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TOTAL SYNTHESIS OF ANTITUMOR AGENT AT-125, (αS,5S)-α-AMINO-3-CHLORO-4,5-DIHYDRO-5-ISOXAZOLEACETIC ACID

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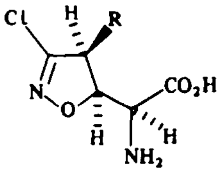
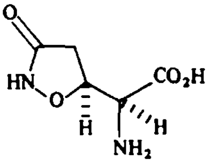
Abstract—A short and efficient total synthesis of racemic AT-125 and its racemic *threo* isomer proceeds via an intramolecular Michael cyclization of a protected α,β-dehydroglutamic acid γ-hydroxamate. Separation of diastereomers and deprotection to racemic AT-125 followed by enzymatic resolution of the N-chloroacetamide with hog-kidney acylase provides the natural αS,5S isomer.

Recently Martin and co-workers at Upjohn disclosed the isolation of AT-125, (1), (αS,5S) - α - amino - 3 - chloro - 4,5 - dihydro - 5 - isoxazoleacetic acid, and its 4-hydroxylated relative 2, (αS,4S,5R) - α - amino - 3 - chloro - 4 - hydroxy - 4,5 - dihydro - 5 - isoxazoleacetic acid, from cultures of *Streptomyces sviceus*. The pronounced antitumor, antibiotic, and antimetabolic properties of 1 and 2 have stimulated considerable interest in the biochemical and pharmacological characterization of these amino acids[2] which bear structural and stereochemical resemblance to the fungal metabolites tricholomic acid 3[3] and ibotenic acid 4.[4]



1 R = H
2 R = OH



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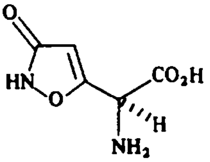

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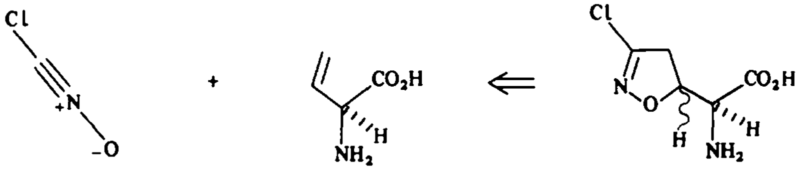

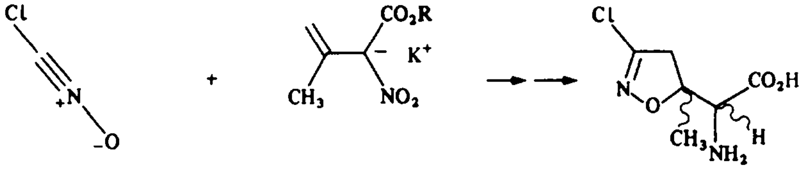

5

The unique substituted heterocyclic ring and the "dense" placement of functional groups in 1 make this antitumor agent a challenging target for total synthesis, a study of some importance given the low availability of AT-125 from fermentation sources. Some time ago we became interested in synthesizing 1 and its structural relatives and advanced the first strategy for constructing the 3-chloro-3,4-dihydroisoxazole ring of 1 by a 1,3-dipolar cycloaddition between chloronitrileoxide and an "activated" vinyl glycine analog, nitronate salt 5.[5] Despite the synthesis of a ring methylated analog of AT-125 by this conceptually appealing cycloaddition strategy, we found it did not provide the natural product in a high yield or reasonable and straightforward fashion. While others have subsequently modified this cycloaddition concept by using protected vinyl glycine or its equivalents and/or the more reactive bromonitrile oxide to produce

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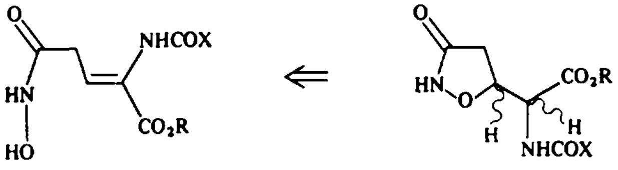
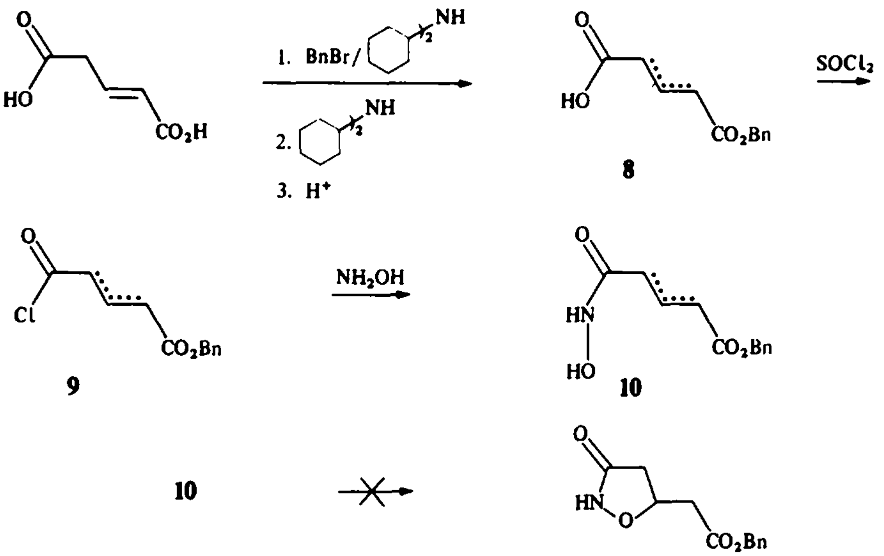
1, the synthetic manipulations implicit in these approaches have not yet allowed the high yield or stereoselective elaboration of the natural product.[6]

Subsequent to our initiation of synthetic approaches to 1 via the cycloaddition strategy the Upjohn group disclosed an elegant, if somewhat lengthy, stereocontrolled total synthesis of 1.[7] After our communication of the present results,[8] a second stereocontrolled synthesis of 1 appeared.[9] We report here the details of our synthetic studies which make AT-125 available by a short and efficient, stereorandom route.



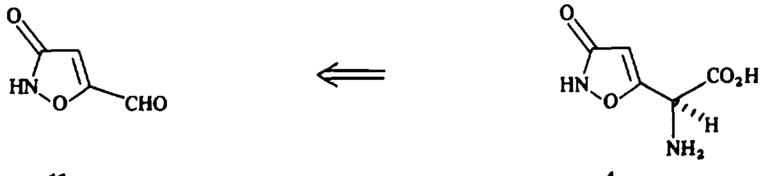
6 **7**



8 **9** **10** **10**

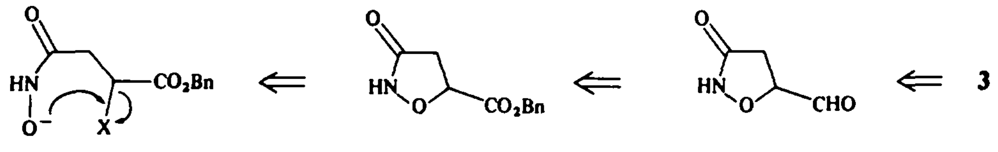
RESULTS

In planning our synthetic route to 1 we became intrigued with constructing the tricholomic acid framework in a stereorandom but single step procedure by an internal Michael reaction of a suitably protected α,β-dehydroglutamic hydroxamate, 6 → 7, a process which bears some resemblance to a postulated biosynthetic scheme to 3.[4] In order to examine this internal Michael reaction in a system simpler than 6, the glutaconic hydroxamic acid 10 was prepared, and attempts were made at cyclization. Unfortunately, despite many attempts employing various solvents and reagents, only complex, highly colored products were formed as 10 slowly disappeared without the formation of cyclic hydroxamic acid. The reasons for this failure, while ultimately understood and circumvented, were sufficiently discouraging at this early stage to convince us of the necessity of constructing the tricholomic acid structure by an entirely different approach.

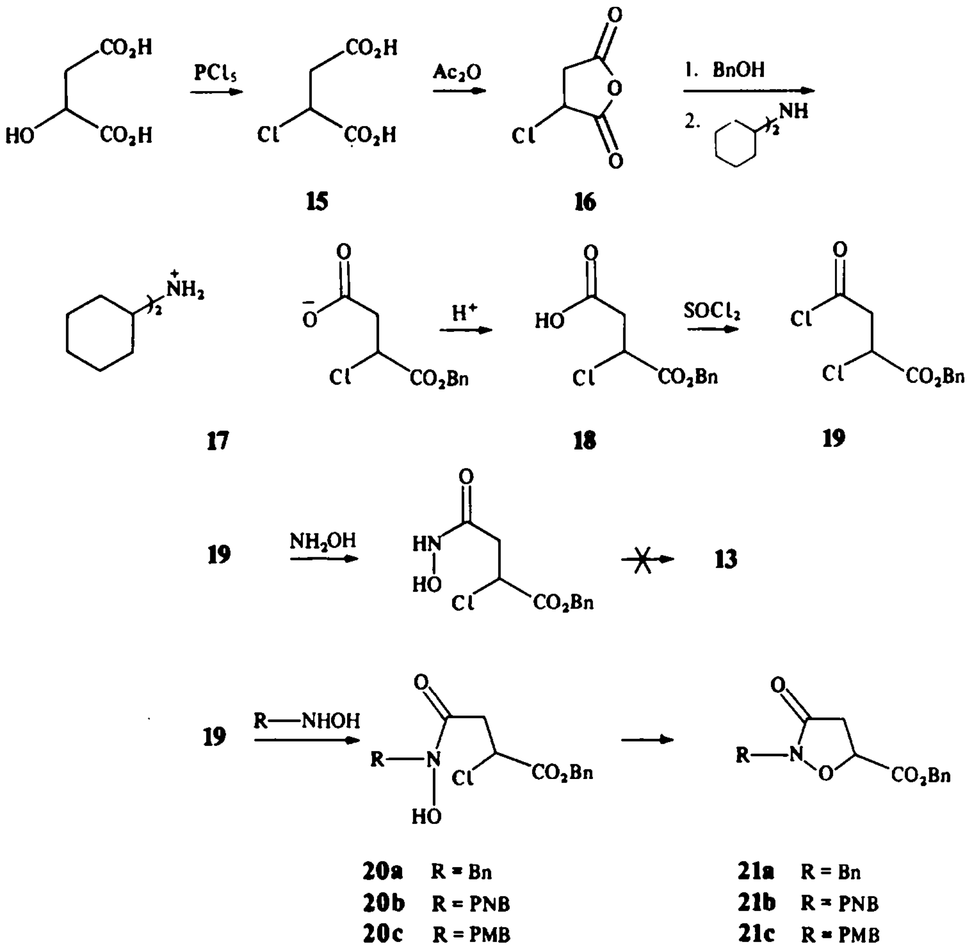


11 **4**

Ibotenic acid, 4, had been constructed from isoxazolealdehyde 11,[10] a precedent which suggested the corresponding saturated aldehyde 12 as a precursor to tricholomic acid. As a precursor to aldehyde 12, ester 13 was sought. This benzyl ester was in turn the expected product of the intramolecular alkylation of



14 **13** **12**



Scheme 1.

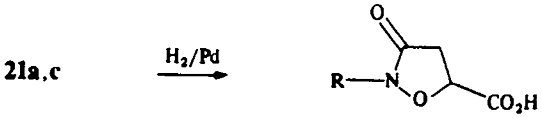
hydroxamic acid **14**, an alkylation reminiscent of that used to prepare cycloserine.[11] Synthesis of acyclic hydroxamic acid **14** proceeded in good yield via the selective alcoholysis[12] of chlorosuccinic anhydride and coupling of the half ester with hydroxylamine, a particularly attractive sequence in that chiral chlorosuccinic acid[13] would be expected to produce aldehyde **12** with the correct stereochemistry (Scheme 1).

Unfortunately, the hydroxamic acid **14** (X = Cl) failed to cyclize to **13** when treated with a variety of bases under different conditions. This failure, and the previous failure of hydroxamic acid **10** to cyclize in the predicted manner suggested the ambient nucleophilicity of the hydroxamic acid as a probable cause of the undesired behavior.[14] Coupling acid chloride **19** with N-benzylhydroxylamine[15] provided **20a** which, unlike **14**, cyclized cleanly to **21a** when treated with a variety of bases (e.g. aqueous $NaHCO_3$, triethylamine, or sodium hydride). Cyclic hydroxamic acid **21a** was most conveniently prepared from acid chloride **19** in a "one pot" procedure without isolation of **20a**. By employing an N-alkylated hydroxamic acid the ambient nucleophilicity of this functional group had been constrained to a single cyclization mode.

With multigram quantities of **21a** available attention was turned to N-dealkylating the hydroxamic acid. Hydrogenolysis over palladium provided acid **22a** but further debenzylation did not occur. Medium- and high-pressure hydrogenolysis caused fission of the N—O bond while attempted chemical reduction led only to complex, intractible mixtures. Multiple attempts to induce a von Braun type of dealkylative chlorination also met with failure, results entirely consistent with the known difficulty of dealkylating N-alkyl amides.[16] The more highly activated benzyl-substituted hydroxamic acids **20b, c** (Scheme 1) were prepared from N-(*p*-nitrobenzyl)hydroxylamine[17] and N-(*p*-methoxybenzyl)hydroxylamine, respectively. In some preparations of **21b** an interesting ring expanded material **23** was produced, presumably by benzylic deprotonation and ring opening followed by reclosure.

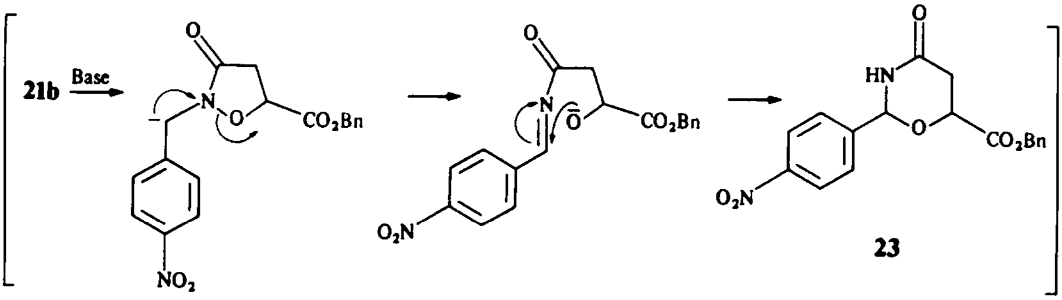
N-(*p*-nitrobenzyl)isoxazolidinone **21b**, like the parent **21a**, failed to N-dealkylate under all conditions tried, but the methoxybenzyl analog **21c** underwent a smooth von Braun dealkylative chlorination to provide **25** in good yield.

The success of this procedure, which was ultimately applied in our synthesis of AT-125, is particularly noteworthy since a direct chlorination of the N-unsubstituted isoxazolidinone parent heterocycle, tricholomic acid, has to date been achieved with only a single reagent, tris(dimethylamino)dichlorophosphorane,[7] a result we have confirmed experimentally with a large number of chlorinating agents. The success of our chlorination with the highly reactive

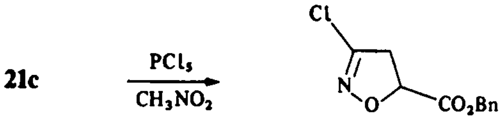


22a R = Bn
22c R = PMB

$\mathbf{20b} \xrightarrow{\text{Base}} \mathbf{21b} + \mathbf{23}$



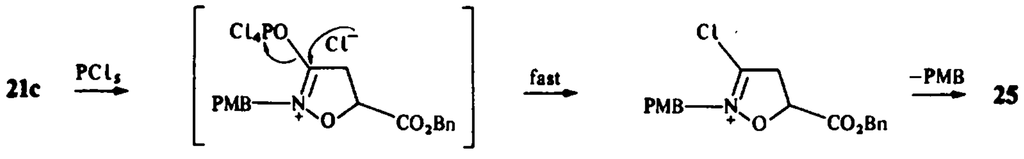
23



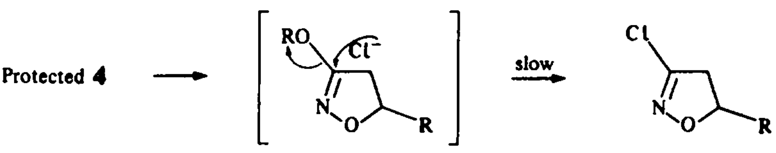
25

PCl$_5$ probably derives from a rapid attack of Cl$^-$ on the oximinium intermediate **24**, while in the N-unsubstituted tricholomic acid analogs, attack of Cl$^-$ on the less activated intermediate **26** is greatly slowed, an event which allows competing fragmentation and degradation reactions to take place.

