, s), 3.44 (1 H, t, J = 9.0 Hz), 3.21 (1 H, d, J = 8.0 Hz), 2.88 (1 H, dd, J = 9.0 and 7.0 Hz), 2.64 (1 H, q, J = 7.0 Hz), 1.57−1.43 (2 H, m), 0.89 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.85, 169.73, 136.09, 128.90, 128.25, 127.87, 54.99, 52,78, 50.75, 47.06, 38.07, 26.90, 11.56; EIMS m/z 261(M^+), 230, 202, 172, 119, 106, 91, 77, 69; HRMS calcd for $C_{15}H_{19}NO_3$ 261.1345, found 261.1363.

Method B. A mixture of 0.259 g (1.0 mmol) of 1-benzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone and 0.39 g of 10% Pd/C in 20 mL of methanol was hydrogenated at room temperature under 50 psi for 4 h. The reduction mixture was passed through a Celite pad, and the methanol was evaporated under vacuum to give 0.261 g (100%) of the product as a colorless oil that was >99% pure by ^1H NMR.

1-Phenethyl-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrrolidinone (29). A mixture of 1-phenethyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (1.2 g, 4.4 mmol), $Pd(OAc)_2$ (99 mg, 0.44 mmol), CuI (85 mg, 0.44 mmol), and (o-toyl)$_3$P (268 mg, 0.88 mmol) in 40 mL of DMF was degassed and then purged with nitrogen. Methyl 4-iodobenzoate (2.31 g, 8.8 mmol) in 30 mL of DMF was degassed and added to the above mixture by a cannula. The resulting mixture was stirred at 70 °C under a nitrogen atmosphere for 18 h. The mixture was poured into 300 mL of ethyl acetate and washed with water (3 × 50 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 2:1 and then 1:1) to give 1.2 g (69%) of **29** as a yellow oil: IR (neat) 3054, 3022, 2947, 1733, 1696, 1598, 1484, 1435, 1278, 1175, 1110, 1040, 1013, 970, 867, 758, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (2 H, d, J = 8.0 Hz), 7.39 (2 H, d, J = 8.5 Hz), 7.33 (2 H, t, J = 7.5 Hz), 7.29−7.24 (3 H, m), 6.52 (1 H, d, J = 16.0 Hz), 6.16 (1 H, dd, J = 16.0 and 8.5 Hz), 3.93 (3 H, s), 3.82 (3 H, s), 3.70−3.57 (2 H, m), 3.57−3.51 (1 H, m), 3.47 (1 H, t, J = 8.5 Hz), 3.37 (1 H, d, J = 8.5 Hz), 3.11 (1 H, t, J = 7.5 Hz), 2.91 (2 H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 169.74, 168.73, 166.87, 140.79, 138.50, 131.80, 130.51, 134.11, 129.51, 128.86, 128.81, 126.83, 126.37, 54.66, 52.92, 52.42, 51.56, 44.57, 40.22, 33.83; EIMS m/z 407 (M^+), 376, 348, 316, 284, 255, 244, 199, 187, 169, 155, 149, 143, 128, 115, 113, 104, 91, 77; HRMS calcd for $C_{24}H_{25}NO_5$ 407.1736, found 407.1735.

1-(4′-Nitrophenethyl)-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrrolidinone (30a) and 1-(2′-Nitrophenethyl)-3-methoxycarbonyl-4-(4′-methoxy-carbonylstyryl)-2-pyrrolidinone (30b). To a mixture of 0.56 g (1.38 mmol) of **29** and 0.122 g (1.52 mmol) of NH_4NO_3 in 10 mL of methylene chloride was added 2.89 g (13.8 mmol, 1.95 mL) of trifluoroacetic anhydride at room temperature. The resulting mixture was stirred for 7 h. The reaction mixture was poured into 150 mL of ethyl acetate, and the mixture was washed with 60 mL of K_2CO_3 solution. The organic layer was separated, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to afford 457 mg (84%) of p-nitro and o-nitro products as well as 40 mg of unchanged starting material. **4′-Nitro product (30a):** IR (neat) 3070, 3037, 2951, 1701, 1604, 1518, 1437, 1340, 1281, 1206, 1136, 1109, 1017, 969, 850, 801, 758, 721, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (2 H, d, J = 8.5 Hz), 8.00 (2 H, d, J = 8.0 Hz), 7.42 (2 H, d, J = 9.0 Hz), 7.40 (2 H, d, J = 8.0 Hz), 6.54 (1 H, J = 16.0 Hz), 6.18 (1 H, dd, J = 16.0 and 7.5 Hz), 3.96 (3 H, s), 3.82 (3 H, s), 3.75−3.53 (4 H, m), 3.45−3.36 (1 H, m), 3.22−3.18 (1 H, m), 3.03 (2 H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.62, 169.22, 166.89, 156.51, 147.19, 146.07, 140.61, 132.23, 130.22, 129.99, 129.80, 126.43, 124.10, 54.43, 53.16, 52.34, 51.64, 44.01, 40.16, 33.63; EIMS m/z 452 (M^+), 421, 407, 393, 376, 361, 348, 316, 284, 256, 244, 216, 215, 184, 170, 155, 149, 143, 133, 129, 115, 104, 91, 77; HRMS calcd for $C_{24}H_{24}N_2O_7$ 452.1591, found 452.1578. **2′-Nitro product (30b):** ^1H NMR ($CDCl_3$) δ 8.00 (2 H, d, J = 8.5 Hz), 7.99 (1 H, d, J = 7.5 Hz), 7.59 (1 H, t, J = 7.0 Hz), 7.45 (2 H, d, J = 7.5 Hz), 7.40 (2 H, d, J = 8.5 Hz), 6.55 (1 H, d, J = 16.0 Hz), 6.22 (1 H, dd, J = 16.0 and 8.0 Hz), 3.92 (3 H, s), 3.81 (3 H, s), 3.70−3.55 (4 H, m), 3.41 (1 H, d, J = 8.5 Hz), 3.29 (1 H, t, J = 8.0 Hz), 3.18 (2 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 169.70, 169.10, 166.90, 149.47, 140.76, 133.60, 132.93, 132.03, 130.22, 130.14, 129.56, 128.87, 128.20, 126.42, 125.21, 54.57, 52.98, 52.26, 51.50, 43.82, 40.30, 31.17.

1-(α-Methylbenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (6a). The following procedure is representative for the preparation of the 2-pyrrolidinethiones described herein. A mixture of 0.9 g (3.3 mmol) of 1-(α-methylbenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinone (**5a**) and 0.88 g (4.0 mmol) of P_4S_{10} in 45 mL of dry THF was heated to reflux. The reaction was monitored by TLC. When the starting material completely disappeared (about 2.5 h), the mixture was cooled to room temperature, and solid was removed by filtration. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to give 0.65 g (68%) of **6a** as a light yellow oil that was a mixture of two diastereomers: IR (neat) 3069, 3021, 2980, 2944, 1741, 1491, 1448, 1290, 1209, 1166, 1124, 1027, 920, 784, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.34 (5 H, m), 6.42−6.33 (1 H, m), 5.82−5.61 (1 H, m), 5.22−5.15 (1 H, m), 5.10−5.07 (1 H, m), 3.86 (3 H, s), 3.90−3.75 and 3.60−3.51 (2 H, m), 3.40−3.03 (2 H, m), 1.66 and 1.64 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 196.02 and 195.65, 170.77 and 170.73, 138.96, 136.16 and 136.05, 129.57 and 129.53, 128.98 and 128.83, 127.98 and 127.69, 118.67 and 118.34, 66.72 and 66.54, 55.00 and 54.84, 53.76 and 53.71, 53.52 and 53.50, 42.92 and 42.67, 15.71 and 15.65; EIMS m/z 289(M^+), 256, 236, 176, 120, 105, 104, 79, 77; HRMS calcd for $C_{16}H_{19}NO_2S$ 289.1136, found 289.1153. Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84; S, 11.08. Found: C, 66.71; H, 6.69; N, 4.85; S, 11.09.

1-Benzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (6b). Isolated as a mixture of two diastereomers as a light yellow oil in 74% yield: IR (neat) 3084, 3060, 3023, 2951, 2864, 1740, 1506, 1453, 1436, 1330, 1250, 1209, 1165, 1029, 1000, 930, 741, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.34 (5 H, m), 5.80−5.71 (1 H, m), 5.18 (1 H, d, J = 16.0 Hz), 5.16 (1 H, d, J = 9.5 Hz), 5.07−4.99 (2 H, m), 3.88−3.82 (4 H, m), 3.78 (1 H, s), 3.44−3.39 (2 H. m); ^{13}C NMR ($CDCl_3$) δ 196.31, 170.16, 135.49, 129.09, 128.40, 128.36, 128.28, 118.03, 65.93, 57.51, 52.97, 51.78, 42.23; EIMS m/z 275 (M^+), 244, 242, 217, 216, 188, 162, 148, 117, 106, 91, 77, 65; HRMS calcd for $C_{15}H_{17}NO_2S$ 275.0980, found 275.0978. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.15; H, 6.36; N, 5.07; S, 12.17.

1-(4′-Methoxybenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (6c). Isolated in 64% as a light yellow oil: IR (neat) 3076, 2949, 2834, 1740, 1695, 1652, 1514, 1436, 1248, 1174, 1024, 924, 813 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (2 H, d, J = 8.5 Hz), 6.93 (2 H, d, J = 8.5 Hz), 5.79−5.70 (1 H, ddd, J = 17.5, 10.5 and 7.5 Hz), 5.18 (1 H, d, J = 16.5 Hz), 5.15 (1 H, d, J = 10.0 Hz), 4.96 (2 H, s), 3.88 (3 H, s), 3.86 (3 H, s), 3.84−3.78 (2 H, m), 3.41−3.37 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 195.98, 170.28, 159.78, 135.62, 129.99, 126.87, 118.10, 114.52, 66.10, 57.47, 55.55, 53.07, 51.37, 42.31; EIMS m/z 305 (M^+), 246, 192, 153, 121, 77; HRMS calcd for $C_{16}H_{19}NO_3S$ 305.1086, found 305.1082.

1-(3′,4′-Dimethoxybenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (6d). Isolated in 85% yield as a mixture of isomers, a yellow oil: IR (neat) 3070, 2950, 1742, 1690, 1438, 1244, 1167, 1023, 918, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (1 H, d, J = 2.0 Hz), 6.85−6.80 (2 H, m), 5.70 (1 H, ddd, J = 17.5, 10.0 and 7.0 Hz), 5.12 (1 H, d, J = 17.5 Hz), 5.10 (1 H, d, J = 10.0 Hz), 4.90 (2 H, AB), 3.86 (3 H, s), 3.85 (3 H, s), 3.81 (3 H, s), 3.79−3.71 (2 H, m), 3.37−3.28 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 196.01, 170.23, 149.53, 149.15, 135.58, 127.31, 120.95, 117.99, 111.45, 111.27, 66.01, 57.48, 56.13, 56.09, 52.99, 51.62, 42.19; EIMS m/z 335 (M^+), 319, 302, 288, 276,

260, 242, 222, 208, 183, 166, 151, 135, 121, 107, 91, 77, 67; HRMS calcd for $C_{17}H_{21}NO_4S$ 335.1191, found 335.1202.

1-(2′-Nitrobenzyl)-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (25). Isolated as a mixture of isomers as a yellow oil in 70% yield: IR (neat) 3076, 2951, 1740, 1527, 1506, 1452, 1339, 1277, 1206, 1162, 992, 910, 855, 784, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15−8.10 (1 H, m), 7.70−7.63 (1 H, m), 7.53−7.46 (2 H, m), 5.85−5.71 (1 H, m), 5.65−5.52 (1 H, m), 5.27−5.14 (3 H, m), 4.19−3.80 (2 H, m), 3.87 (3 H, s), 3.55−3.44 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 198.44, 170.76, 149.16, 136.01, 134.80, 130.56, 129.72, 129.57, 126.06, 118.78, 66.20, 59.17, 53.65, 49.05, 42.86; EIMS *m*/*z* 321 (MH^+), 289, 276, 275, 274, 214, 200, 188, 154, 151, 137, 136, 135, 123, 122, 121, 105, 97, 92, 91, 78, 67; HRMS calcd for $C_{15}H_{17}N_2O_4S$ (MH) 321.0831, found 321.0885. Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74; S, 10.01; Found: C, 56.41; H, 4.79; N, 8.61; N, 10.30.