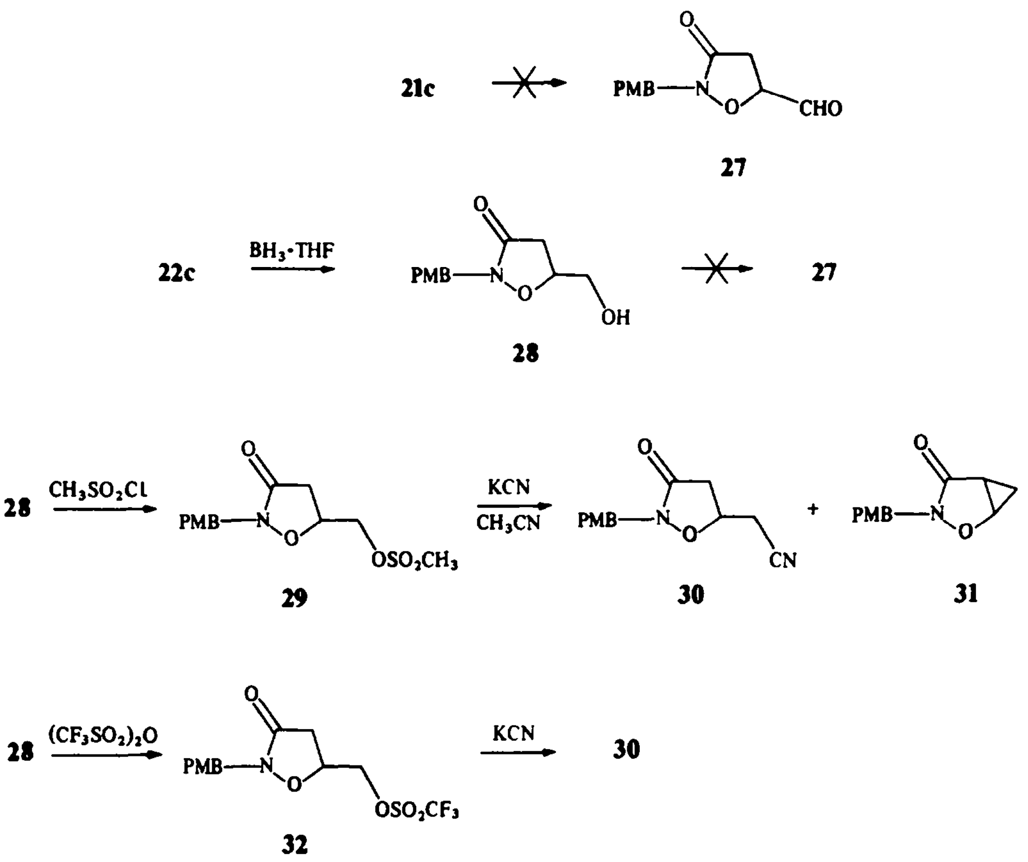
Once having established the viability of constructing the chloroisoxazoline ring of AT-125 on a multigram scale from the chlorosuccinic acid precursor, attention was turned to completing the synthesis by introducing the α-amino acid functionality. Unfortunately, we were never able to prepare aldehyde **27**, the N-protected analog of **12** by selective reduction of the ester group in **21c**. Moreover, while alcohol **28** was available by a borane reduction of acid **22c**, this alcohol proved entirely resistant toward oxidation, a result in accord with a recent study published by Stevens.[6c] In view of these disappointing results a different strategy was employed to construct the five carbon backbone of AT-125 from **28**. Activation of **28** as the methanesulfonate **29** and nucleophilic substitution with "naked cyanide"[18] produced the desired nitrile **30** along with an unexpected product whose structure was determined to be cyclopropane **31**, apparently formed by



24



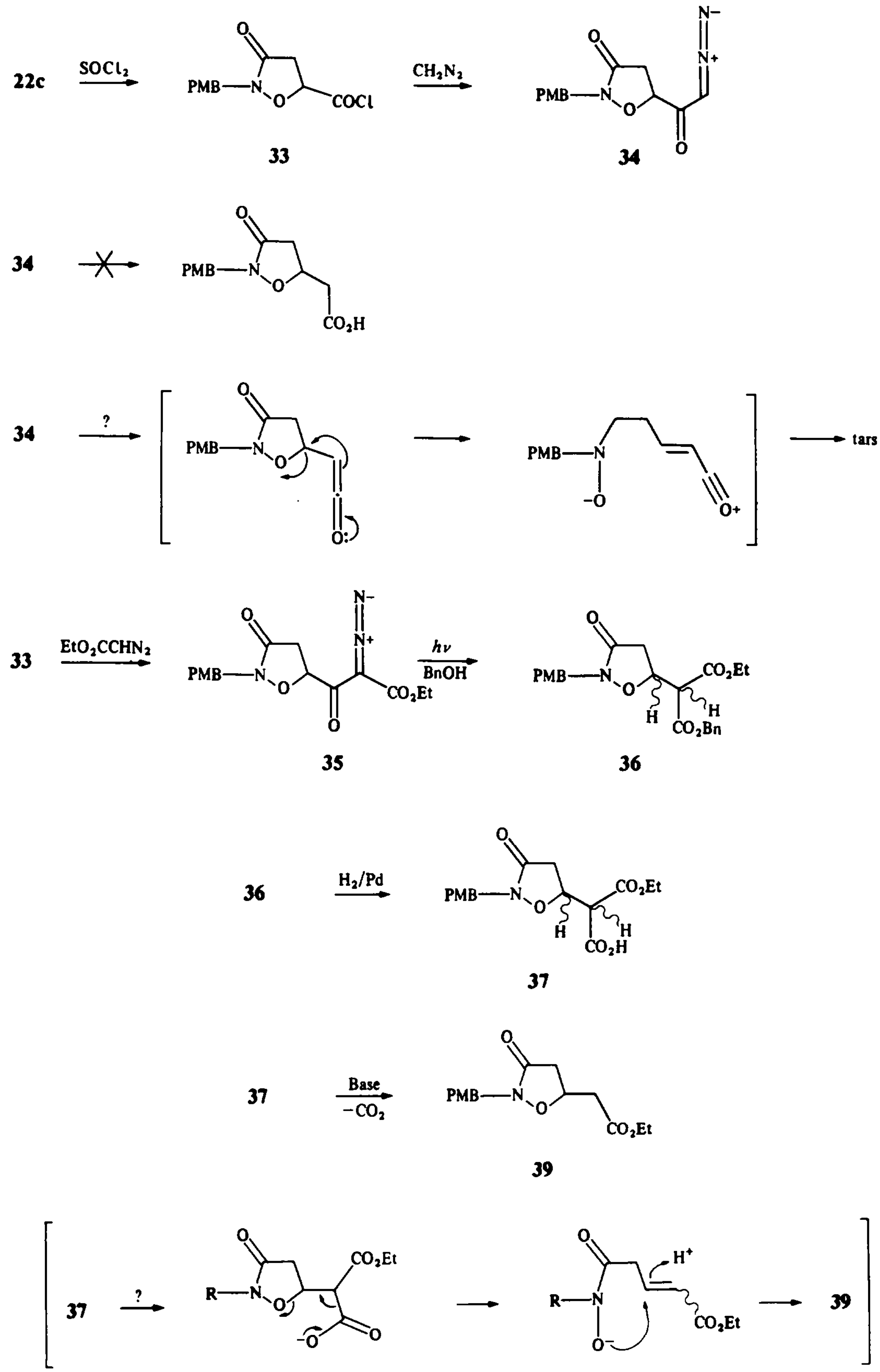
26



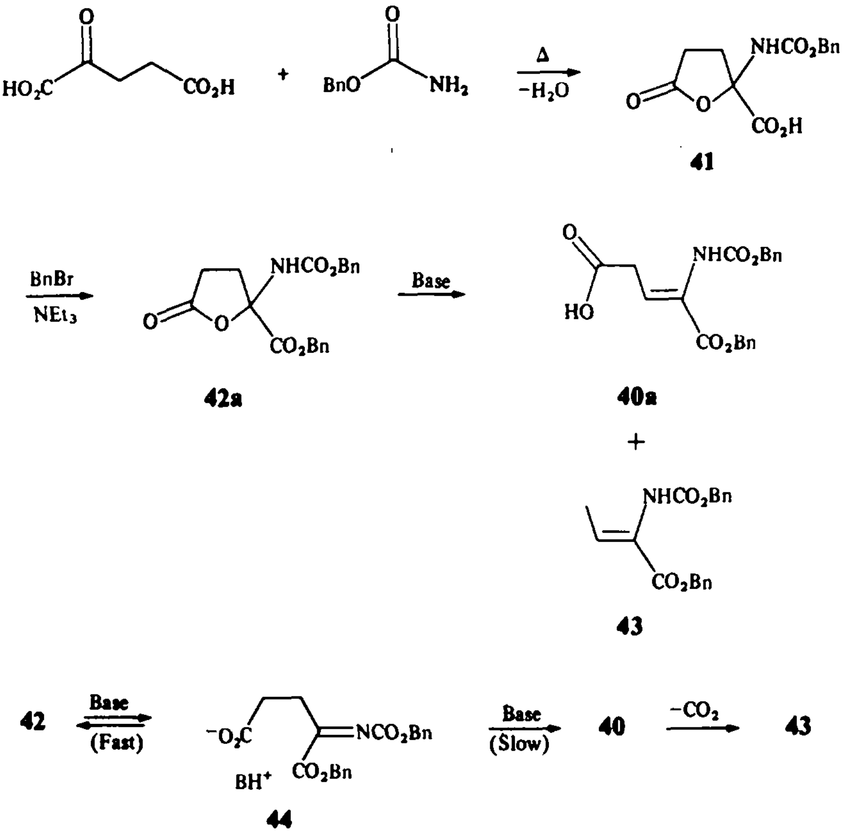
deprotonation and cyclization promoted by the strongly basic "naked cyanide". Even though formation of **31** could be suppressed by working with the much more reactive trifluoromethanesulfonate **32**, and the preparation of nitrile **30** was readily accomplished on a large scale, conversion to the corresponding acid with introduction of the α-amino group found in AT-125 was never achieved.

In view of these discouraging results, attention was focussed on an alternate strategy for effecting the one carbon homologation (Scheme 2). It was hoped diazoketone **34**, readily available from acid chloride **33** by treatment with diazomethane, would undergo Wolff rearrangement to a ketene intermediate with potential utility for α-functionalization. Unfortunately, photochemical or transition metal induced Wolff rearrangement of **34** with or without nucleophiles present never produced the desired homologation, giving instead complex dark tars. A facile retro-Michael reaction of the ketene intermediate was thought responsible for production of the tars observed, and attempts were made to prepare an analog of the diazoketone whose ketene intermediate would be resonance stabilized. Coupling acid chloride **33** with ethyl diazoacetate provided the very stable, crystalline diazoketoester **35** which underwent a photochemically induced Wolff rearrangement in the presence of benzyl alcohol to produce mixed ester **36**. Apparently the addition of the carboethoxy group was sufficient to stabilize the intermediate ketene to allow trapping with an alcohol nucleophile. Diester **36** upon catalytic hydrogenolysis provided half acid **37**, a compound whose structure is dauntingly reminiscent of the desired, protected tricholomic acid intermediate. Unfortunately the conversion of α-carboxyester **37** to the corresponding α-aminoester could not be accomplished in reasonable yield. Most remarkable about **37** was the observation that a facile base-promoted decarboxylation occurred in protic solvents even at very low temperatures, to provide excellent yields of the homologated ester **39**. Upon detailed investigation it was found *the facile decarboxylation of* **37** *occurred by a β-elimination, readdition of the* N-*substituted hydroxamic acid.* The desired Michael reaction, **6** → **7**, was in fact a tenable process which failed in the simple glutaconic hydroxamic acid **10** merely as a result of the ambient nucleophilicity of the hydroxamate anion which apparently caused competing reactions that ultimately led to tar formation.

Bolstered by the success of this internal Michael reaction, and cognizant of the difficulties involved in preparing intermediates of type **37** in reasonable yield by a slow photochemical Wolff rearrangement, we returned to the original concept of preparing **7** by a Michael reaction. In order to complete the synthesis of protected tricholomic acid **7** we required **6**, in turn thought to be available from α,β-dehydroglutamic acid **40**. A potential precursor to **40** was found in the known lactone acid **41**, a compound prepared in excellent yield by the fusion of 2-oxoglutaric acid and benzyl carbamate.[19] It was anticipated the lactone ring of **41** would afford selectivity between α- and β-carboxylates of glutamic acid, while simultaneously providing the desired dehydroamino acid oxidation state. Repreparation of **41** allowed us to confirm not only its structure, but its ease of synthesis. Alkylation of **41** with

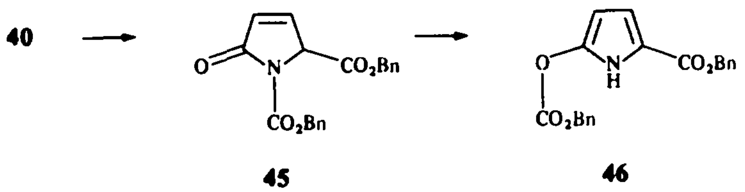

22c
SOCl2
33
CH2N2
34
34
?
tars
33
EtO2CCHN2
35
hν
BnOH
36
36
H2/Pd
37
37
Base
−CO2
39
37
?
H+
39

Scheme 2.

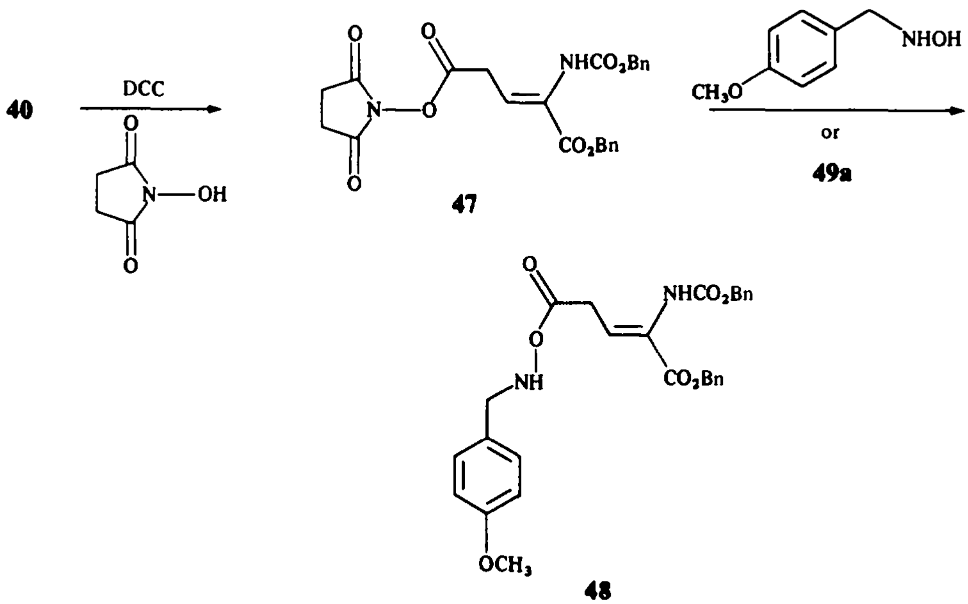


Scheme 3.

benzyl bromide provided ester **42** in excellent yield. While it was anticipated that **42** would provide selectively protected α,β-dehydroglutamic acid **40** upon isomerization with base, in initial experiments a complex mixture of products was obtained in which decarboxylated compound **43** usually predominated (Scheme 3). The base-catalyzed isomerization of **42** to **40** was thought to involve a rapid equilibration of **42** with **44** followed by a second, slower deprotonation to give deprotonated **40**, while decarboxylation of **40** was thought to occur independently of the desired isomerization. In accord with this thinking, highly concentrated suspensions of **42** in tetrahydrofuran could be isomerized quantitated to **40** upon treatment with excess DBU at 0°. Dehydroglutamate **40** and compound **43** were obtained as a single regioisomer, to which the indicated *Z*-regiochemistry was assigned based on proton NMR chemical shift values for the methylene group[20] and previous observations which suggested the *Z*-regioisomer of α,β-unsaturated amino acids to be thermodynamically preferred.[21] This regiochemical assignment was further substantiated by the chemical reactivity of compound **40**. Attempted activation of the carboxylic acid to allow conversion to the corresponding hydroxamic acid were frustrated by a facile intramolecular trapping of the activated carbonyl by the α-amino group to yield initially the pyrrolone **45** and subsequently the isomeric pyrrole **46**.



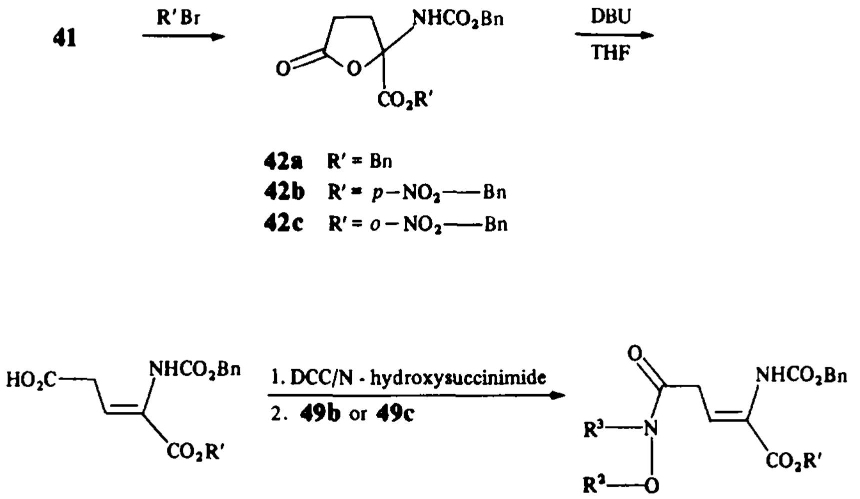
Careful investigation of numerous carbonyl activating reagents finally led to the observation that DCC/N-hydroxysuccinimide would provide the highly activated hydroxysuccinimide ester **47**. This ester reacted with N-(*p*-methoxybenzyl)hydroxylamine to yield an acylated hydroxylamine product which, unfortunately, was found to possess the undesired O-acyl structure **48**. Since under certain conditions hydroxylamines acylate kinetically on oxygen rather than nitrogen,[22] and this appeared to be the case for the reaction of **47** with N-(*p*-methoxybenzyl)hydroxylamine, an N,O-doubly protected hydroxylamine was required to promote the desired N-acylation. The O-trimethylsilylhydroxylamine **49a** was prepared,



but reaction with **47** produced only **48**, apparently a result of the lability of this silyl group.

The more stable O-(t-butyl-dimethylsilyl)-N-(p-methoxybenzyl)hydroxylamine **49b** was prepared and was found to give **50a** cleanly upon coupling with **40a** (Scheme 4) followed by *in situ* desilylation. Moreover, treatment of **50a** with aqueous sodium bicarbonate induced the long-sought intramolecular Michael reaction to give an excellent yield of protected tricholomic acids **51a** as a 1 : 1 mixture of diastereomers (Scheme 5).[23] This ratio of diastereomers produced by the internal Michael reaction was independent of solvent, base or conditions employed.

A large number of protecting group variations were studied in an attempt to influence diastereoselectivity and length of the synthetic sequence, of which **40** → **50a–d** (Schemes 4 and 5) are the most interesting. Since the ambient nucleophilicity of the hydroxamic acid



42a R' = Bn
42b R' = p–NO₂—Bn
42c R' = o–NO₂—Bn

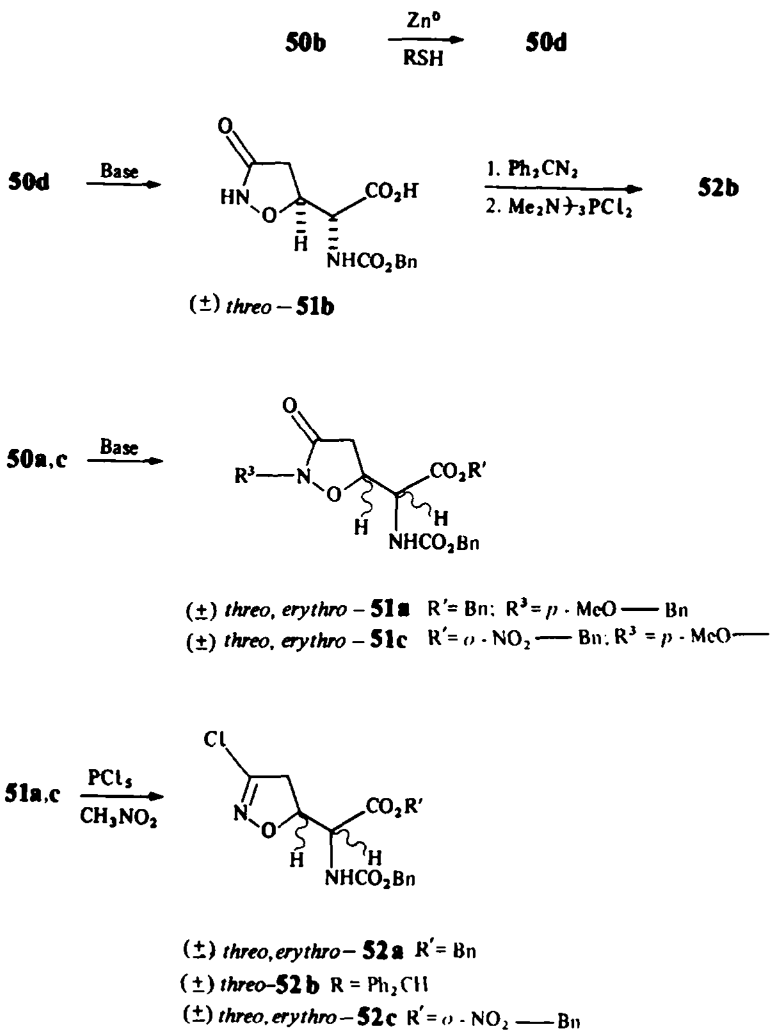
40a R' = Bn
40b R' = p–NO₂—Bn
40c R' = o–NO₂—Bn

50a R' = Bn; R² = H; R³ = p–MeO—Bn
50b R' = p–NO₂—Bn; R² = p–NO₂—Bn; R³ = H
50c R' = o–NO₂—Bn; R² = H; R³ = p–MeO—Bn
50d R' = H; R² = H; R³ = H

R³NHOR²

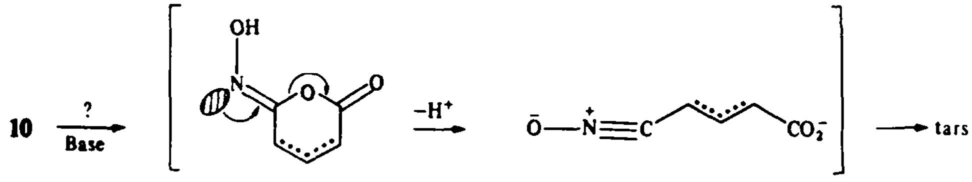
49a R² = Me₃Si; R³ = p–MeO—Bn
49b R² = t–BuMe₂Si; R³ = p–MeO—Bn
49c R² = p–NO₂—Bn; R³ = H

Scheme 4.



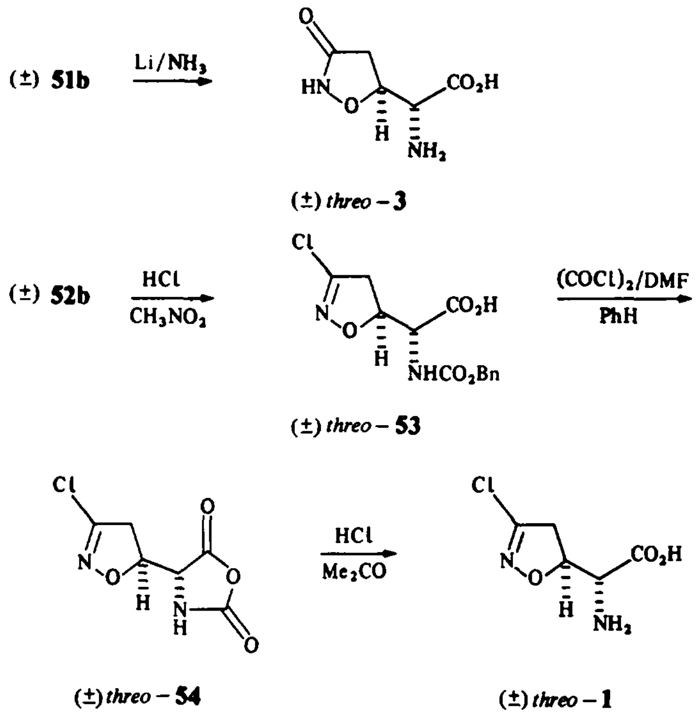
Scheme 5.

was identified as being responsible for the failure of **10** to cyclize and this difficulty had been circumvented by using the fully blocked hydroxamic acid **50a**, we were interested in exploring alternate methods to provide the same result by modulating functional group reactivities in a less highly protected system. It was hypothesized the complex mixtures which resulted when **10** was treated with base arose by an intramolecular acylation of the hydroxamic acid with the ultimate production of highly reactive species. While this unfortunate reactivity had been circumvented in the case of **50a** → **51a**, an alternate, appealing way to effect the same result would be to lower the acylating capacity of the α-carbonyl by utilizing the free acid rather than the ester. It was expected, and indeed found, that the free carboxylic acid, which exists as the carboxylate anion under the strongly basic reaction conditions, effectively prevents internal acylation of the unprotected hydroxamic acid, **50d** → **51b** (Scheme 5).



Remarkably, it was found that this cyclization produced the protected tricholomic acid **51** as a *single diastereomer* and in excellent yield. That it was the unnatural diastereomer which had formed *exclusively* (>95% by NMR) was shown by deprotection to (±)-*threo*-tricholomic acid and thence to (±)-*threo-β*-hydroxyglutamic acid,[3] as well as by chlorination[7] (Scheme 5) and deprotection to (±)-*threo*-AT-125.

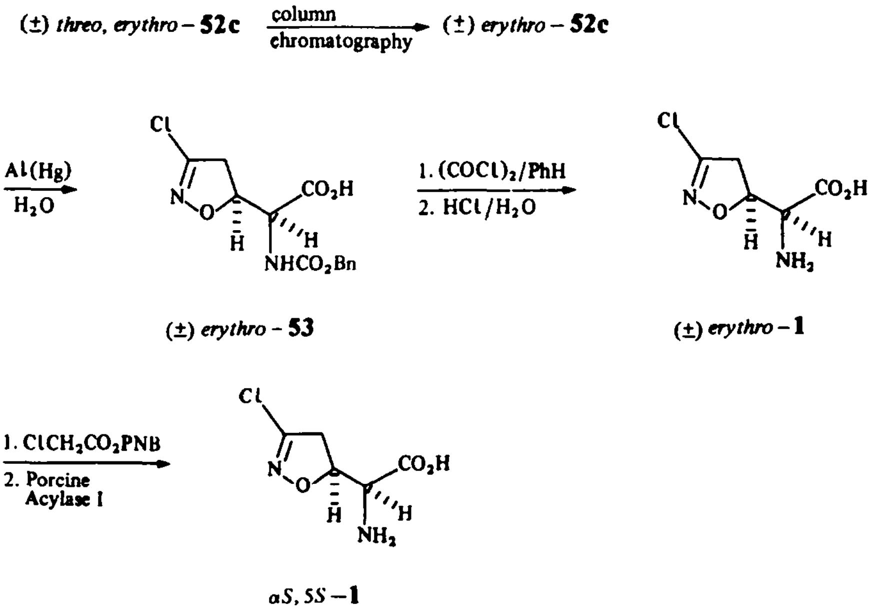
Deprotection of the benzyl carbamate was readily



achieved by heating the amino acid chloride derived from **53** for a very brief time,[24] followed by acid hydrolysis of the resulting Leuch's anhydride **54**.

The exclusive production of *threo* diastereomer (**51b**) in the base-induced cyclization of hydroxamic acid **50d** merits discussion. Presumably, the nucleophilic species under the strongly basic reaction conditions is the hydroxamic acid trianion. A net *trans* addition of hydroxamic acid dianion and a proton across the *Z*-unsaturated carboxylate could lead to the observed racemic *threo* diastereomer. The unfortunate stereochemical consequences of cyclizing the mono-protected hydroxamic acid **51b** prompted further transformations of the more highly protected, but readily available tricholomic acid **51a**.

Application of the direct von Braun-dealkylative (**21c** → **25**) formation of the chloroisoxazoline ring to hydroxamic acid **51a** produced only modest yields of **52a**, a result attributed to the lability of the benzyl ester group toward the vigorous conditions required to dealkylate/chlorinate the substituted isoxazolidone ring. After some experimentation it was discovered a deactivated nitrobenzyl ester combined the minimum requirements of stability toward the vigorously reactive



Scheme 6.

von Braun conditions and lability toward deprotective conditions which could be employed in the presence of the sensitive chloroisoxazoline ring.[25] By repeating the synthetic sequence in Scheme 4 with the *o*-nitrobenzyl ester series (**41** → **42c** → **40c** → **50c**) the suitably protected hydroxamic acid **50c** was conveniently and efficiently prepared on a 100–500 g scale through a series of crystalline intermediates without chromatography or extensive purification. Cyclization of **50c** and von Braun chlorination of the crude cyclization products, protected tricholomic acids **51c**, provided protected AT-125 derivatives **52c** as a 1:1 diastereomeric mixture. The single chromatographic separation in this synthesis, the separation of *erythro* and *threo* diastereomers of **52c** was readily achieved on a 10–20 g scale by silica gel chromatography. Subsequent deprotection of the pure *erythro* diastereomer of **52c** and enzymatic resolution of the N-chloroacetyl derivative yielded optically pure, synthetic AT-125 (Scheme 6).

DISCUSSION

The synthesis of AT-125 described here allows a reasonably efficient preparation of this natural product and its stereochemical isomers. Despite the need for certain protecting group manipulations, the sequence ultimately adopted has allowed the synthesis of protected racemic AT-125 on a multigram scale through a series of highly crystalline intermediates with only a single chromatography. Insofar as the intramolecular Michael addition of dehydroglutamic acids **50a–d** resembles a postulated biosynthetic route to related isoxazolidine amino acids,[4] this synthesis may be viewed as "biomimetic." If in fact the biological precursor to AT-125 is the corresponding ring hydrolyzed amino acid, tricholomic acid, **3**, the extremly low reactivity of the cyclic hydroxamic acid toward chlorination implies a rather unusual biological process for this transformation.

EXPERIMENTAL

General procedures. M.ps were taken on a Gallenkamp or Büchi 510 capillary m.p. apparatus and are uncorrected. Microanalyses were performed by Dr F. B. Strauss of this laboratory. IR spectra were recorded on a Perkin–Elmer Model 257 spectrophotomer and were calibrated against a polystyrene film. NMR spectra at 60 MHz were recorded on a Hitachi Perkin–Elmer Model R-24B spectrometer; 90 MHz spectra were taken on a Hitachi Perkin–Elmer Model R-32 spectrometer; 300 MHz spectra were taken on a Bruker WH-300 spectrometer. Chemical shifts are reported in ppm (δ) relative to internal TMS or sodium 2,2 - dimethyl - 2 - silapentane - 5 - sulfonate as standards, with the notations giving the multiplicity of the signals, the coupling constants (if applicable), and the number of protons: spin multiplicity is given by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Low resolution mass spectra were determined on a VG Micromass ZAB-16F spectrometer. Field desorption, field ionization and chemical ionization mass spectra were recorded on a VG Micromass ZAB-1F spectrometer, and obtained through the courtesy of Dr R. T. Aplin of this laboratory. Optical rotations were measured using a Perkin-Elmer 241 automatic polarimeter in a 10 cm cell. Silica gel for column chromatography was Merck silica gel 60, No. 7734, or Merck silica gel 60, No. 9385. Analytical TLC was performed on precoated Merck 60F-254. Preparative TLC was carried out on Merck silica gel 60 GF 254, No. 7730, on 200 × 200 × 1.25 mm layers. Solvents and reagents were purified by standard procedures.[26]

Mixture of 1-, *and 5-benzyl glutaconates* (**8**)

A soln of glutaconic acid (7.8 g, 60 mmol) in N,N-dimethylformamide (9 ml) was heated at 80° and stirred vigorously during the addition of dicyclohexylamine (12 ml, 60 mmol) and a single portion of benzyl bromide (7.15 ml, 60 mmol). The resulting solid mass was cooled, triturated with EtOAc, filtered and washed several times with EtOAc. The combined filtrates were washed four times with water, concentrated, and the residue was dissolved in diethyl ether and extracted three times with sat NaHCO$_3$ aq. The extracts were combined, acidified with conc HCl and washed three times with diethyl ether. The washes were combined, dried (brine, Na$_2$SO$_4$) and concentrated yielding 4.3 g (33%) of mixture **8** as a light yellow oil: R_f 0.4 in 1:4 MeOH–benzene; IR (CHCl$_3$) 3400–2400, 1720, 1660 cm^{-1}; NMR (CDCl$_3$) δ 3.3 (br d, J = 8 Hz, 2H), 5.14 and 5.2 (2 × s, 2H total), 5.9 and 6.18 (2 × m, 1H total), 6.8–7.3 (m, 1H), 7.42 (s, 5H).