1-(4′-Nitrophenethyl)-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrrolidinethione (31). A mixture of 210 mg (0.456 mmol) of 1-(4′-nitrophenethyl)-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrrolidinone (**30a**) and 0.6 g (1.3 mmol) of P_4S_{10} in 15 mL of dry THF was stirred at 70 °C for 7 h. The mixture was cooled to room temperature, and 30 mL of hexane was added. The resulting mixture was passed through a column (silica gel, hexane/ethyl acetate 1:1) to afford 165 mg (76%) of **31** as a yellow oil: IR (neat) 3070, 3037, 2945, 1720, 1607, 1518, 14955, 1346, 1261, 1178, 1111, 1018, 963, 912, 855, 765, 732, 691, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (2 H, d, J = 8.0 Hz), 7.98 (2 H, d, J = 8.0 Hz), 7.45 (2 H, d, J = 8.5 Hz), 7.37 (2 H, d, J = 8.0 Hz), 6.52 (1 H, d, J = 15.5 Hz), 6.16 (1 H, dd, J = 15.5 and 8.0 Hz), 4.13−4.07 (1 H, m), 4.01−3.94 (1 H, m), 3.91 (3 H, s), 3.89−3.83 (2 H, m), 3.82 (3 H, s), 3.57−3.49 (2 H, m), 3.24−3.11 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 195.88, 169.85, 166.77, 147.12, 145.70, 140.38, 132.46, 130.11, 129.91, 129.67, 129.09, 126.39, 124.04, 65.98, 59.50, 53.07, 52.25, 49.03, 42.12, 31.98; EIMS *m*/*z* 468 (M^+), 437, 409, 332, 286, 260, 231, 215, 184, 149, 129, 128, 103, 91, 77; HRMS calcd for $C_{24}H_{24}N_2O_6S$ 468.1384, found 468.1381.

1-(4′-Nitrophenethyl)-2-methylthio-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrroline (32). To a mixture of 1-(4′-nitrophenethyl)-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrrolidinethione (**31**) (100 mg, 0.214 mmol) and K_2CO_3 (94 mg, 0.684 mmol) in 10 mL of acetone was added 97 mg (0.684 mmol) of methyl iodide at room temperature. The resulting mixture was stirred at room temperature overnight. Residual solid was removed by filtration, and the solvent was evaporated under reduced pressure to give 97 mg (94%) of **32** as a yellow oil: IR (neat) 2948, 1718, 1670, 1606, 1520, 1495, 1345, 1278, 1102, 1110, 971, 911, 851, 764, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (2 H, d, J = 8.5 Hz), 7.98 (2 H, d, J = 8.5 Hz), 7.39 (2 H, d, J = 8.0 Hz), 7.38 (2 H, d, J = 8.5 Hz), 6.41 (1 H, d, J = 15.5 Hz), 6.26 (1 H, dd, J = 15.5 and 7.5 Hz), 3.92 (3 H,. s), 3.84−3.79 (1 H, tm, J = 10.5 Hz), 3.78−3.58 (3 H, m), 3.32 (3 H, s), 3.32 (1 H, dd, J = 10.0 and 3.5 Hz), 2.99−2.89 (2 H, m), 2.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 167.04, 165.27, 160.89, 146.96, 146.51, 141.98, 134.18, 130.05, 129.91, 128.86, 128.64, 126.22, 123.94, 103.22, 57.45, 52.20, 50.69, 48.62, 42.99, 34.97, 18.25; EIMS *m*/*z* 482(M^+), 480, 433, 376, 246, 330, 312, 266, 209, 175, 131, 104, 91; HRMS calcd for $C_{25}H_{26}N_2O_6S$ 482.1511, found 482.1355.

1-(4′-Nitrophenethyl)-2-methylthio-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)pyrrole (33). To a mixture of 135 mg (0.28 mmol) of 1-(4′-nitrophenethyl)-2-methylthio-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)-2-pyrroline (**32**) in 20 mL of acetonitrile was added 0.47 g (3.0 mmol) of DBU at room temperature. The resulting mixture was stirred for 7 h, and the color of the mixture changed slowly to brown. The acetonitrile was evaporated under reduced pressure, and the residue was purified by column chromatorgaphy (silica gel, ethyl acetate/hexane 1:2 and then 1:1) to afford 74 mg (55%) of **33** as a yellow oil: IR (neat) 3112, 3061, 2927, 2854, 1716, 1615, 120, 1473, 1437, 1346, 1314, 1276, 1213, 1177, 1108, 1059, 951, 854, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14 (2 H, d, J = 8.5 Hz), 7.96 (2 H, d, J = 8.5 Hz), 7.62 (1 H, d, J = 16.5 Hz), 7.46 (2 H, d, J = 8.5 Hz), 7.23 (2 H, d, J = 8.5 Hz), 6.93 (1 H, s), 6.69 (1 H, d, J = 16.5 Hz), 4.38 (2 H, t, J = 7.0 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 3.14 (2 H, t, J = 7.0 Hz), 2.46 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 167.10, 164.93, 147.26, 145.34, 142.49, 130.12, 129.91, 128.58, 126.40, 126.16, 124.42, 124.40, 124.10, 120.36, 118.17, 52.19, 51.50, 48.34, 38.07, 20.49; EIMS *m*/*z* 408(M^+), 433, 405, 344, 331, 312, 298, 284, 266, 256, 238, 225, 210, 150, 139, 120, 104, 103, 91, 77; HRMS calcd for $C_{25}H_{24}N_2O_6S$ 480.1355, found 480.1344.

1-(4′-Nitrophenethyl)-2-methylsulfonyl-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)pyrrole (34). To a mixture of 15 mg (0.031 mmol) of 1-(4′-nitrophenethyl)-2-methylthio-3-methoxycarbonyl-4-(4′-methoxycarbonylstyryl)pyrrole in 1 mL of trifluoroacetic acid at 0 °C (ice−salt) was added 10 μL of H_2O_2 (30% in H_2O). The mixture changed immediately to a deeper color. The progress of the reaction was monitored by TLC. After 1 h, the starting material had completely disappeared. The TFA was evaporated under reduced pressure at 0 °C, and the residue was purified by column chromatography (silica gel, ethyl acetate) to afford 4.6 mg (30%) of **34** as a light pink oil: ^1H NMR ($CDCl_3$) δ 8.18 (2 H, d, J = 8.0 Hz), 8.01 (2 H, d, J = 8.5 Hz), 7.54 (1 H, d, J = 16.5 Hz), 7.49 (2 H, d, J = 8.0 Hz), 7.41 (2 H, d, J = 8.0 Hz), 6.96 (1 H, s), 6.76 (1 H, d, J = 16.5 Hz), 4.90 (1 H, m), 4.56 (1 H, m), 3.92 (3 H, s), 3.90 (3 H, s), 3.37 (1 H, m), 3.28 (1 H, m), 3.01 (3 H, s); EIMS *m*/*z* 512(M^+), 496, 481, 465, 449, 433, 417, 401, 347, 333, 312, 300, 256, 196, 163, 155, 120, 104, 78; HRMS calcd for $C_{25}H_{24}N_2O_8S$ 512.1253, found 512.1244.