Mixture of 1-, *and 5-benzyl glutaconyl chlorides* (**9**)

Carboxylic acid mixture **8** (110 mg, 0.5 mmol) and SOCl$_2$ (44 µl, 0.6 mmol) was heated at 50° for 20 min under a drying tube (CaCl$_2$) then concentrated *in vacuo* yielding 119 mg (100%) of **9** as a brown oil: IR (CHCl$_3$) 3050, 1790, 1740 cm^{-1}; NMR (CDCl$_3$) δ 3.36 and 3.72 (2 × q, J = 2 Hz, 2H total), 5.13 and 5.16 (2 × s, 2H total), 5.9–6.3 (m, 1H), 6.6–7.2 (m, 1H), 7.3 (s, 5H).

Mixture of 1-, *and 5-benzyl glutaconic hydroxamic acids* (**10**)

A soln of hydroxylamine hydrochloride (556 mg, 8 mmol) in 1N NaOH (8 ml, 8 mmol) and THF (5 ml) was stirred at 0° during the addition of a soln of acid chloride mixture **9** (952 mg, 4 mmol) in THF (3 ml). The soln was stirred for 20 min at 0°, diluted with diethyl ether, washed twice with sat NaHCO$_3$ aq dried (brine, MgSO$_4$) and concentrated yielding 473 mg (46%) of mixture **10** as a light brown oil which gave a deep purple coloration when dissolved in aqueous acetone containing iron trichloride: R_f 0.65 in 1:3 MeOH—benzene; IR (CHCl$_3$) 3600–2700, 1725, 1680–1630 cm^{-1}; NMR (CDCl$_3$) δ 2.7–3.3 (br m, 2H), 5.2 (br s, 2H), 5.8–6.2 (br m, 1H), 6.8 (m, 1H), 7.33 (s, 5H); MS (90 eV) *m/e* 318 (M – OH).

Chlorosuccinic acid (**15**)[13]

A mixture of DL-malic acid (200 g, 1.49 mol) and PCl$_5$ (1 kg, 4.8 mol) was shaken at room temp until the HCl evolution ceased. The semi-liquid mass was diluted with CHCl$_3$ (1 l) and heated on a steam-bath to evaporate the CHCl$_3$. The resulting mixture was added in small portions to water (750 ml) with vigorous stirring and cooling to maintain the temp below 55°. The aqueous soln was extracted seven times with diethyl ether, and the extracts were combined, dried (brine, Na$_2$SO$_4$) and concentrated yielding 89.8 g (40%) of **15** as white crystals: m.p. 154–156° [lit.[99] m.p. 151–152°]; NMR (acetone d$_6$) δ 3.0 (2 × q, AB of ABX, J_{AB} = 18 Hz, 2H), 4.63 (t, X of ABX, J_{AX+BX} = 14 Hz, 1H), 9.8 (br s, 2H).

Chlorosuccinic anhydride (**16**)

A mixture of diacid **15** (25.4 g, 0.165 mol) and acetyl chloride (140 ml) was heated at reflux under N$_2$ for 3 hr, then concentrated and distilled yielding 19.4 g (87%) of **16** as a clear oil: b.p. 95–98° (0.5 Torr); IR (neat) 3000, 1870, 1800 cm^{-1}; NMR (CDCl$_3$) δ 3.45 (2 × q, AB of ABX, J_{AB} = 19 Hz, 2H), 4.95 (q, X of ABX, J_{AX+BX} = 15 Hz, 1H).

1-*Benzyl 2-chlorosuccinic dicyclohexylammonium salt* (**17**)

A mixture of anhydride **16** (8.04 g, 60 mmol) and benzyl alcohol (6. 6 ml, 63.6 mmol) was allowed to stand overnight at room temp. EtOAc (120 ml) and dicyclohexylamine (12 ml, 60.3 mmol) were added, and the soln was cooled and filtered. The crude product was washed three times with diethyl ether and dried yielding 19.9 g (78%) of **17** as white crystals: m.p. 120–122° (d); IR (CHCl$_3$) 3300–2400, 2950, 2850, 1740, 1630 cm^{-1}; NMR (CDCl$_3$) δ 0.95–2.2 (br m, 2OH), 2.9 (m, 4H), 4.75

(t, J = 7 Hz, 1H), 5.2 (s, 2H), 7.35 (s, 5H), 9.2 (br s, 2H). (Found: C, 65.23; H, 8.13; N, 3.22; Cl, 8.26. Calc for $C_{23}H_{34}NO_4Cl$: C, 65.16; H, 8.08; N, 3.30; Cl, 8.36%.)

1-*Benzyl 2-chlorosuccinate* (**18**)

A soln of **17** (19 g, 45 mmol) in 1 : 1 water–acetone (550 ml) was shaken for 70 min at room temp with Dowex 50W-X4 cation-exchange resin (85 ml) and filtered. The filtrate was concentrated to remove acetone, and the aqueous residue was extracted four times with EtOAc. The extracts were combined, dried (brine, Na_2SO_4) and concentrated yielding 10.67 g (99%) of **18** as a clear oil: IR (neat) 3600–2500, 1745, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (2 × q, AB of ABX, J_{AB} = 17 Hz, 2H), 4.65 (t, X of ABX, J = 7 Hz, 1H), 5.2 (s, 2H), 7.35 (s, 5H), 10.5 (s, 1H); MS (70 eV) *m/e* 242, 244 (M).

1-*Benzyl 2-chlorosuccinyl chloride* (**19**)

A mixture of acid **18** (10.67 g, 44.1 mmol) and $SOCl_2$ (5 ml, 69.1 mmol) was heated at 65° for 90 min under a drying tube ($CaCl_2$) then concentrated yielding 11.52 g (100%) of **19** as a light yellow oil: IR (neat) 3000, 1800, 1745 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (2 × q, AB of ABX, J_{AB} = 18 Hz, 2H), 4.6 (t, X of ABX, J = 7 Hz, 1H), 5.2 (s, 2H), 7.35 (s, 5H).

1-*Benzyl 2-chlorosuccinic hydroxamic acid* (**14**)

A soln of acid chloride **19** (130 mg, 0.5 mmol) in diethyl ether (1 ml) was added to an ice-cold, stirred soln of hydroxylamine hydrochloride (42 mg, 0.604 mmol) in sat $NaHCO_3$ aq (1 ml) overlayered with diethyl ether (2 ml). The mixture was stirred for 15 min at 0° then acidified to pH 1 with 2 N HCl and extracted twice with diethyl ether. The extracts were combined, dried (brine, Na_2SO_4) and concentrated yeilding 113 mg (88%) of **14** as a clear oil which gave a deep purple coloration when dissolved in aqueous acetone containing iron trichloride: R_f 0.12 in 1 : 1 EtOAc–hexane; IR ($CHCl_3$) 3500–2500, 1745, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.8 (br m, 2H), 4.7 (t, J = 7 Hz, 1H), 5.15 (s, 2H), 7.3 (s, 5H), 8.6 (br m, 2H); MS (70 eV) *m/e* 240, 242 (M − OH).

1-*Benzyl 2-chlorosuccinic* N-*benzylhydroxamic acid* (**20a**)

A soln of acid chloride **19** (1.65 g, 6.35 mmol) in diethyl ether (10 ml) was cooled at 0° and stirred under N_2 during the addition (20 min) of a soln of N-benzylhydroxylamine[15] (1.56 g, 12.7 mmol) in diethyl ether. After the addition was completed, the mixture was stirred for an additional 10 min, diluted with diethyl ether and filtered. The clear filtrate was washed with 1 N HCl, dried (brine, Na_2SO_4) and concentrated. The crude product was recrystallized from EtOAc–hexane yielding 1.36 g (62%) of **20a** as white needles which gave a deep purple coloration when dissolved in aqueous acetone containing iron trichloride: m.p. 93–94°; R_f 0.2 in 1 : 4 diethyl ether–benzene; IR ($CHCl_3$) 3600–2900, 1740, 1650 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (br m, 2H), 4.8 (m, 1H), 4.8 (s, 2H), 5.15 (s, 2H), 7.34 (s, 5H); MS (70 eV) *m/e* 347, 349 (M). (Found: C, 62.12; H, 5.24; N, 3.95; Cl, 10.12. Calc for $C_{18}H_{18}NO_4Cl$: C, 62.16; H, 5.22; N, 4.02; Cl, 10.19%.)

Benzyl 2-benzyl-3-oxo-5-isoxazolidinecarboxylate (**21a**)

A soln of hydroxamic acid **20a** (100 mg, 0.288 mmol) in diethyl ether (10 ml) and sat $NaHCO_3$ aq (10 ml) was shaken overnight at room temp. The aqueous layer was separated and extracted twice with diethyl ether. The extracts were combined with the original organic layer, dried (brine, Na_2SO_4) and concentrated yielding 85 mg (96%) of **21** as white crystals: m.p. 86–87°; R_f 0.25 in 1 : 4 diethyl ether–benzene; IR ($CHCl_3$) 3000, 1750, 1705, 1500 cm^{-1}; NMR ($CDCl_3$) δ 3.05 (q, AB of ABX, 2H), 4.8 (d, J = 2 Hz, 2H), 4.9 (q, X of ABX, J_{AX+BX} = 16 Hz, 1H), 5.16 (s, 2H), 7.3 (s, 5H), 7.32 (s, 5H); MS *m/e* 311 (M). (Found: C, 69.36; H, 5.63; N, 4.39. Calc for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%.)

"One-pot" formation of **21a** *from acid chloride* **19**

A soln of **19** (9.2 g, 35.4 mmol) in THF (100 ml) was stirred at 0° under N_2 during the addition (1 hr) of a soln of N-benzylhydroxylamine[15] (4.37 g, 35.4 mmol) and Et_3N (4.93 ml, 35.4 mmol) in THF (100 ml). After the addition was completed, the soln was stirred for 30 min at 0°, and a soln of Et_3N (5.7 ml, 40.7 mmol) in THF (20 ml) was added dropwise. The resulting soln was stirred at room temp for 6 hr and concentrated. The residue was partitioned between water and EtOAc, and the organic layer was washed with 1 N HCl, water, dried (brine, Na_2SO_4), decolorized (charcoal) and concentrated. The solid residue was recrystallized from diethyl ether yielding 8 g (73%) of **21** as white crystals: m.p. 86–87°.

2-*Benzyl 3-oxo-5-isoxazolidinecarboxylic acid* (**22a**)

A soln of ester **21a** (4.66 g, 15 mmol) in THF (100 ml) was hydrogenated over 10% Pd–C (750 mg) for 30 min at room temp. The soln was filtered, concentrated, and the residue was recrystallized from benzene yielding 3.04 g (92%) of **22a** as white crystals: m.p. 126–128°; IR ($CHCl_3$) 3600–2400, 1750–1660 cm^{-1}; NMR ($CDCl_3$–acetone-d_6) δ 3.1 (br d, AB of ABX, 2H), 4.75 (d, J = 4 Hz, 2H), 4.95 (t, X of ABX, J = 7 Hz, 1H), 6.8 (br s, 1H), 7.32 (s, 5H); MS (70 eV) *m/e* 221 (M). (Found: C, 59.78; H, 5.03; N, 6.24. Calc for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33%.)

1-*Benzyl 2-chlorosuccinic* N-(p-*nitrobenzyl*)*hydroxamic acid* (**20b**)

A soln of **19** (260 mg, 1 mmol) in THF (4 ml) was cooled at 0° and stirred under N_2 during the dropwise addition of a soln of N-*p*-nitrobenzyl hydroxylamine[17] (168 mg, 1 mmol) and Et_3N (142 μl, 1 mmol) in THF (6 ml). After the addition was completed, the mixture was stirred for 30 min at 0° and concentrated. The residue was partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried (brine, $NaSO_4$) and concentrated yielding 405 mg (94%) of **21b** as a light yellow oil which gave a deep purple coloration when dissolved in aqueous acetone containing iron trichloride: R_f 0.3 in 3 : 2 EtOAc–hexane; IR (neat) 3500–2800, 1740, 1660–1600, 1530 cm^{-1}; NMR ($CDCl_3$) δ 3.25 (br m, 2H), 4.75 (m, 1H), 4.83 (s, 2H), 5.2 (s, 2H), 7.35 (s, 5H), 7.4 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.15 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 357 (M − Cl).

N-(p-*Methoxybenzyl*)*hydroxylamine*

To a soln of anisaldoxime[27] (151 g, 1 mol) and sodium cyanoborohydride (44 g, 0.7 mol) in MeOH (110 ml) was added a trace of methyl orange. A soln of 2 N HCl–MeOH was then added with stirring to maintain the red color (pH 3). The mixture was stirred for 2 hr and the MeOH was removed under reduced pressure. The residue was dissolved in water (800 ml), raised to pH > 9 with 6 N NaOH, extracted four times with EtOAc, dried (brine, Na_2SO_4), concentrated and recrystallized from EtOH affording 108 g (71%) of N-(*p*-methoxybenzyl)hydroxylamine as white crystals: m.p. 75–77° [lit.[27] m.p. 76°]; R_f 0.20 in EtOAc; IR ($CHCl_3$) 3580, 3500–3100, 1610, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.92 (s, 2H), 5.46 (s, 2H, exchangeable with D_2O), 6.81 (d, A_2 of A_2B_2, J = 8 Hz, 2H), 7.17 (d, B_2 of A_2B_2, J = 8 Hz, 2H); MS (70 eV) *m/e* 153 (M). (Found: C, 62.49; H, 7.38; N, 8.87. Calc for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14%.)

1-*Benzyl 2-chlorosuccinic* N-(p-*methoxybenzyl*)*hydroxamic acid* (**20c**)

A soln of **19** (63 g, 0.242 mol) in THF (150 ml) was stirred at 0° under N_2 during the dropwise addition of a soln of N-(*p*-methoxybenzyl)hydroxylamine (37.1 g, 0.242 mol) and Et_3N (33.6 ml, 0.242 mol) in THF (230 ml). After the addition was completed, the mixture was stirred for 1 hr at room temp, concentrated, and the residue was partitioned between 2 N HCl and EtOAc. The aqueous layer was extracted with EtOAc and the organic layers were combined, washed with sat $NaHCO_3$ aq, dried (brine, Na_2SO_4), decolorized (charcoal) and concentrated yielding 87 g (95%) of **20c** as a light yellow oil which gave a deep purple coloration when dissolved in aqueous acetone containing iron trichloride: R_f 0.3 in 1 : 4 diethyl ether–benzene; IR (neat) 3500–3000, 1745, 1660–1600, 1520 cm^{-1}; NMR ($CDCl_3$) δ 3.08 (br m, 2H), 3.75 (s, 3H), 4.6 (br s, 3H), 5.2 (s, 2H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.2 (d, B_2 of A_2B_2, J = 9 Hz, 2H), 7.35 (s, 5H); MS (70 eV) *m/e* 360, 362 (M − OH).

Benzyl 2 - (p - *nitrobenzyl*) - 3 - *oxo* - 5 - *isoxazolidinecarboxylate* (**21b**)

A soln of **19** (520 mg, 2 mmol) in THF (8 ml) was stirred at 0° under N_2 during the addition (10 min) of a soln of N-(*p*-nitrobenzyl)hydroxylamine (336 mg, 2 mmol) in THF (12 ml). After the addition was completed, the mixture was stirred for 30 min at room temp, and Et_3N (1.15 ml, 8.3 mmol) was added. The mixture was stirred for 45 min, concentrated, and the residue was partitioned between water and EtOAc. The organic layer was dried (brine, Na_2SO_4), concentrated and chromatographed on silica gel (25 g) using 1 : 4 diethyl ether–benzene as eluant: IR (neat) 3000, 1750–1700, 1600, 1530, 1350 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (m, AB of ABX, 2H), 4.75 (d, J = 2 Hz, 2H), 4.95 (q, X of ABX, J_{AX+BX} = 15 Hz, 1H), 5.18 (s, 2H), 7.35 (s, 5H), 7.42 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.07 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 356 (M). (Found: C, 60.42; H, 4.60; N, 7.68. Calc for $C_{18}H_{16}N_2O_6$: C, 60.69; H, 4.53; N, 7.86%.)