2-Amino-4-oxo-5-vinyl-7-(α-methylbenzyl)-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (7a). The following procedure is representative for the preparation of the 5,6-dihydropyrrolo[2,3-*d*]pyrimidines reported herein. To a suspension of 4.3 g (45 mmol) of guanidine hydrochloride in 20 mL of dry methanol was added 2.43 g (45 mmol) of freshly made sodium methoxide in methanol. After stirring at room temperature for 30 min, the solution was filtered and added to a mixture of 2.6 g (8.99 mmol) of 1-(a-methylbenzyl-3-methoxycarbonyl-4-vinyl-2-pyrrolidinethione (**6a**). The resulting mixture was stirred for 5 min, concentrated in vacuo to remove most of the methanol, and then slowly heated to 90 °C for 1 h under reduced pressure (about 15 Torr). After cooling to ambient temperature, 40 mL of water was added, and the mixture was boiled for 30 min. The resulting suspension was cooled to room temperature, adjusted to pH 7 by addition of 1 N HCl, filtered, washed with water followed with ethyl ether, and dried under vacuum to give 1.27 g (50% yield) of **7a** as a white solid, mp 180 °C (decomp): IR (KBr) 3312, 3123, 2977, 2874, 1653, 1617, 1669, 1533, 1438, 1384, 1362, 1340, 1317, 775, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.70 (1 H, s), 7.37−7.26 (5 H, m), 6.44 (2 H, s), 5.71 (1 H, ddd, J = 17.0, 10.0 and 6.0 Hz), 5.32−5.28 (1 H, q, J = 7.0 Hz), 4.91 (1 H, d, J = 17.0 Hz), 4.86 (1 H, d, J = 10.0 Hz), 3.63−3.46 (2 H, m), 2.78 (1 H, m), 1.47 (3 H, d, J = 6.5 Hz); ^{13}C NMR (DMSO-d_6) δ 167.93, 159.81, 158.28, 142.50, 141.20, 129.52, 128.13, 127.89, 114.37, 88.68, 50.90, 50.31, 39.58, 17.49; EIMS *m*/*z* 282 (M^+), 267, 178, 176, 177, 163, 151, 134, 105, 79; HRMS calcd for $C_{16}H_{18}N_4O$ 282.1481, found 282.1498.

2-Amino-4-oxo-5-vinyl-7-benzyl-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (7b). Isolated in 74% yield as a white solid, mp 220 °C (decomp): IR (KBr) 3410, 3302, 3107, 2851, 1654, 1616, 1545, 1449, 1366, 1325, 1234, 911, 773, 701 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.82 (1 H, s), 7.36−7.28 (2 H, m), 7.26−7.15 (3 H, m), 6.48 (2 H br s), 5.83−5.76 (1 H, m), 4.97 (1 H, d, J = 17.0 Hz), 4.90 (1 H, d, J = 10.5 Hz), 4.41 (2 H, AB, J = 21.5 Hz), 3.58 (1 H, br s), 3.43 (1 H, t, J = 9.8 Hz), 3.04 (1 H, br s); ^{13}C NMR (DMSO-d_6) δ 167.36, 158.72, 157.20, 139.93, 137.72, 128.47, 127.50, 127.03, 113.32, 87.55, 54.03, 47.46, 38.68; EIMS *m*/*z* 268 (M^+), 253, 241, 215, 201, 177, 175, 163, 149, 135, 133, 120, 106, 91, 78, 63; HRMS calcd for $C_{15}H_{16}N_4O$ 268.1324, found 268.1346. This compound was too insoluble for recrystallization and purification, and it was therefore converted to the much more soluble **2-pivaloylamino-4-oxo-5-vinyl-7-benzyl-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine**. To a solution of 52 mg (0.19 mmol) of **7b** in 5 mL of dry pyridine was added 0.59 g (0.6 mL, 4.9 mmol) of pivaloyl chloride. The resulting mixture was heated to 80−90 °C for 2 h. The solution was evaporated to dryness under vacuum, and

the residue was dissolved in 3 mL of methanol followed by addition of NH_4OH to adjust the pH to 7. Methylene chloride was added, and the mixture was washed with water (2 × 20 mL). The organic layer was separated, dried, and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2 1:1) to give 51 mg (76% yield) of the 2-pivaloyl derivative of **7b** as a white solid, mp 150−152 °C: IR (KBr) 3214, 2962, 1655, 1601, 1553, 1473, 1435, 1271, 1318, 1215, 1162, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.34 (1 H, s), 8.33 (1 H, s), 7.36−7.28 (3 H, m), 7.21 (2 H, d, J = 7.0 Hz), 5.90 (1 H, ddd, J = 17.0, 10.0 and 7.0 Hz), 5.14 (1 H, d, J = 17.5 Hz), 5.05 (1 H, d, J = 10.0 Hz), 4.44 (2 H, AB, J = 13.5 Hz), 3.90−3.86 (1 H, m), 3.54 (1 H, t, J = 10.0 Hz), 3.18 (1 H, dd, J = 10.0 and 5.5 Hz), 1.32 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 179.86, 165.99, 157.84, 152.05, 138.24, 137.07, 128.83, 127.76, 127.65, 114.91, 94.63, 54.89, 48.49, 40.36, 39.43, 27.14; EIMS *m*/*z* 352 (M^+), 350, 337, 3255, 295, 268, 261, 225, 177, 175, 141, 91; HRMS calcd for $C_{20}H_{24}N_4O_2$ 352.1900, found 352.1901. Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.37; H, 6.88; N, 15.96.

2-Amino-4-oxo-5-vinyl-7-(4′-methoxybenzyl)-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (7c). Isolated in 72% yield as a white solid, mp 208 °C (decomp): IR (KBr) 3407, 3310, 3110, 2836, 1653, 1616, 1541, 1515, 1443, 1386, 1361, 1324, 1250, 1174, 1036, 914, 773 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (1 H, s), 7.14 (2 H, d, J = 8.5 Hz), 6.89 (2 H, d, J = 8.0 Hz), 6.45 (2 H, s), 5.77 (1 H, quintet, J = 7.5 Hz), 4.96 (1 H, d, J = 17.0 Hz), 4.89 (1 H, d, J = 10.0 Hz), 4.34 (2 H, AB, J = 15.0 Hz), 3.72 (3 H, s), 3.56 (1 H, m), 3.39 (1 H, t, J = 9.8 Hz), 3.00 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 167.28, 158.64, 158.34, 157.14, 139.94, 129.42, 128.90, 113.84, 113.27, 87.61, 55.00, 53.82, 46.88, 38.63; EIMS *m*/*z* 298 (M^+), 245, 177, 170, 141, 97, 85, 77, 57; HRMS calcd for $C_{16}H_{18}N_4O_2$ 298.1430, found 298.1435. Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.40; H, 6.08; N, 18.79. Found: C, 63.99; H, 6.17; N, 18.13. **2-Pivaloylamino-4-oxo-5-vinyl-7-(4′-methoxybenzyl)-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine** was prepared from **7c** as described above as a further confirmation of its assigned structure; it was isolated in 85% as a light yellow solid, mp 88−90 °C: IR (KBr) 3218, 2968, 1653, 1603, 1559, 1540, 1512, 1437, 1246, 1168, 1031, 925 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.42 (1 H, s), 10.94 (1 H, s), 7.17 (2 H, d, J = 8.0 Hz), 6.92 (2 H, d, J = 8.0 Hz), 5.82 (1 H, m), 5.00 (1 H, d, J = 17.5 Hz), 4.96 (1 H, d, J = 10.0 Hz), 4.47 (2 H, q, J = 22.0 Hz), 3.74 (3 H, s), 3.70 (1 H, br s), 3.50 (1 H, t, J = 10.0 Hz), 3.10 (1 H, br s), 1.24 (9 H, s), ^{13}C NMR ($CDCl_3$) δ 179.86, 165.91, 159.19, 157.83, 152.04, 138.29, 129.12, 128.98, 114.85, 114.21, 94.66, 55.46, 54.72, 47.93, 40.38, 39.38, 27.16; EIMS *m*/*z* 382 (M^+), 380, 261, 177, 122, 121, 91, 77, 57; HRMS calcd for $C_{21}H_{26}N_4O_3$ 382.2005, found 382.2013; Anal. Calcd. for $C_{21}H_{26}N_4O_3$: C, 65.95; H, 6.85; N, 14.65. Found: C, 65.46; H, 6.44; N, 14.09.