In some experiments **23** could be isolated as white crystals: m.p. 173–175°; R_f 0.06 in 1 : 4 diethyl ether–benzene; IR (KBr) 3400, 3000, 1745, 1670, 1530 cm^{-1}; NMR ($CDCl_3$–acetone-d_6) δ 2.8 (m, 2H), 4.7 (q, X of ABX, J_{AX+BX} = 16 Hz, 1H), 5.2 (s, 2H), 6.1 (d, J = 7 Hz, 1H), 7.45 (s, 5H), 7.8 and 7.88 (2 × d, 2 × A_2 of A_2B_2, J = 8 Hz, 2H), 8.0 (br s, 1H), 8.3 (d, B_2 of A_2B_2, J = 8 Hz, 2H); MS (70 eV) *m/e* 265 (M − benzyl).

Benzyl 2 - (p - *methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinecarboxylate* (**21c**)

Ventron 50% sodium hydride–oil dispersion (11 g, 0.230 mol) was washed three times with dry diethyl ether and added portionwise as an ethereal slurry to a stirred soln of hydroxamic acid **20c** (87 g, 0.230 mol) in N,N-dimethylformamide (250 ml) under N_2 at 0°. After the addition was completed, the soln was stirred overnight at room temp, then quenched with 2 N HCl and EtOAc. The aqueous layer was washed with EtOAc, and the combined organic layers were dried (brine, Na_2SO_4) and concentrated yielding 76 g (97%) of **21c** as a brown oil. A portion (400 mg) of the crude product was chromatographed on silica gel (50 g) using 1 : 4 diethyl ether–benzene as eluant yielding pure **21c** as a light yellow oil: R_f 0.4 in 1 : 1 $CHCl_3$–EtOAc; IR (neat) 2950, 1750–1680, 1520 cm^{-1}; NMR ($CDCl_3$) δ 3.02 (m, AB of ABX, m, 2H), 3.78 (s, 3H), 4.62 (br s, 2H), 4.85 (q, X of ABX, J_{AX+BX} = 15 Hz, 1H), 5.2 (s, 2H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.25 (d, B_2 of A_2B_2, J = 9 Hz, 2H), 7.32 (s, 5H); high resolution mass spectrum: calc for $C_{19}H_{19}NO_5$: 341.12632; found: 341.12958. (Found: C, 66.75; H, 5.68; N, 4.03. Calc for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10%.)

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinecarboxylic acid* (**22c**)

A soln of crude **21c** (76 g, 0.223 mol) in EtOAc (200 ml) was hydrogenated over 10% Pd–C (10 g) for 1 hr, filtered, concentrated, and the residue was triturated with benzene, filtered, and recrystallized from benzene yielding 23.2 g (42%) of **22c** as white crystals: m.p. 115–117°; R_f 0.17 in EtOAc; IR ($CHCl_3$) 3400–2800, 1750–1680, 1500 cm^{-1}; NMR ($CDCl_3$–acetone d_6) δ 3.1 (m, AB of ABX, 2H), 3.8 (s, 3H), 4.5 (d, A of AB, J = 16 Hz, 1H), 4.82 (d, B of AB, J = 16 Hz, 1H), 4.9 (q, X of ABX, J_{AX+BX} = 15 Hz, 1H), 5.8 (br s, 1H), 6.82 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.28 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 251 (M). (Found: C, 57.16; H, 5.32; N, 5.46. Calc for $C_{13}N_{13}NO_5$: C, 57.37; H, 5.21; N, 5.57%.)

Benzyl 3 - *chloro* - 4,5 - *dihydro* - 5 - *isoxazolecarboxylate* (**25**)

A soln of **21c** (100 mg, 0.293 mmol) and PCl_5 (64 mg, 0.308 mmol) in nitromethane (2 ml) was heated at reflux under N_2 for 1 hr. The soln was concentrated *in vacuo*, and the residue was purified by preparative TLC on silica gel using 1 : 9 diethyl ether–benzene as eluant yielding 30 mg (43%) of **25** as a light yellow oil: R_f 0.4 in 1 : 9 diethyl ether–benzene; IR ($CHCl_3$) 3000, 1740, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (d, J = 9 Hz, 2H), 5.18 (t, J = 9 Hz, 1H), 5.2 (s, 2H), 7.35 (s, 5H); high resolution mass spectrum: calc for $C_{11}H_{10}NO_3Cl$: 239.03492; found: 239.03448.

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinemethanol* (**28**)

A soln of **22c** (3.75 g, 15 mmol), in THF (45 ml) was stirred at − 15° under N_2 during the addition (5 min) of 0.91 M borane–THF (18 ml, 16.4 mmol). After the addition was completed, the soln was stirred overnight at room temp. MeOH (15 ml) was added and the soln was concentrated. The residue was dissolved in EtOAc, washed with 1 N HCl, sat $NaHCO_3$ aq, water, then dried (brine, Na_2SO_2) and concentrated yielding 1.63 g (46%) of **28** as a colorless oil which solidified: R_f 0.1 in 1 : 4 hexane–ethyl acetate; IR ($CHCl_3$) 3600–3300, 2950, 1695, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.3 (s, 1H), 2.75 (d, J = 8 Hz, 2H), 3.6 (m, AB of ABX, 2H), 3.8 (s, 3H), 4.4–4.7 (m, 1H), 4.63 (s, 2H), 6.85 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.23 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 237 (M).

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinemethanol methanesulfonate* (**29**)

A soln of **28** (1.48 g, 6.25 mmol) in pyridine (10 ml) was stirred at 0° under N_2 during the addition of methanesulfonyl chloride (530 μl, 6.89 mmol). After the addition was completed, the soln was warmed and stirred at room temp overnight. The soln was diluted with EtOAc, washed twice with 2 N HCl, dried (brine, Na_2SO_4) and concentrated giving a yellow solid which was purified by dissolving in a small amount of warm EtOAc and adding hexane. The soln was cooled, filtered, and the product dried *in vacuo* yielding 1.64 g (83%) of **29** as white crystals: m.p. 72–74°; R_f 0.2 in 1 : 3 hexane–EtOAc; IR (neat melt) 3000, 1700, 1510, 1260 cm^{-1}; NMR ($CDCl_3$) δ 2.7–2.9 (m, 2H), 2.82 (s, 3H), 3.78 (s, 3H), 4.2 (d, J = 5 Hz, 2H), 4.4–4.8 (m, 1H), 4.6 (s, 2H), 6.85 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.2 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 315 (M). (Found: C, 49.74; H, 5.59; N, 4.37; S, 9.99. Calc for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.44; N, 4.44; S, 10.17%.)

Reaction of methanesulfonate **29** *with potassium cyanide*; 2 - (p - *methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidineacetonitrile* **30** *and* 3 - (p - *methoxybenzyl*) - 4 - *oxo* - 2 - *oxa* - 3 - *azabicyclo* - [3.1.0]*hexane* (**31**)

A soln of **29** (100 mg, 0.318 mmol), anhyd KCN (31 mg, 0.48 mmol), and 18-crown-6 ether–acetonitrile complex (10 mg) in acetonitrile (4 ml) was heated at reflux under N_2 for 1 day with vigorous stirring. The soln was filtered through a plug (2 cm) of silica gel, concentrated, and purified by preparative TLC on silica gel using 1 : 4 MeOH–benzene as eluant yielding 44 mg (60%) of nitrile **30** as a clear oil: R_f 0.3 in 1 : 4 MeOH–benzene; IR ($CHCl_3$) 3000, 2250, 1700, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.6 (d, J = 6 Hz, 2H), 2.6–3.2 (m, 2H), 3.76 (s, 3H), 4.6 (m, 3H), 6.8 (d, A_2 of A_2B_2, J = 8 Hz, 2H), 7.25 (d, B_2 of A_2B_2, J = 8 Hz, 2H); MS (70 eV) *m/e* 246 (M).

Cyclopropane **31** was isolated as 19 mg (28%) of a clear oil: R_f 0.35 in 1 : 4 MeOH–benzene; NMR ($CDCl_3$) δ 0.95 (m, 2H), 2.25 (m, 1H), 3.8 (s, 3H), 4.55 (m, 1H), 4.56 (s, 2H), 6.9 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.25 (d, B_2 of A_2B_2, J = 9 Hz, 2H); high resolution mass spectrum: calc for $C_{11}H_{13}NO_3$: 220.08881; found: 220.09054.

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinemethanol trifluoromethanesulfonate* (**32**)

A soln of **28** (106 mg, 0.447 mmol) and pyridine (73 μl, 0.90 mmol) in CH_2Cl_2 (2 ml) was cooled at − 78° and stirred under N_2 during the addition of trifluoromethanesulfonic anhydride (79 μl, 0.47 mmol). The soln was warmed slowly to room temp, diluted with EtOAc, washed with ice-cold 0.2 N HCl, ice-cold water, then dried (ice-cold brine, Na_2SO_4) and concentrated yielding 140 mg (85%) of **32** as an extremely unstable oil: IR (neat) 3000, 1700, 1510, 1260, 1210 cm^{-1}; NMR ($CDCl_3$) δ 2.76 (2 × q, AB of ABX, J_{AB} = 17 Hz, 2H), 3.8 (s, 3H), 4.4–4.8 (m, 5H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.23 (d, B_2 of A_2B_2, J = 9 Hz, 2H).

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidineacetonitrile* (**30**)

A soln of trifluoromethanesulfonate **32** (140 mg, 0.38 mmol), anhyd KCN (37 mg, 0.57 mmol), and 18-crown-6 ether–acetonitrile complex (10 mg) in acetonitrile (1.5 ml) was stirred for 1 hr at room temp, then 3 hr at 60°. After standing overnight at room temp, the soln was filtered through a plug (2 cm) of silica gel, diluted with EtOAc, washed with water, sat $NaHCO_3$ aq, dried (brine, Na_2SO_4) and concentrated yielding 84 mg (90%) of **30** as a light yellow oil: R_f 0.3 in 1:4 MeOH–benzene.

2 - (p - *Methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidinecarbonyl chloride* (**33**)

A mixture of acid **22c** (1.25 g, 5 mmol) and $SOCl_2$ (1.5 ml, 20.5 mmol) was heated at 60° for 30 min under a drying tube ($CaCl_2$) then concentrated *in vacuo* yielding 1.33 g (99%) of **33** as a yellow oil: IR ($CHCl_3$) 3000, 1805, 1760–1680, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.2 (br s, 2H), 3.8 (s, 3H), 4.5–5.2 (br m, 3H), 6.85 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.32 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 269, 271 (M).

1 - *Oxo* - 1 - [2′ - (p - *methoxybenzyl*) - 3′ - *oxo* - 5′ - *isoxazolidine*] - 2 - *diazoethane* (**34**)

A soln of diazomethane (5 mmol) in diethyl ether (25 ml) was stirred under N_2 at 0° during the dropwise addition of a soln of **33** (240 mg, 1 mmol) in diethyl ether (5 ml). The soln was stirred at room temp for 90 min, concentrated, and the residue was purified by preparative TLC using 1:3 CH_2Cl_2–diethyl ether as eluant yielding 178 mg (65%) of **34** as a light yellow oil: R_f 0.2 in 1:3 dichloromethane–diethyl ether; IR (neat) 3000, 2150, 1705, 1640, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.02 (d, J = 7 Hz, 2H), 3.8 (s, 3H), 4.36 (d, A of AB, J = 16 Hz, 1H), 4.71 (m, 1H), 4.82 (d, B of AB, J = 16 Hz, 1H), 5.25 (s, 1H), 6.85 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.22 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 275 (M).

Ethyl 2 - *diazo* - 3 - *oxo* - 3 - [2′ - (p - *methoxybenzyl*) - 3′ - *oxo* - 5′ - *isoxazolidine*]*propionate* (**35**)

A soln of **33** (1.33 g, 5 mmol) in THF (5 ml) was stirred at 0° under N_2 during the rapid addition of ethyl diazoacetate (1.26 ml, 12 mmol). After the vigorous evolution of N_2 had ceased, the soln was stirred at room temp overnight, concentrated, and the residue was dissolved in EtOAc and washed with sat $NaHCO_3$ aq. The aqueous wash was extracted with EtOAc. The combined organic layers were dried (brine, Na_2SO_4) and concentrated, and the residue was triturated three times with hexane, then recrystallized from EtOAc–hexane yielding 1.36 g of **35**. The crystallization filtrates were combined, concentrated, and chromatographed on silica gel (25 g) using 1:1 EtOAc–hexane as eluant yielding an additional 220 mg (92%) of **35** as light yellow crystals: m.p. 86–87°; R_f 0.25 in 1:1 EtOAc–hexane; IR ($CHCl_3$) 3000, 2170, 1720–1650, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3H), 3.08 (m, AB of ABX, 2H), 3.75 (s, 3H), 4.23 (q, J = 7 Hz, 2H), 4.62 (s, 2H), 5.52 (q, X of ABX, J_{AX+BX} = 14 Hz, 1H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.2 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 347 (M). (Found: C, 55.44; H, 5.09; N, 12.16. Calc for $C_{16}H_{17}N_3O_6$: C, 55.33; H, 4.93; N, 12.10%.)

2 - *Ethoxycarbonyl* - 2 - [2′ - (p - *methoxybenzyl*) - 3′ - *oxo* - 5′ - *isoxazolidine*] *acetic acid benzyl ester diastereomeric mixture* (**36**)

A soln of **35** (1.75 g, 5 mmol) and benzyl alcohol (520 μl, 5 mmol) in THF (50 ml) was degassed with N_2, then stirred under N_2 and irradiated for 8 hr with a Hanovia 450 watt medium pressure UV light (pyrex filter). The soln was concentrated, and the residue was chromatographed on silica gel (75 g) using 1:1 EtOAc–hexane as eluant yielding 1.35 g (63%) of **36** as an oily 1:1 mixture of diastereomers: R_f 0.5 in 1:1 EtOAc–hexane; IR (neat) 3000, 1750–1680, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (2 × t, J = 7 Hz, 3H total), 2.7–3.3 (m, 2H), 4.6 (m, 1H), 4.65 (s, 3H), 4.15 (br q, J = 7 Hz, 2H), 4.5 and 6.2 (2 × s, 2H total), 4.8–5.16 (m, 1H), 5.16 (s, 2H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.13 (d, B_2 of A_2B_2, J = 9 Hz, 2H), 7.16 (s, 5H).

2 - *Ethoxycarbonyl* - 2 - [2′ - (p - *methoxybenzyl*) - 3′ - *oxo* - 5′ - *isoxazolidine*] *acetic acid diastereomeric mixture* (**37**)

A soln of **36** (1.35 g, 3.16 mmol) in EtOAc (50 ml) was hydrogenated over 10% Pd–C (200 mg) for 3 hr. The mixture was filtered and concentrated yielding 1.01 g (95%) of **37** as a thick oil: IR (neat) 3500–2500, 3000, 1740–1600, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.1 (2 × t, J = 8 Hz, 3H total), 2.8–3.2 (m, 2H), 3.6 (d, J = 4 Hz, 1H), 3.76 (s, 3H), 4.15 (br q, J = 8 Hz, 2H), 4.56 (s, 2H), 5.0 (m, 1H), 6.76 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.15 (d, B_2 of A_2B_2, J = 9 Hz, 2H), 9.6 (br s, 1H).

Ethyl 2 - (p - *methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidineacetate* (**39**)

A soln of **37** (82 mg, 0.243 mmol) and Et_3N (35 μl, 0.255 mmol) in benzene (3 ml) was stirred under N_2 at room temp for 1 day, then concentrated yielding 70 mg (99%) of **39** as a light yellow oil: R_f 0.2 in 1:1 EtOAc–hexane; IR (neat) 3000, 1740–1680, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 3H), 2.5–2.95 (m, 4H), 3.8 (s, 3H), 4.16 (q, J = 7 Hz, 2H), 4.55 (s, 2H), 4.8 (m, 1H), 6.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.19 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 293 (M).

Benzyl carbamate[19]

Benzyl chloroformate (500 ml, 3.51 mol) was added slowly to conc NH_4OH (d = 0.88) (2 l) in an ice-salt bath with vigorous stirring. After the addition was completed, the mixture was warmed to room temp, stirred for 30 min and filtered. The product was washed with cold water, dried *in vacuo* and recrystallized from toluene (750 ml), affording 421 g (79%) of benzyl carbamate as white rectangular plates: m.p. 86° [lit.[19] m.p. 86°]; R_f 0.32 in 1:1 EtOAc–hexane; IR ($CHCl_3$) 3540, 3430, 3010, 1725, 1585 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (br s, 2H), 5.03 (s, 2H), 7.25 (s, 5H); MS (70 eV) *m/e* 151 (M). (Found: C, 63.36; H, 6.15; N, 9.41. Calc for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27%.)

N - *Benzyloxycarbonyl* - 2 - *aminotetrahydro* - 5 - *oxo* - 2 - *furancarboxylic acid* (**41**)[19]

A 3-l, three-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser, was charged with finely powdered benzyl carbamate (302 g, 2 mol) and 2-ketoglutaric acid (298 g, 2.04 mol). The reaction mixture was stirred vigorously and heated at 80° for 4 hr under reduced pressure (10–15 Torr). A homogeneous yellow-colored mixture was obtained and solidified on further heating. The solid product was recrystallized from EtOAc to give 396 g (71%) of **41** as white crystals: m.p. 175° [lit.[19] m.p. 176°]; R_f 0.21 in 5% AcOH–EtOAc; IR (nujol) 3290, 1785, 1750, 1690, 1550 cm^{-1}; NMR (acetone d_6) δ 2.69 (s, 4H), 5.14 (s, 2H), 6.18 (br s, 2H, exchangeable with D_2O), 7.38 (s, 5H); MS (field desorption) *m/e* 279 (M), 234 ($M - CO_2H$). (Found: C, 56.05; H, 4.81; N, 5.04. Calc for $C_{13}H_{13}NO_6$: C, 55.92; H, 4.69; N, 5.02%.)

Benzyl N - *benzyloxycarbonyl* - 2 - *aminotetrahydro* - 5 - *oxo* - 2 - *furancarboxylate* (**42**)

A soln of **41** (27.9 g, 0.1 mol) and Et_3N (13.9 ml, 0.1 mol) in N,N-dimethylformamide (100 ml) was stirred under nitrogen during the addition of benzyl bromide (12 ml, 0.1 mol). The mixture was heated at 90° for 2 hr, poured into water (1.5 l) and filtered. The product was washed twice with water, dried in air at room temp and recrystallized from $CHCl_3$–hexane yielding 31 g (84%) of **42** as white crystals: m.p. 132–134°; IR ($CHCl_3$) 3400, 1795, 1740, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (br s, 4H), 5.15 (s, 2H), 5.25 (s, 2H), 7.4 (s, 10H). (Found: C, 65.04; H, 5.26; N, 3.69. Calc for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.97%.)

Benzyl N - *benzyloxycarbonyl* - (Z) - α - *aminobut* - 2 - *enoate* (**43**)

A soln of **42** (111 mg, 0.3 mmol) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (89 μl, 0.6 mmol) in

THF (5 ml) was heated at reflux under N_2 for 12 hr. The soln was concentrated, the residue was dissolved in EtOAc, washed with 1 N HCl, water, dried (brine, Na_2SO_4) and concentrated yielding 88 mg (93%) of **43** as a yellow foam: R_f 0.55 in 1:1 EtOAc–hexane; IR (neat) 3350, 3000, 1710, 1660, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (d, J = 7 Hz, 3H), 5.1 (s, 2H), 5.15 (s, 2H), 6.4 (br s, 1H), 6.75 (q, J = 7 Hz, 1H), 7.3 (s, 10H); MS (70 eV) *m/e* 235 (M – benzyl), 191 (M – benzyloxycarbonyl).

N-Benzyloxycarbonyl-α-benzyl-(Z)-α,β-dehydroglutamate (40)

Lactone ester **42** (18.4 g, 50 mmol) was suspended in THF (100 ml) under N_2 at 0° and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (15 ml, 0.1 mol) was added. The resulting soln was stirred at 0° for 30 min, then diluted with 2 N HCl (60 ml, 0.12 mol) and EtOAc. The organic layer was separated, washed twice with 1 N HCl and water. The combined aqueous layers were extracted with EtOAc, and the organic layers were combined, dried (brine, Na_2SO_4) and concentrated yielding 18 g (98%) of **40** as light yellow crystals: m.p. 119–121°; IR ($CHCl_3$) 3500–2900, 3400, 1720, 1500 cm^{-1}; NMR ($CDCl_3$) δ 3.3 (d, J = 7 Hz, 2H), 5.1 (s, 2H), 5.2 (s, 2H), 6.4 (br s, 1H), 6.5 (t, J = 7 Hz, 1H), 7.2 (s, 10H), 8.0 (br s, 1H); MS (70 eV) *m/e* 351 (M–H_2O). (Found: C, 65.22; H, 5.31; N, 3.86. Calc for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79%.)

Attempted activation of dehydroglutamate **40**; *benzyl N-benzyloxycarbonyl-Δ^3-pyrrolin-2-one-5-carboxylate* (45) *and benzyl 2-(benzyloxycarbonylhydroxy)-pyrrole-5-carboxylate* (46)

A soln of **40** (100 mg, 0.27 mmol) in THF (1 ml) was stirred under N_2 at room temp during the addition of trifluoroacetic anhydride (40 μl, 0.29 mmol). The soln was stirred for 10 min at room temp and concentrated yielding **45** as a yellow oil: IR (neat) 3000, 1780, 1750, 1730 cm^{-1}; NMR ($CDCl_3$) δ 5.05 (s, 2H), 5.2 (s, 2H), 5.25 (m, 1H), 6.2 (d of d, J = 2 Hz, 6 Hz, 1H), 7.1 (d of d, J = 3 Hz, 6 Hz, 1H), 7.3 (s, 10H); MS (70 eV) *m/e* 351 (M).

Pyrrolinone **45** was dissolved in EtOAc (1 ml), treated with EtOAc (100 μl) and concentrated yielding **46** as a yellow oil: R_f 0.2 in 1:1 EtOAc–hexane; IR ($CHCl_3$) 3400, 3000, 1800, 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.0 (s, 1H), 5.1 (s, 2H), 5.2 (s, 2H), 6.2 (d, J = 6 Hz, 1H), 6.85 (d, J = 6 Hz, 1H), 7.2 (s, 10H); MS (70 eV) *m/e* 351 (M).

N-Benzyloxycarbonyl-α-benzyl-(Z)-α,β-dehydroglutamic-γ-(N-hydroxysuccinimide) ester (47)

A soln of **40** (287 mg, 0.78 mmol) and N-hydroxysuccinimide (276 mg, 2.33 mmol) in THF (5 ml) was stirred under N_2 during the addition of N,N-dicyclohexylcarbodiimide (DCC) (161 mg, 0.781 mmol). The mixture was stirred at room temp for 15 min and filtered. The clear filtrate was diluted with EtOAc (10 ml), washed with water and dilute $NaHCO_3$ aq, dried (brine, Na_2SO_4) and concentrated affording a semi-crystalline mass. The crude product was triturated with EtOAc (1.5 ml), filtered and concentrated yielding 251 mg (69%) of the N-hydroxysuccinimide active ester as a white foam: R_f 0.39 in 1:1 EtOAc–hexane; IR ($CHCl_3$) 3400, 1815, 1785, 1740, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.63 (s, 4H), 3.54 (d, J = 7 Hz, 2H), 5.05 (s, 2H), 5.10 (s, 2H), 6.65 (t, J = 7 Hz, 1H), 6.95 (br s, 1H), 7.35 (s, 10H); MS (70 eV) *m/e* 351 (M).

O-Trimethylsilyl-N(p-methoxybenzyl)hydroxylamine (49a)

To a soln of N(*p*-methoxybenzyl)hydroxylamine (3.06 g, 20 mmol) and Et_3N (2.84 ml, 20.4 mmol) in anhyd ether (30 ml) and CH_2Cl_2 (20 ml), which had been cooled in an ice bath, was added trimethylchlorosilane (2.60 ml, 20.4 mmol) in ether (10 ml) under N_2. After the addition was completed the mixture was stirred for 15 min at room temp and more ether (60 ml) was added. The mixture was filtered and the clear filtrate was concentrated under vacuum to give a light yellow oil. The product was distilled under reduced pressure affording 3.56 g (79%) of **49a** as a colorless, hygroscopic oil: b.p. 120°/1.1 Torr (Kugelrohr); R_f 0.83 in 1:1 EtOAc–hexane; IR (film) 3230, 2960, 1615, 1515, 1250, 1035 cm^{-1}; NMR (CCl_4) δ 0.01 (s, 9H), 3.70 (s, 3H), 3.85 (s, 2H), 5.09 (s, 1H), 6.73 (d, A_2 of A_2B_2, J = 8 Hz, 2H), 7.12 (d, B_2 of A_2B_2, J = 8 Hz, 2H); MS (70 eV) *m/e* 225 (M).

t-Butyldimethylsilyl chloride[28]

To a soln of commercial t-BuLi in pentane (64 g, 1 mol) there was added, dropwise, a soln of dimethyldichlorosilane (143 g, 1.1 mol) in pentane (300 ml) at room temp under N_2 with stirring. The mixture was heated at reflux for 2 hr and filtered from LiCl. Distillation at atmospheric pressure gave 166 g (61%) of chlorosilane as a colorless solid: b.p. 123° [lit. b.p. 125°/733 Torr]; m.p. 90° [lit.[28] m.p. 91.5°].

O-(t-Butyldimethylsilyl)-N-(p-methoxybenzyl)-hydroxylamine (49b)

A soln of N-(*p*-methoxybenzyl)hydroxylamine (114 g, 0.74 mol), t-butyldimethylsilyl chloride (118 g, 0.78 mol) and imidazole (128 g, 1.88 mol) in dry N,N-dimethylformamide (250 ml) was stirred under N_2 at room temp overnight. The mixture was diluted with EtOAc, washed three times with water, dried (brine, Na_2SO_4) and concentrated under vacuum affording a yellow oil (197 g, 100%). The crude oil was distilled under vacuum to yield 172 g (87%) of **49b** as a colorless oil: b.p. 148–149°/1.4 Torr; R_f 0.74 in 1:1 EtOAc–hexane; IR (film) 3250, 2950, 2930 cm^{-1}; NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 3.70 (s, 3H), 3.87 (s, 2H), 4.95 (br s, 1H), 6.75 (d, A_2 of A_2B_2, J = 8 Hz, 2H), 7.13 (d, B_2 of A_2B_2, J = 8 Hz, 2H); MS (70 eV) *m/e* 267 (M). (Found: C, 62.69; H, 9.59; N, 5.44. Calc for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24%.)

N-Benzyloxycarbonyl-α-benzyl-(Z)-α,β-dehydroglutamic-γ-N-(p-methoxybenzyl)hydroxamic acid (50a)

A soln of **40a** (11.1 g, 30 mmol) and N-hydroxysuccinimide (3.92 g, 33 mmol) in THF (60 ml) was stirred under N_2 at room temp during the addition of N,N-dicyclohexylcarbodiimide (DCC) (6.26 g, 30 mmol). The mixture was stirred for 15 min and **49b** (9.49 g, 35 mmol) was added. The whole mixture was stirred for two days, diluted with EtOAc (60 ml), cooled at 0° overnight and filtered. The clear filtrate was washed twice with water, 1 N HCl, dried (brine, Na_2SO_4) and concentrated yielding 20.7 g of crude solid. The solid was dissolved in EtOAc (110 ml) and added to a soln of anhyd KF (9.6 g, 0.16 mol) in EtOH (45 ml) at 0°. The mixture was stirred at 0° for 30 min and quenched with aqueous 1 N HCl (120 ml). The soln was diluted with EtOAc. The organic layer was separated, washed three times with water, dried (brine, Na_2SO_4), concentrated, and recrystallized from EtOAc–hexane to yield 9.5 g (51%) of **50a** as white crystals: m.p. 133–136°; R_f 0.56 in 2:1 EtOAc–hexane; IR ($CHCl_3$) 3400, 3030, 1740–1690, 1660–1630, 1515 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (d, J = 7 Hz, 2H), 3.72 (s, 3H), 4.64 (s, 2H), 5.02 (s, 2H), 5.25 (s, 2H), 6.71 (s, 1H), 6.80 (d, A_2 of A_2B_2, J = 8 Hz, 2H), 6.81 (t, J = 7 Hz, 1H), 7.16 (d, B_2 of A_2B_2, J = 8 Hz, 2H), 7.28 (s, 5H), 7.30 (d, 5H); MS (field desorption) *m/e* 504 (M). (Found: C, 66.66; H, 5.44; N, 5.55. Calc for $C_{28}H_{28}N_2O_7$: C, 66.66; H, 5.59; N, 5.55%.)

erythro, threo-DL-N-*Benzyloxycarbonyl-α-amino-2-(p-methoxy-benzyl)-3-oxo-5-isoxazolidine acetic acid benzyl ester* (51a)

A suspension of **50a** (2.28 g, 4.51 mmol) in sat $NaHCO_3$ aq (200 ml) was heated at reflux for 40 min. The mixture was extracted five times with EtOAc, dried (brine, Na_2SO_4) and concentrated to give 1.89 g (83%) of **51a** as a yellow oil: R_f 0.56 in 2:1 EtOAc–hexane; IR ($CHCl_3$) 3420, 1750–1705, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.73–2.90 (m, 2H), 3.66 and 3.71 (2 × s, 3H total), 4.40–4.70 (m, 1H), 5.05 (s, 2H), 5.12 (s, 2H), 6.74 (d, A_2 of A_2B_2, J = 8 Hz, 1H), 6.77 (d, A'_2 of $A'_2B'_2$, J = 8 Hz, 1H), 7.13 (d, B_2 of $A_2B_2 + B'_2$ of $A'_2B'_2$, J = 8 Hz, 2H), 7.30 (s, 10H), 7.80 (br s, 1H).

p-Nitrobenzyl-N-benzyloxycarbonyl-2-aminotetrahydro-5-oxo-2-furancarboxylate (42b)

A soln of **41** (279 g, 1 mol) and Et_3N (145 ml, 1.05 mol) in EtOAc (1150 ml) was warmed during the addition of *p*-

nitrobenzylbromide (238 g, 1.1 mol), then heated at reflux for 2 hr and concentrated to dryness. The solid product was digested with hot water, filtered, washed with water, dil $NaHCO_3$ aq, water, and two 600 ml portions of 1 : 3 EtOAc–hexane. The product was dried *in vacuo* yielding 376 g (91%) of **42b** as white crystals: m.p. 126–127°; R_f 0.35 in 2 : 1 EtOAc–hexane; IR ($CHCl_3$) 3400, 3000, 1790, 1770–1710, 1530 cm^{-1}; NMR (acetone d_6) δ 2.65 (s, 4H), 5.16 (s, 2H), 5.4 (s, 2H), 7.4 (s, 5H), 7.7 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.1 (br s, 1H), 8.28 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 278 (M – *p*-nitrobenzyl). (Found: C, 57.87; H, 4.43; N, 6.68. Calc for $C_{20}H_{18}N_2O_8$: C, 57.92; H, 4.38; N, 6.76%.)

N-*Benzyloxycarbonyl-α-*(p*-nitrobenzyl)-*(Z)*-α,β-dehydroglutamate* (**40b**)

Lactone ester **42b** (376 g, 0.91 mol) was suspended in THF (1270 ml) under N_2 at 0° and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (280 ml, 1.88 mol) was added. The soln was stirred at 0° for 30 min, then 2 N HCl (1 l, 2 mol) was added and the mixture was diluted with EtOAc. The organic layer was separated, washed twice with 1 N HCl and water. The washes were combined and extracted with EtOAc. The organic extracts were combined, dried (brine, Na_2SO_4) and concentrated yielding 372 g (99%) of **40b** as light yellow crystals: m.p. 134–136°; R_f 0.1 in 2 : 1 EtOAc–hexane; IR ($CHCl_3$) 3500–2900, 3400, 1740–1690, 1530 cm^{-1}; NMR (acetone d_6) δ 3.35 (d, J = 7 Hz, 2H), 5.15 (s, 2H), 5.35 (s, 2H), 6.8 (t, J = 7 Hz, 1H), 7.35 (s, 5H), 7.65 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.1 (br s, 1H), 8.2 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 279 (MH – *p*-nitrobenzyl). (Found: C, 57.70; H, 4.45; N, 6.69. Calc for $C_{20}H_{18}N_2O_8$: C, 57.92; H, 4.38; N, 6.76%.)