2-Amino-4-oxo-5-vinyl-7-(3′,4′-dimethoxybenzyl)-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (7d). Isolated in 68% yield as a white solid, mp 214 °C (decomp): IR (KBr) 3404, 3314, 3086, 2837, 1663, 1619, 1544, 1516, 1448, 1384, 1358, 1318, 1257, 1234, 1153, 1139, 1029, 911, 770, 659 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.72 (1 H, s), 6.91 (1 H, d, J = 8.5 Hz), 6.82 (1 H, d, J = 1.0 Hz), 6.47 (1 H, d, J = 8.5 Hz), 6.64 (2 H, br s), 5.79 (1 H, ddd, J = 17.5, 10.0 and 6.5 Hz), 4.97 (1 H, d, J = 17.5 Hz), 4.90 (1 H, d, J = 10.0 Hz), 4.33 (2 H, AB, J = 32.5 Hz)), 3.72 (3 H, s), 3.70 (3 H, s), 3.57 (1 H, dt, J = 9.5 and 6.0 Hz), 3.41 (1 H, t, J = 10.0 Hz), 3.03 (1 H, dd, J = 9.5 and 5.0 Hz); ^{13}C NMR (DMSO-d_6) δ 167.33, 158.66, 157.14, 148.69, 147.86, 139.95, 129.93, 119.69, 113.23, 111.76, 111.45, 87.66, 55.46, 55.37, 53.94, 47.26, 38.59; EIMS *m*/*z* 328 (M^+), 313, 299, 275, 256, 241, 227, 213, 191, 177, 163, 151, 135, 121, 107, 91, 78, 69; HRMS calcd for $C_{17}H_{20}N_4O_3$ 328.1535, found 328.1534.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(α-methylbenzyl)pyrrolo-[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (9a). To a well-degassed mixture of $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and (*o*-toyl)$_3$P (66 mg, 0.22 mmol) in 40 mL of dry DMF were added 1.1 g (1.5 mL, 11 mmol) of triethylamine and a degassed solution of 2-amino-4-oxo-5-vinyl-7-(α-methylbenzyl)-3,4,5,6-tetrahydro-pyrrolo-[2,3-*d*]pyrimidine (**7a**) (200 mg, 0.71 mmol) in 10 mL of dry DMF. After stirring for 15 min, a degassed solution of 0.84 g (2.0 mmol) of diethyl 4-iodobenzoyl-L-glutamate in 10 mL of DMF was added. The resulting mixture was stirred at 75 °C under nitrogen for 48 h. The mixture was cooled to room temperature, poured into 300 mL of ethyl acetate, and washed with water (2 × 200 mL) followed with brine (50 mL). The organic layer was separated, dried over sodium sulfate, and then concentrated to give a dark solid that was purified by chromatography (silica gel, 10% methanol in ethyl acetate) to give 284 mg (68%) of **9a** as a light pink solid as a mixture of two diastereomers, mp 164−166 °C: IR (KBr) 3412, 3344, 2980, 2936, 1734, 1653, 1522, 1442, 1340, 1206, 1189, 1101, 1021, 766, 757, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.48 (1 H, s), 7.73 (2 H, d, J = 8.0 Hz), 7.34−7.31 (2 H, m), 7.28 (1 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 7.16 (2 H, d, J = 7.5 Hz), 6.25 (1 H, s), 5.86 (1 H, q, J = 7.0 Hz), 5.37 (2 H, s), 4.84 (1 H, q, J = 4.5 Hz), 4.27−4.20 (2 H, qm, J = 7.5 Hz), 4.14−4.08 (2 H, qm, J = 7.5 Hz), 3.06−2.92 (4 H, m), 2.59−2.44 (2 H, m), 2.40−2.29 (1 H, m), 2.32−2.15 (1 H, m), 1.75 (3 H, d, J = 7.5 Hz), 1.31 (3 H, t, J = 7.5 Hz), 1.22 (3 H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 173.98 and 173.97, 173.00 and 172.98, 168.00, 162.10, 152.47, 151.86, 147.39, 142.73 and 142.69, 131.75, 129.53, 129.30 and 129.28, 128.12 and 128.10, 127.78, 127.06, 119.01, 115.87, 100.15, 62.48, 61.57, 53.12, 52.43, 37.37, 31.30, 29.05, 28.04, 21.39, 14.92 and 14.89; EIMS *m*/*z* 587 (M^+), 267, 163, 129, 105, 84, 69, 55; HRMS calcd for $C_{32}H_{37}N_5O_6$ 587.2743, found 587.2727. Anal. Calcd. for $C_{32}H_{37}N_5O_6$: C, 65.40; H, 6.35; N, 11.92. Found: C, 65.28; H, 6.29; N, 11.90.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-benzylpyrrolo[2,3-*d*]pyri-midin-5-yl)ethyl]benzoyl}-L-glutamate (9b). Starting with 2-amino-4-oxo-5-vinyl-7-benzyl-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (**7b**), the same procedure and conditions were applied as in the preparation of **9a** above except that after the solvent was evaporated, the dark solid was washed with ethyl acetate and then with diethyl ether, and dried under vacuum to give **9b** as a light pink solid in 51% yield, mp 192−194 °C: IR (KBr) 3439, 3327, 3182, 2934, 1734, 1650, 1525, 1502, 1454, 1376, 1338, 1203, 1009, 1023, 732, 701 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.26 (1 H, s), 8.62 (1 H. d, J = 7.5 Hz), 7.77 (2 H, d, J = 7.5 Hz), 7.29−7.20 (5 H, m), 7.03 (2 H, d, J = 7.0 Hz), 6.38 (1 H, s), 6.19 (2 H, br s), 5.05 (2 H, s), 4.43 (1 H, td, J = 9.5 Hz), 4.10 (2 H, q, J = 6.0 Hz), 4.04 (2 H, q, J = 7.0 Hz), 2.99 (2 H, t, J = 7.3 Hz), 2.86 (2 H, t, J = 7.3 Hz), 2.43 (2 H, t, J = 7.5 Hz), 2.14−2.07 (1 H, m), 2.03−1.96 (1 H, m), 1.18 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 172.19, 171.82, 166.57, 159.11, 152.47, 150.49, 146.07, 138.44, 131.00, 128.42, 128.25, 127.34, 127.05, 126.70, 117.47, 117.23, 98.68, 60.53, 59.92, 51.94, 46.58, 35.87, 30.17, 27.85, 25.71, 14.07 (two carbons); EIMS *m*/*z* 573 (M^+), 527, 371, 286, 254, 253, 222, 207, 194, 186, 91, 84, 77; HRMS calcd for $C_{31}H_{35}N_5O_7$ 573.2587, found 573.2613. Anal. Calcd. for $C_{31}H_{35}N_5O_7$: C, 64.91; H, 6.15; N, 12.21. Found: C, 64.87; H, 6.41; N, 11.95.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(4′-methoxybenzyl)pyrrolo-2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (9c). From 2-amino-4-oxo-5-vinyl-7-(4′-methoxybenzyl)-3,4,5,6-tetrahydropyrrolo[2,3-*d*]pyrimidine (**7c**); product isolated in 61% yield as a light pink solid, mp 220−222 °C: IR (KBr) 3470, 3329, 2981,2935, 1734, 1670, 1636, 1539, 1514, 1457, 1249, 1179, 1099, 1031, 785, 759 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.24 (1 H, s), 8.62 (1 H, d, J = 7.5 Hz), 7.77 (2 H, d, J = 8.0 Hz), 7.26 (2 H, d, J = 8.5 Hz), 7.02 (2 H, d, J = 8.5 Hz), 6.85 (2 H, d, J = 8.5 Hz), 6.37 (1 H, s), 6.18 (2 H, s), 4.96 (2 H, s), 4.44−4.40 (1 H, m), 4.10 (2 H, q, J = 7.0 Hz), 4.04 (2 H, q, J = 7.0 Hz), 3.70 (3 H, s), 2.97 (2 H, t, J = 7.5 Hz), 2.84 (2 H, t, J = 8.0 Hz), 2.41 (2 H, t, J = 15 Hz), 2.14−2.07 (1 H, m), 2.03−1.96 (1 H, m), 1.80 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 172.18, 171.80, 166.58, 159.08, 158.40, 152.42, 150.33, 146.10, 131.02, 130.31, 128.27, 128.21, 127.35, 117.44, 116.96, 113.82, 98.65, 60.51, 59.90, 55.02, 51.95, 46.07, 35.93, 30.16, 27.88, 25.70, 14.05 (two carbons); EIMS *m*/*z* 603 (M^+), 303, 283, 225, 145, 121, 84, 63; HRMS calcd for $C_{32}H_{37}N_5O_7$ 603.2693, found 603.2717. Anal. Calcd for $C_{32}H_{37}N_5O_7$: C, 63.57; H, 6.18; N, 11.60. Found: C, 63.53; H, 6.30; N, 11.40.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(3′,4′-dimethoxybenzyl)-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]-benzoyl}-L-glutamate (9d). Isolated on column chromatography (silica gel, EtOAc/MeOH 8:2) in 65% yield as a light yellow solid, mp 203−205 °C: IR (KBr) 3345, 2935, 1735, 1668, 1629, 1596, 1516, 1452, 1419, 1378, 1261, 1237, 1188, 1156, 1097, 1026, 855, 785, 766, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.41 (1 H, s), 7.71 (2 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 7.18 (1 H, d, J = 7.5 Hz), 6.80 (1 H, d, J = 8.0 Hz), 6.73 (1 H, d, J = 1.5 Hz), 6.65 (1 H, dd, J = 8.0 and 1.5 Hz), 6.18 (1 H, s), 5.41 (2 H, br s), 5.00 (2 H, s), 4.78 (1 H, q, J = 5.5 Hz), 4.22 (2 H, q, J = 7.5 Hz), 4.11 (2 H, q, J = 7.0 Hz), 3.85 (3 H, s), 3.80 (3 H, s), 3.01 (2 H, m), 2.99 (2 H, m), 2.55−2.41 (2 H, m), 2.35−2.28 (1 H, m), 2.19−2.12 (1 H, m), 1.30 (3 H, t, J = 7.0 Hz), 1.21 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.37, 172.37, 167.43, 161.40, 152.01, 151.41, 149.20, 148.67, 146.75, 131.20, 130.06, 128.83, 127.23, 119.95, 118.66, 117.85, 111.37, 110.99, 99.59, 61.85, 60.94, 56.04 (two carbons), 52.54, 47.50, 36.73, 30.68, 28.25, 27.32, 14.27, 14.25; EIMS m/z 633 (M^+), 615, 588, 566, 504, 476, 459, 418, 364, 341, 313, 191, 151, 122, 107, 90, 84, 78; HRMS calcd for $C_{33}H_{39}N_5O_8$ 633.2798, found 633.2766.