N-*Phthalimido*-O-(p*-nitrobenzyl)hydroxylamine*

A soln of N-hydroxyphthalimide (163 g, 1 mol) and *p*-nitrobenzyl bromide (216 g, 1 mol) in N,N-dimethylformamide (750 ml) was heated at 65° and stirred during the slow (15 min) addition of a solution of KOH (66 g, 1 mol) in water (100 ml). The hot mixture was poured into water (4.5 l), filtered, and the ppt was dried yielding 203 g (68%) of product as light yellow crystals: m.p. 196–197°; NMR ($CDCl_3$–acetone-d_6) δ 5.4 (s, 2H), 7.8 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.85 (s, 4H), 8.25 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS *m/e* 151 (M). (Found: C, 60.18; H, 3.54; N, 9.33. Calc for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39%.)

O-(p*-Nitrobenzyl)hydroxylamine* (**49c**)

A soln of crude N-phthalimido-O-(*p*-nitrobenzyl)-hydroxylamine (203 g, 0.68 mol) in N,N-dimethylformamide (1 l) was warmed and stirred during the addition of hydrazine hydrate (50 g, 1.0 mol). The mixture was allowed to stand for 45 min, then poured into a soln of Na_2CO_3 (106 g, 1 mol) in water (2 l), and extracted five times with $CHCl_3$. The extracts were combined, washed six times with water, dried (brine, Na_2SO_4) and concentrated giving a semicrystalline oil which was dissolved in EtOAc, washed three times with water and dried (brine, Na_2SO_4). The soln was concentrated and distilled yielding 54 g (50%) of **49c** as a yellow oil which solidified: b.p. 130° (0.3 Torr); m.p. 55° [lit.[29] m.p. 56°]; R_f 0.3 in 1 : 1 EtOAc–hexane; IR (neat) 3600–3000, 1600, 1520 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (s, 2H), 5.5 (br s, 2H), 7.55 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.25 (d, B_2 of A_2B_2, J = 9 Hz, 2H); MS (70 eV) *m/e* 168 (M). (Found: C, 50.08; H, 4.93; N, 16.44. Calc for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66%.)

N-*Benzyloxycarbonyl-α-*(p*-nitrobenzyl)-*(Z)*-α,β-dehydroglutamic-γ-*O*-*(p*-nitrobenzyl)hydroxamic acid* (**50b**)

A soln of **40b** (372 g, 0.91 mol) and N-hydroxysuccinimide (115 g, 1 mol) in THF (1 l) was stirred under N_2 and cooled during the addition (15 min) of N,N-dicyclohexylcarbodiimide (DCC) (188 g, 0.91 mol). The mixture was cooled in an ice-salt bath and filtered, and the ppt was washed with two 250 ml portions of THF. O-(*p*-Nitrobenzyl)-hydroxylamine **49c** (161 g, 0.96 mol) was added to the filtrate, and the resulting soln was stirred overnight at room temp, filtered, concentrated, and the residue was triturated with EtOAc, water, then dried *in vacuo* yielding 300 g (59%) of **50b** as a light yellow solid: m.p. 157–158° (d); R_f 0.6 in ethyl acetate; IR ($CHCl_3$) 3400, 3000, 1720, 1530 cm^{-1}; NMR (acetone-d_6) δ 3.2 (br d, J = 7 Hz, 2H), 5.1 (s, 2H), 5.2 (s, 2H), 5.4 (s, 2H), 7.35 (s, 5H), 7.65 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 7.6 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 8.23 (d, 2 × B_2 of A_2B_2, J = 9 Hz, 4H); MS (70 eV) *m/e* 337 (M – benzyl and *p*-nitrobenzyl). (Found: C, 57.45; H, 4.35; N, 9.99. Calc for $C_{27}H_{24}N_4O_{10}$: C, 57.44; H, 4.28; N, 9.92%.)

N-*Benzyloxycarbonyl-*(Z)*-α,β-dehydroglutamic-γ-hydroxamic acid* (**50d**)

To a soln of **50b** (50.0 g, 88.6 mmol) in N,N-dimethylformamide (200 ml) was added thiophenol (188 ml, 0.18 mol). The soln was warmed at 60° and stirred vigorously during the slow (1 hr) addition of Zn–Cu couple (100 g, 1.53 g-atom). During the addition the temp of the mixture was maintained at 55° with occasional ice-cooling. After the addition was completed the mixture was heated at 65° for 1 hr. The resulting thick mixture was filtered to remove excess Zn and the ppt was washed with warm N,N-dimethylformamide (3 × 50 ml). The filtrate was concentrated under high vacuum to a thick yellow oil which was decomposed with a mixture of 6 N HCl (200 ml) and EtOAc (250 ml). The aqueous layer was sat with NaCl and extracted six times with EtOAc. The organic extracts were combined, extracted three times with dil $NaHCO_3$ aq and water. The combined aqueous extracts were washed twice with EtOAc, acidified to pH 2 with conc HCl, sat with NaCl, and extracted eight times with EtOAc. The ethyl acetate extracts were combined, dried (brine, Na_2SO_4) and concentrated, affording a thick red oil. The original aqueous layer was concentrated under high vacuum to a thick white oil. To the concentrate was added sat Na_2CO_3 aq (600 ml). The mixture was filtered to remove $ZnCO_3$ and the ppt was washed twice with sat Na_2CO_3 aq. The filtrate was washed twice with EtOAc, acidified to pH 2 with conc HCl, saturated with NaCl and extracted eight times with EtOAc. The EtOAc extracts were combined, dried (brine, Na_2SO_4) and concentrated affording a thick red oil. The red oils were combined, triturated with $CHCl_3$ and left overnight in the refrigerator. The product was filtered, washed twice with cold $CHCl_3$ and dried *in vacuo* yielding 14.9 g (57%) of **50d** as white crystals: m.p. 130–132° (d); IR (nujol) 3480–3100, 1710, 1660, 1640 cm^{-1}; NMR (acetone-d_6) δ 3.14 (br d, J = 7 Hz, 2H), 5.10 (s, 2H), 6.71 (br t, J = 7 Hz, 1H), 7.35 (s, 5H), 7.7–7.9 (br s, 3H); MS (field desorption) *m/e* 295 (MH). (Found: C, 53.17; H, 4.99; N, 9.43. Calc for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52%.)

threo-DL-N-*Benzyloxycarbonyl-α-amino-3-oxo-5-isoxazolidineacetic acid* (**51b**)

A soln of **50d** (10 g, 34 mmol) in 1 N NaOH (73.5 ml, 73.5 mmol) was degassed with N_2 for 15 min, and heated at reflux for 40 min under N_2. The soln was cooled, washed twice with EtOAc, the pH was adjusted to 2 with conc HCl, and the soln was extracted five times with EtOAc. The extracts were combined, dried (brine, Na_2SO_4) and concentrated yielding 8.63 g (86%) of **51b** as a tan foam: IR ($CHCl_3$) 3400, 3400–2800, 1720, 1500 cm^{-1}; NMR (acetone d_6) δ 2.6 (br s, 1H), 2.8 (br d, J = 8 Hz, 2H), 4.58 (d of d, J = 4 Hz, 10 Hz, 1H), 5.0–5.4 (m, 3H), 6.8 (br d, J = 10 Hz, 1H), 7.3 (s, 5H), 8.25 (br s, 1H).

threo-DL-N-*Benzyloxycarbonyl-α-amino-3-oxo-5-isoxazolidineacetic acid diphenylmethyl ester*

A soln of crude **51b** (8.36 g, 28.4 mmol) in EtOAc (50 ml) was stirred at room temp as diphenyldiazomethane was added until a slight excess was present (TLC on silica gel using 2 : 1 EtOAc–hexane as eluant). The brown soln was concentrated and chromatographed on silica gel (350 g) using a 20–60% EtOAc–cyclohexane solvent gradient yielding 9.35 g (71%) of product as a pure white foam: R_f 0.4 in 2 : 1 EtOAc–hexane; IR ($CHCl_3$) 3400, 3000, 1720, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (d, J = 8 Hz, 2H), 4.65 (br d, J = 9 Hz, 1H), 5.02 (s, 2H), 5.02 (m, 1H), 5.72 (d, J = 9 Hz, 1H), 6.8 (s, 1H), 7.2 (s, 15H); mass spectrum (70 eV) *m/e* 312 (M − benzyloxycarbonylamino). (Found: C, 67.59; H, 5.38; N, 6.16. Calc for $C_{26}H_{24}N_2O_6$: C, 67.87; H, 5.26; N, 6.09%.)

threo-DL-α-*Amino-3-oxo-5-isoxazolidineacetic acid* (threo-DL-*tricholomic acid*) (3)

A soln of **51b** (2.94 g, 10 mmol) in anhyd liquid ammonia (150 ml) was stirred at reflux under N_2 while slivers of Li metal were added until a persistent blue color formed. The mixture was *immediately* quenched by the addition of solid NH_4Cl and warmed to room temp to remove the ammonia. The solid residue was partitioned between water and EtOAc, and the aqueous phase was acidified to pH 4 with conc HCl, then stirred with Dowex 50W-X4 cation-exchange resin (5 g). The soln was filtered, the resin was washed twice with water, then four times with 0.5 N NH_4OH. The NH_4OH washes were combined, concentrated to dryness, and dissolved in water. The pH of the soln was adjusted to 11 by the addition of 1 N LiOH aq and the soln was concentrated to dryness. The solid residue was dissolved in a minimum amount of water, and the pH was adjusted to 4 by the addition of conc HCl. EtOH was added, the soln was cooled and filtered, and the ppt was washed with EtOH and dried yielding 690 mg (43%) of *threo*-DL-tricholomic acid as white needles: m.p. 192–193° (d); R_f 0.1 on silica gel with 3:5:12 AcOH–water–n-BuOH as eluant, R_f 0.4 on silica gel with 1:5:20 pyridine–water–MeOH as eluant; IR (KBr) 3500–2400, 1710, 1650, 1585, 1410 cm^{-1}; NMR (NaOD–D_2O) δ 2.93 (2 × q, AB of ABX, J_{AB} = 15 Hz, 2H), 3.45 (d, J = 8 Hz, 1H), 4.72 (2 × t, X of ABX, 1H); MS (field desorption) *m/e* 161 (MH). (Found: C, 37.23; H, 5.04; N, 17.25. Calc for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.50%.)

threo-DL-N-*Benzyloxycarbonyl-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid diphenylmethyl ester* (**52b**)

A soln of *threo*-DL-N-benzyloxycarbonyl-α-amino-3-oxo-5-isoxazolidine acetic acid diphenylmethyl ester (9.35 g, 20.3 mmol) and *tris*(dimethylamino)dichlorophosphorane (5.22 g, 22.3 mmol) in dioxan (180 ml) was stirred under N_2 at room temp during the addition of Et_3N (3.54 ml, 25.6 mmol), followed by heating at reflux for 72 hr. The light brown mixture was concentrated, diluted with EtOAc, washed twice with water, dried (brine, Na_2SO_4) and concentrated yielding a brown oil. The crude product was filtered through silica gel (500 g) using 1:1 EtOAc–hexane as eluant yielding 6.3 g (65%) of **52b** as a light yellow oil which solidified: R_f 0.8 in 2:1 EtOAc–hexane; IR ($CHCl_3$) 3400, 3000, 1725, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 3.12 (d, J = 10 Hz, 2H), 4.6 (d of d, J = 2 Hz, 8 Hz, 1H), 5.05 (s, 2H), 5.5 (d of t, J = 2 Hz, 10 Hz, 1H), 6.8 (s, 1H), 7.2 (s, 15 Hz); MS (chemical ionization) *m/e* 479, 481 (MH), 313, 315 (MH − diphenylmethyl).

threo-DL-N-*Benzyloxycarbonyl-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid* (**53**)

A soln of **52b** (6.3 g, 13.2 mmol) and anisole (2.85 ml, 26.4 mmol) in trifluoroacetic acid (64 ml) was stirred under N_2 for 30 min at room temp, concentrated, and triturated with CCl_4. The residue was dissolved in EtOAc, extracted three times with dil $NaHCO_3$ aq, and once with water. The extracts were combined, washed twice with EtOAc, acidified with 1 N HCl and extracted six times with EtOAc. The extracts were combined, dried (brine, Na_2SO_4) and concentrated yielding 3.32 g (80%) of **53** as a tan solid: R_f 0.6 in 5% AcOH–EtOAc; IR ($CHCl_3$) 3500–2500, 3400, 1725, 1510 cm^{-1}; NMR (acetone-d_6) δ 3.3 (2 × q, AB of ABX, J_{AB} = 18 Hz, 2H), 4.6 (d of d, J = 4 Hz, 10 Hz, 1H), 5.1 (s, 2H), 5.25 (d of t, X of ABX, J = 4 Hz, 10 Hz, 1H), 6.6 (br m, 2H), 7.3 (s, 5H); mass spectrum (70 eV) *m/e* 313, 315 (MH). (Found: C, 50.09; H, 4.13; N, 8.71. Calc for $C_{13}H_{13}N_2O_5Cl$: C, 49.84; H, 4.18; N, 8.94%.)

threo-DL-α-*Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid* (**1**)

A suspension of finely-ground *threo*-DL-**53** (2.53 g, 8.09 mmol) in benzene (27 ml) and N,N-dimethylformamide (54 μl) was stirred at room temp under N_2 during the addition of oxalyl chloride (1.5 ml, 17.2 mmol). After all of the acid **53** had dissolved, the soln was heated at reflux for 3.5 min, then *immediately* cooled to room temp, diluted with pentane (150 ml) and cooled at −20° overnight. The solvent was decanted, and the light yellow residue was washed twice with pentane and dried *in vacuo* yielding the unstable Leuchs anhydride **54**: NMR (acetone d_6) 3.6 (2 × q, AB of ABX, J_{AB} = 18 Hz, 2H), 4.85 (d, J = 4 Hz, 1H), 5.0–5.4 (m, 1H), 8.2 (br s, 1H). The crude anhydride **54** was immediately dissolved in reagent acetone (27 ml) and treated with 4 N HCl (27 ml). The dark colored soln was allowed to stand at room temp for 5 hr, then diluted with water, extracted four times with EtOAc and concentrated yielding 1.55 g (90%) of impure amino acid hydrochloride: NMR (D_2O) δ 3.8 (2 × q, AB of ABX, J_{AB} = 12 Hz, 2H), 4.65 (d, J = 5 Hz, 1H), 5.6 (d of t, X of ABX, J = 5 Hz, 6 Hz, 1H). The crude hydrochloride was dissolved in water (3 ml) and a soln of lithium hydroxide monohydrate (306 mg, 7.28 mmol) in water (3 ml) was added in one portion. The resulting paste was diluted with absolute EtOH (25 ml), cooled, filtered, and the product was washed twice with absolute EtOH and dried *in vacuo* yielding 966 mg (67%) of *threo*-DL-(**1**) as tan crystals: m.p. 178–202° (d); R_f 0.46 on silica gel using 6:1.5:2.5 n-BuOH–AcOH–water, R_f 0.26 on silica gel using 7:2:1.5:0.5 methyl ethyl ketone–acetone–water–AcOH, R_f 0.6 on silica gel using 20:1:5 MeOH–pyridine–water; IR (KBr) 3700–2600, 1645, 1585, 1510, 1400 cm^{-1}; NMR (D_2O) δ 3.9 (2 × q, AB of ABX, J_{AB} = 13 Hz, 2H), 4.2 (d, J = 8 Hz, 1H), 5.6 (d of q, X of ABX, J = 8 Hz, J_{AB+BX} = 10 Hz, 1H); MS (chemical ionization) *m/e* 179, 181 (MH), 104, 106. (Found: C, 33.74; H, 4.06; N, 15.61. Calc for $C_5H_7N_2O_3Cl$: C, 33.63; H, 3.95; N, 15.69%.)

erythro, threo-DL-N-*Benzyloxycarbonyl-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid benzyl ester* (**52a**)