Diethyl *N*-{4-[2-(2-Pivaloylamino-3,4-dihydro-4-oxo-7-(4′-methoxybenzyl)-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]-benzoyl}-L-glutamate (16). Isolated in 71% yield as a colorless oil: IR (neat) 3227, 2976, 2929, 1729, 1659, 1606, 1537, 1447, 1240, 1170, 1094, 1024, 913, 785, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.65 (1 H, s), 7.96 (1 H, s), 7.66 (2 H, d, J = 8.0 Hz), 7.21 (2 H, d, J = 8.5 Hz), 6.99 (2 H, d, J = 8.5 Hz), 6.92 (1 H, d, J = 7.5 Hz), 6.84 (2 H, d, J = 8.5 Hz), 6.25 (1 H, s), 5.03 (2 H, s), 4.78 (1 H, q, J = 4.5 Hz), 4.26−4.21 (2 H, m), 4.14−4.06 (2 H, m), 3.78 (3 H, s), 2.53−2.47 (2 H, m), 2.44−2.38 (2 H, m), 2.34−2.27 (2 H, m), 2.17−2.09 (2 H, m), 1.34 (9 H, s), 1.29 (3 H, t, J = 7.0 Hz), 1.21 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 179.48, 173.42, 172.26, 167.31, 159.39, 158.14, 147.32, 146.85, 145.92, 131.16, 129.38, 129.15, 128.60, 127.12, 119.88, 119.59, 114.34, 103.72, 61.88, 60.99, 55.51, 52.49, 47.41, 40.33, 36.77, 30.70, 28.09, 27.57, 27.34, 14.37, 14.34; EIMS m/z 687(M^+), 485, 367, 207, 121, 84; HRMS calcd for $C_{37}H_{45}N_5O_8$ 687.2368, found 687.2366. Anal. Calcd for $C_{37}H_{45}N_5O_8$: C, 64.61; H, 6.59; N, 10.18. Found: C, 64.62; H, 6.48; N, 9.93.

Diethyl *N*-{4-[2-(2-Amino-4-oxo-3,4,5,6-tetrahydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (14). A mixture of 230 mg (0.392 mmol) of diethyl *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7-(α-methylbenzyl)pyrrolo-[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (**9a**) and 200 mg of 10% Pd/C in 20 mL of methanol (or ethanol) was hydrogenated under 55 psi. The reaction was monitored by TLC. At room temperature, no reaction occurred after 24 h. At 50 °C, after 24 h, new spots appeared, and the mixture was continually hydrogenated for 3 days. The mixture was passed through a Celite filter, concentrated, and then dried under vacuum. The proton NMR spectrum of the crude mixture showed considerable starting material. The residue was purified by column chromatography (silica gel, EtOAc/MeOH 9:1) to give 11 mg (6% yield) of **14** as a white solid. Proton and carbon NMR spectra are consistent with the reported data:[16] ^1H NMR (DMSO-d_6) δ 9.76 (1 H, s), 8.64 (1 H, d, J = 5.5 Hz), 7.78 (2 H, d, J = 7.5 Hz), 7.31 (2 H, d, J = 7.5 Hz), 6.32 (1 H, s), 6.28 (2 H, br s), 4.43 (1 H, m), 4.12 (2 H, q, J = 7.0 Hz), 4.06 (2 H, q, J = 7.0 Hz), 3.49 (1 H, m), 3.02 (2 H, m), 2.68 (2 H, t, J = 6.5 Hz), 2.36 (2 H, t, J = 7.5 Hz), 2.1−2.0 (3 H, m), 1.62 (1 H, m), 1.21 (3 H, t, J = 7.0 Hz), 1.18 (3 H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 172.70, 172.32, 170.04, 167.12, 159.53, 157.24, 146.99, 131.58, 128.71, 127.99, 89.32, 61.03, 60.42, 52.46, 49.75, 37.51, 36.43, 33.06, 30.68, 26.21, 14.56 (two carbons).

***N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(α-methylbenzyl)-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic Acid (10a).** The following procedure is representative for the preparation of the glutamic acids described herein. To a solution of 109 mg of diethyl *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7-(α-methylbenzyl)pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (**9a**) in a mixture of THF (2 mL) and H_2O (1 mL) was added 1 mL of 1.0 N aqueous NaOH solution. The resulting solution was stirred at room temperature for 3 h. The THF was evaporated under reduced pressure, and the residual solution was acidified with acetic acid. The resulting light yellow precipitate was collected by filtration, washed successively with water, hexane, and diethyl ether, and dried under vacuum to give 65 mg (62%) of **10a** as a light yellow solid, mp 164−168 °C: IR (KBr) 3342, 3204, 2973, 1637, 1526, 1434, 1210, 1177, 1091, 782, 742, 697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.52 (2 H, br s), 10.24 (1 H, s), 8.47 (1 H, d, J = 6.0 Hz), 7.79 (2 H, d, J = 7.5 Hz), 7.28−7.22 (5 H, m), 7.05 (2 H, d, J = 7.0 Hz), 6.52 (1 H, s), 6.14 (2 H, br s), 5.68 (1 H, q, J = 6.5 Hz), 4.40 (1 H, q, J = 6.5 Hz), 3.02−2.84 (4 H, m), 2.36 (2 H, m), 2.08 (1 H, m), 1.97 (1 H, m), 1.68 (3 H, d, J = 6.5 Hz); MS m/z 532 (MH^+), 459, 385, 320, 301, 300, 154, 153, 152, 135, 119; FABMS calcd for $C_{28}H_{30}N_5O_6$ (MH^+) 532.2196, found (MH^+) 532.2203.

***N*-{4-[2-(2-Amino-3,4-dihyro-4-oxo-7-benzylpyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic Acid (10b).** From 89 mg of diethyl *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7-benzylpyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (**9b**), compound **10b** was obtained in 88% yield as a off-white solid, mp 196−198 °C: IR (KBr) 3424, 3317, 3192, 2936, 1694, 1631, 1519, 1494, 1457, 1339, 1257, 1207, 1095, 776, 732, 695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (2 H, br, s), 10.26 (1 H, s), 8.48 (1 H, d, J = 8.0 Hz), 7.78 (2 H, d, J = 8.0 Hz), 7.30−7.21 (5 H, m), 7.02 (2 H, d, J = 7.5 Hz), 6.38 (1 H, s), 6.18 (2 H, br s), 5.05 (2 H, s), 4.39 (1 H, q, J = 8.5 Hz), 2.99 (2 H, t, J = 7.5 Hz), 2.86 (2 H, t, J = 7.5 Hz), 2.35 (2 H, t, J = 7.5 Hz), 2.12−2.05 (1 H, m), 1.99−1.91 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 173.93, 173.52, 166.39, 159.11, 152.46, 150.51, 145.93, 138.45, 131.28, 128.44, 128.24, 127.31, 127.09, 126.71, 117.49, 117.27, 98.69, 51.92, 46.59, 35.88, 30.48, 27.87, 26.02; EIMS m/z 518 (MH^+), 459, 371, 339, 321, 308, 1554, 12, 135, 119; FABMS calcd for $C_{27}H_{28}N_5O_6$ (MH^+) 518.2040, found (MH^+) 518.2046. Anal. Calcd for $C_{27}H_{27}N_5O_6 \cdot HOAc$: C, 60.31; H, 5.41; N, 12.12. Found: C, 60.63; H, 5.34; N, 12.36.

***N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(4′-methoxybenzyl)pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic Acid (10c).** From 86 mg of diethyl *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7-(4′-methoxybenzyl)pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (**9c**), compound **10c** was isolated in 85% yield as a light yellow solid, mp 198−200 °C: IR (KBr) 3421, 3329, 2930, 1692, 1634, 1516, 14551, 1339, 1241, 1169, 1104, 1032, 782 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (2 H, s), 10.26 (1 H, s), 8.48 (1 H, d, J = 7.5 Hz), 7.78 (2 H, d, J = 7.5 Hz), 7.27 (2 H, d, J = 8.0 Hz), 7.04 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.5 Hz), 6.38 (1 H, s), 6.19 (2 H, br s), 4.97 (2 H, s), 4.40 (1 H, m), 3.71 (3 H, s), 2.98 (2 H, t, J = 8.0 Hz), 2.85 (2 H, t, J = 8.0 Hz), 2.36 (2 H, t, J = 7.5 Hz), 2.12−2.06 (1 H, m), 1.99−1.92 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 173.92, 173.49, 166.44, 159.10, 158.44, 152.41, 150.35, 145.97, 131.31, 130.33, 128.32, 128.21, 127.34, 118.95, 117.50, 116.99, 113.85, 55.05, 51.93, 46.09, 35.95, 30.48, 27.91, 26.00; MS m/z 548(MH^+), 459, 428, 391, 339, 322, 321, 308, 154, 153, 135, 119; FABMS calcd for $C_{28}H_{30}N_5O_7$ (MH^+) 548.2152, found (MH^+) 548.2138. Anal. Calcd for $C_{28}H_{29}N_5O_7$: C, 61.42; H, 5.34; N, 12.79. Found: C, 61.31; H, 5.34; N, 12.59.

***N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-(3′,4′-dimethoxybenzyl)-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic Acid (10d).** Isolated in 88% yield as a light yellow solid: IR (KBr) 3355, 3215, 2935, 1636, 1517, 1451, 1420, 1339, 1262, 1237, 1141, 1024, 785, 763 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.55 (2 H, br s), 10.24 (1 H, s), 8.46 (2 H, d, J = 7.0 Hz), 7.89 (2 H, d, J = 8.0 Hz), 7.26 (2 H, d, J = 8.0 Hz), 6.89 (1 H, s), 6.83 (1 H, d, J = 8.0 Hz), 6.51 (1 H, d, J = 8.0 Hz), 6.39 (1 H, s), 6.19 (2 H, s), 4.96 (2 H, s), 4.37 (1 H, q, J = 3.5 Hz), 3.69 (6 H, s), 2.95(2 H, t, J = 6.0 Hz), 2.86 (2 H, t, J = 6.0 Hz), 2.10−2.00 (1 H, m), 2.00−1.85 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 173.95, 173.50, 166.39, 159.11, 152.41, 150.39, 148.61, 148.01, 145.98, 131.34, 130.71, 128.19, 127.33, 119.21, 117.48, 117.02, 111.81, 111.31, 98.67, 55.51, 55.45, 51.98, 46.47, 35.99, 30.55, 27.88, 26.07; EIMS m/z 578 (MH^+), 562, 546, 528, 514, 504,

488, 476, 462, 446, 379, 313, 281, 215, 151, 135, 107, 86; FABHRMS calcd for $C_{29}H_{32}N_5O_8$ (MH^+) 578.2251, found 578.2267.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7*H*-pyrrolo-[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate (9, R = H). To a mixture of 40 mg (0.065 mmol) of diethyl *N*-{4-[2-(2-amino-3,4-dihydro-4-oxo-7-(3′,4′-dimethoxybenzyl)pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate in 0.3 mL of dry trifluoroacetic acid were added 0.05 mL of dry anisole and 0.6 mL of concentrated sulfuric acid. The resulting mixture was stirred at room temperature for 4 h. Methylene chloride (4 mL) was added, and the mixture was washed with water (4 × 1 mL) and dried over Na_2SO_4. Solvent was evaporated, and the solid was washed with diethyl ether (2 × 0.5 mL) and ethyl acetate (2 × 0.5 mL) and dried under reduced pressure. The residue was purified by a TLC plate (silica gel, CH_2Cl_2/MeOH 9:1) to afford 9.0 mg (29.5% yield) of product as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 10.62 (1 H, s), 10.14 (1 H, s), 8.62 (1 H, d, J = 7.0 Hz), 7.77 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 6.31 (1 H, s), 5.99 (2 H, br s), 4.43 (1 H, q, J = 7.5 Hz), 4.11 (2 H, q, J = 7.0 Hz), 4.06 (2 H, q, J = 7.0 Hz), 2.98 (2 H, t, J = 8.5 Hz), 2.85 (2 H, t, J = 8.5 Hz), 2.42 (2 H, t, J = 7.5 Hz), 2.13−2.05 (1 H, m), 2.03−1.95 (1 H, m), 1.18 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz).[27]

Acknowledgment. We are indebted to Eli Lilly & Company both for financial support of this work and for the in vitro cell growth inhibition studies. We thank Professor Jeffrey Schwartz of Princeton University for stimulating discussions regarding the double bond rearrangement observed during the Heck reaction.

JO001580L