A soln of **51a** (1.07 g, 2.12 mmol) and PCl_5 (442 mg, 2.12 mmol) in nitromethane (15 ml) was heated under reflux for 40 min. The mixture was concentrated and filtered through a short silica gel column using 1:1 EtOAc–hexane as eluant to give 265 mg (31%) of **52a** as a yellow oil: R_f 0.54 in 1:1 ethyl acetate–hexane; IR ($CHCl_3$) 3410, 1750–1720, 1505 cm^{-1}; NMR ($CDCl_3$) δ 3.10–3.32 (m, 2H), 4.48–4.67 (m, 1H), 5.09–5.29 (m, 1H), 5.09 (s, 1H), 5.11 (s, 1H), 5.15 (s, 1H), 5.19 (s, 1H), 7.31 (s, 10H); MS (field desorption) *m/e* 402 (M).

o-*Nitrobenzyl bromide*[30]

A 2-l flask fitted with a reflux condenser was charged with *o*-nitrotoluene (137 g, 1 mol), N-bromosuccinimide (178 g, 1 mol), benzoyl peroxide (1.25 g, 5 mmol) and dry CCl_4 (600 ml). The mixture was heated under reflux for 9 hr. The hot mixture was filtered with suction through a Büchner funnel, and the solid in the funnel was washed with two 50 ml portions of hot CCl_4. The soln was concentrated under reduced pressure. The red–brown oil thus obtained was crystallized from EtOH to give 89 g (41%) of yellow crystals: m.p. 46–47° [lit.[30] m.p. 46–47°]; R_f 0.56 in chloroform; IR ($CHCl_3$) 1528, 1348 cm^{-1}; NMR ($CDCl_3$) δ 4.79 (s, 2H), 7.50 (m, 3H), 7.95 (m, 1H); MS (70 eV) *m/e* 217.

o-*Nitrobenzyl* N-*benzyloxycarbonyl-2-aminotetrahydro-5-oxo-2-furancarboxylate* (**42c**)

A soln of **41** (140 g, 0.5 mol) and Et_3N (74 ml, 0.53 mol) in EtOAc (500 ml) was warmed. *o*-Nitrobenzyl bromide (108 g, 0.5 mol) was added. The mixture was then heated under reflux for 4 hr and concentrated to dryness. The solid product was digested with hot water and then filtered. The residue was washed with water, dil $NaHCO_3$ aq, water and two 400 ml portions of 1:3 EtOAc–hexane. The product was dried *in vacuo* yielding 184 g (89%) of **42c** as white crystals: m.p. 136.5–137.5°; R_f 0.54 in 2:1 EtOAc–hexane; IR ($CHCl_3$) 3410, 3020, 1790, 1755, 1735, 1530, 1345 cm^{-1}; NMR ($CDCl_3$) δ 2.67 (s, 4H), 5.09 (s, 2H), 5.54 (s, 2H), 7.25 (s, 5H), 7.66 (s, 3H), 8.04 (m, 1H); MS (field desorption) *m/e* 415 (MH), 371 (MH − CO_2). (Found: C, 57.80; H, 4.56; N, 6.84. Calc for $C_{20}H_{18}N_2O_8$: C, 57.97; H, 4.38; N, 6.76%.)

N - *Benzyloxycarbonyl* - α - (o - *nitrobenzyl*) - (Z) - *α,β* - *dehydroglutamate* (**40c**)

To a suspension of **42c** (331.5 g, 0.8 mol) in THF (1600 ml) at 0° under N_2 was added DBU (254 g, 1.6 mol). The soln was stirred at 0° for 30 min, aqueous 2 N HCl (920 ml) was then added and the mixture was diluted with EtOAc. The organic layer was separated and washed twice with 1 N HCl and water. The washes were combined and extracted with EtOAc. The organic extracts were combined, dried (brine, Na_2SO_4) and concentrated yielding 311 g (100%) of **40c** as yellow crystals: m.p. 110–112°; R_f 0.53 in 7:2:1 $CHCl_3$–acetone–AcOH; IR ($CHCl_3$) 3410, 3030, 1740–1700, 1530, 1350 cm^{-1}; NMR (acetone-d_6) δ 3.30 (d, J = 7 Hz, 2H), 5.07 (s, 2H), 5.51 (s, 2H), 6.78 (t, J = 7 Hz, 1H), 7.20 (s, 5H), 7.46 (s, 3H), 7.97 (m, 1H), 8.70 (br s, 1H); MS (field desorption) *m/e* 415 (MH). (Found: C, 57.96; H, 4.56; N, 6.94. Calc for $C_{20}H_{18}N_2O_8$: C, 57.97; H, 4.38; N, 6.76%.)

N - *Benzyloxycarbonyl* - α - (o - *nitrobenzyl*) - (Z) - *α,β* - *dehydroglutamic* - γ - (N - p - *methoxybenzyl*)*hydroxamic acid* (**50c**)

Method 1. A soln of **40c** (24.5 g, 59 mmol) and N-hydroxysuccinimide (7.83 g, 66 mmol) in THF (120 ml) was stirred under N_2 at room temp during the addition of DCC (12.38 g, 60 mmol). After the mixture had stirred for 15 min, N - (*p* - methoxybenzyl) - O - (t - butyldimethylsilyl)hydroxylamine (**49b**) (19.0 g, 71 mmol) was added and the mixture was stirred at room temp for one day. The mixture was diluted with EtOAc (120 ml), cooled at 0° overnight and filtered. The clear filtrate was washed three times with 1 N HCl, twice with water, dried (brine, Na_2SO_4) and concentrated, affording a semicrystalline mass. The solids were dissolved in EtOAc (250 ml) and the soln was added to a soln of anhyd KF (20 g, 0.34 mol) in absolute EtOH (100 ml) at 0°. The whole mixture was stirred at 0° for 30 min, quenched with 1 N HCl (250 ml) and diluted with EtOAc. The organic layer was separated, washed three times with water, dried (brine, Na_2SO_4), concentrated and recrystallized from EtOAc–hexane, affording 14.60 g of **50c** (45%) as slightly yellow crystals: m.p. 147–148°; R_f 0.52 in 2:1 EtOAc–hexane; IR ($CHCl_3$) 3420, 1735, 1660–1640, 1540, 1525, 1350 cm^{-1}; NMR ($CDCl_3$) δ 3.41 (d, J = 7 Hz, 2H), 3.73 (s, 3H), 4.68 (s, 2H), 5.07 (s, 2H), 5.58 (s, 2H), 6.83 (d, A_2 of A_2B_2, J = 9 Hz, 2H), 6.75–6.90 (m, 1H), 7.19 (d, B_2 of A_2B_2, J = 9 Hz, 2H), 7.28 (s, 5H), 7.55 (m, 3H), 8.09 (m, 1H); MS (field desorption) *m/e* 549 (M). (Found: C, 61.09; H, 4.92; N, 7.60. Calc for $C_{28}H_{27}N_3O_9$: C, 61.20; H, 4.95; N, 7.65%.)

Method 2. A soln of **40c** (207 g, 0.50 mol) and N-hydroxysuccinimide (66 g, 0.66 mol) in THF (1 l) was stirred under N_2 at room temp during the addition of DCC (104 g, 0.50 mol). After the mixture had stirred for 15 min, **49b** (160 g, 0.60 mol) was added and the mixture was stirred at room temp for three days. The mixture was diluted with EtOAc (1 l), cooled at 0° overnight and filtered. The clear filtrate was washed three times with 1 N HCl, twice with water, dried (brine, Na_2SO_4) and concentrated, affording a semicrystalline mass. The solids were dissolved in EtOAc (1.5 l), *p*-toluenesulfonic acid monohydrate (9.90 g, 50 mmol) and MeOH (1.5 l) was added and the mixture was stirred at room temp for one day, concentrated and recrystallized from EtOAc–hexane to give 132 g (48%) of **50c** as yellow crystals.

erythro, threo - DL - N - *Benzyloxycarbonyl* - α - *amino* - 2 - (p - *methoxybenzyl*) - 3 - *oxo* - 5 - *isoxazolidineacetic acid* o - *nitrobenzyl ester* (**51c**)

A suspension of **50c** (55.0 g, 0.10 mol) in sat $NaHCO_3$ aq (4 l) was refluxed for 40 min. The mixture was cooled and extracted four times with EtOAc. The combined extracts were dried (brine, Na_2SO_4) and concentrated to yield 52.3 g (95%) of **51c** as a yellow oil. The crude product was subsequently used without further purification. An analytical sample was obtained by chromatography using 2:1 EtOAc–hexane as eluants: R_f 0.52 in EtOAc–hexane; IR ($CHCl_3$) 3440, 3005, 1735–1690, 1540, 1525, 1350 cm^{-1}; 300 MHz NMR ($CDCl_3$) δ 2.75–2.96 (m, AB of ABX and A′B′ of A′B′X′, 2H), 3.66 and 3.71 (2 × s, 3H total), 4.41–4.82 (m, 3H), 4.95–5.12 (m, 1H), 5.06 (s, 2H), 5.25–5.34 and 5.47–5.58 (2 × m, 2H total), 6.74–6.79 (2 × d, 2H), 7.13–7.16 (d, 2H), 7.30 and 7.33 (2 × s, 5H total), 7.45–7.79 (m, 4H); MS (field desorption) *m/e* 549 (M). (Found: C, 61.27; H, 5.05; N, 7.43. Calc for $C_{28}H_{27}N_3O_9$: C, 61.20; H, 4.95; N, 7.65%.)

erythro - DL - N - *Benzyloxycarbonyl* - α - *amino* - 3 - *chloro* - 4,5 - *dihydro* - 5 - *isoxazoleacetic acid* o - *nitrobenzyl ester* (**52c**)

A mixture of crude **51c** (55 g, 0.10 mol), PCl_5 (23.95 g, 0.115 mol), and $CaCO_3$ (1 g, 10 mmol) in nitromethane (550 ml) was refluxed for 40 min. The reaction mixture was filtered through celite and the dark brown filtrate was concentrated under reduced pressure. The crude product was filtered through silica gel using 3:1 petroleum ether–EtOAc as eluant, yielding 31.80 g (71%) of **52c** as a yellow oil. The diastereomeric mixture was separated by column chromatography using 9:1 benzene–ether as eluants. *Erythro*-**52c** (11.20 g, 25%) was obtained as a yellow oil: R_f 0.17 in 9:1 benzene–ether; IR ($CHCl_3$) 3430, 3130, 1725, 1530, 1510, 1345 cm^{-1}; 300 MHz NMR ($CDCl_3$) δ 3.23–3.39 (m, 2H), 4.62–4.69 (m, 1H), 4.97–5.05 (m, 1H), 5.13 (s, 2H), 5.57 (s, 2H), 5.84 (br d, J = 7 Hz, 1H), 7.32 (s, 5H), 7.45–7.69 (m, 3H), 8.10 (d, J = 8 Hz, 1H); MS (field desorption) *m/e* 450, 448 (MH). Exact mass field desorption mass spectrum: calc for $C_{20}H_{18}{}^{35}ClN_3O_7$: 447.0833; found: 447.0825.

From less polar fractions *threo*-**52c** (14.33 g, 32%) was obtained as a white foam: R_f 0.23 on 9:1 benzene–ether; IR ($CHCl_3$) 3425, 3030, 1755, 1725, 1530, 1510, 1350 cm^{-1}; 300 MHz NMR ($CDCl_3$) δ 3.08 (q, A of ABX, J_{AB} = 18 Hz, J_{AX} = 8 Hz, 1H), 3.22 (q, B of ABX, J_{AB} = 18 Hz, J_{BX} = 11 Hz, 1H), 4.62 (d of d, J = 9.6 Hz, 1.8 Hz, 1H), 5.06 (s, 2H), 5.24 (t, X of ABX, 1H), 5.54 (s, 2H), 7.25 (s, 5H), 7.38–7.56 (m, 3H), 8.02 (d, J = 8 Hz, 1H); MS (field desorption) *m/e* 450, 448 (MH). Field desorption mass spectrum: calc for $C_{20}H_{18}{}^{35}ClN_3O_7$: 447.0833; found: 447.0843.

erythro - DL - N - *Benzyloxycarbonyl* - α - *amino* - 3 - *chloro* - 4,5 - *dihydro* - 5 - *isoxazoleacetic acid* (erythro - **53**)

To a soln of *erythro*-**52c** (355 mg, 0.82 mmol) in a 10:1 mixture of ether–water (13 ml) was added aluminum amalgam (221 mg, 8.2 mg-atom). The mixture was heated under reflux for 60 min, quenched with 1 N HCl (4 ml), and filtered through celite. The filtrate was extracted five times with EtOAc. The combined organic extracts were washed four times with dil $NaHCO_3$. The aqueous washings were combined, back-washed with EtOAc, acidified to pH 2 with conc HCl, extracted five times with EtOAc, dried (brine, Na_2SO_4) and concentrated to give 157 mg (61%) of *erythro*-**53** as white crystals: R_f 0.6 in 5% AcOH–EtOAc; IR ($CHCl_3$) 3500–3000, 1720, 1510 cm^{-1}; NMR (acetone-d_6) δ 3.42 (d of d, A of ABX, J_{AB} = 17 Hz, J_{AX} = 8 Hz, 1H), 3.50 (d of d, B of ABX, J_{AB} = 17 Hz, J_{BX} = 11 Hz, 1H), 4.62 (d of d, J = 9, 4 Hz, 1H), 5.10 (s, 2H), 5.19 (m, X of ABX, 1H), 6.92 (br d, 1H), 7.35 (m, 5H); MS (field desorption) *m/e* 314, 312.

erythro - DL - α - *Amino* - 3 - *chloro* - 4,5 - *dihydro* - 5 - *isoxazoleacetic acid* (erythro - **1**)

To a suspension of finely pulverized *erythro*-**53** (126 mg, 0.4 mmol) in benzene (1.6 ml) and N,N-dimethylformamide (2 μl) was added oxalyl chloride (76 μl, 0.85 mmol). Upon stirring the mixture became clear. The soln was heated at reflux for 3.5 min, *immediately* cooled to room temp, diluted with pentane (8 ml), and cooled at 20° overnight. The solvent was removed by decantation, and the light yellow residue was washed twice with pentane and dried *in vacuo* yielding the unstable Leuchs anhydride: 300 MHz NMR (acetone d_6) δ 3.52 (d of d, A of ABX, J_{AB} = 17.7 Hz, J_{AX} = 8 Hz, 1H), 3.62 (d of d, B of ABX, J_{AB} = 17.7 Hz, J_{BX} = 11 Hz, 1H), 4.94 (d, J = 2.4 Hz, 1H), 5.23 (d of d of d, X of ABX, J = 11, 8, 2.4 Hz, 1H). The crude anhydride was immediately dissolved in acetone (1 ml) and treated 4 N HCl (1 ml). The soln was stirred at room temp for 5 hr, diluted with water, washed four times with EtOAc and concentrated, yielding 69 mg (80%) of impure amino acid hydrochloride as a pale yellow solid: 300 MHz NMR (D_2O) δ 3.38 (d of d, A of ABX, J_{AB} = 17.7 Hz, J_{AX} = 8 Hz, 1H), 3.48 (d of d, B of ABX, J_{AB} = 17.7 Hz, J_{BX} = 11 Hz, 1H), 4.16 (d, J = 2.4 Hz, 1H), 5.16 (d of d of d, X of ABX, 1H). The crude hydrochloride was dissolved in water (1 ml) and a soln of lithium hydroxide monohydrate (13.46 mg, 0.32 mmol) in water (0.5 ml) was added in one portion. The resulting soln was diluted with absolute EtOH, washed twice with absolute EtOH and dried *in vacuo* yielding 47 mg (66%) of racemic AT-125 as tan crystals: m.p. 174 ~ 179°; R_f 0.46 in 6:1.5:2.5 n-BuOH–AcOH–water, R_f 0.26 in 6:2:1.5:0.5 methyl ethyl ketone–acetone–water–AcOH; IR (KBr) 1625, 1590, 1500, 1410 cm^{-1}; 300 MHz NMR (D_2O) δ 3.30 (d of d, A of ABX, J_{AB} = 18 Hz, J_{AX} = 8 Hz, 1H), 3.39 (d of d, B of ABX, J_{AB} = 18 Hz, J_{BX} = 11 Hz, 1H), 3.91 (d, J = 3 Hz, 1H), 5.15 (d of d of d, X of ABX, 1H); MS (chemical ionization) *m/e* 181, 179, 145, 135, 133, 111, 99. (Found: C, 33.74; H, 4.15; N, 15.53; Cl, 20.00. Calc for $C_5H_7N_2O_3Cl$: C, 33.63; H, 3.95; N, 15.69; Cl, 19.85%.)

erythro-DL-N-*Chloroacetyl-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid*

The racemic AT-125 (**1**) (20 mg, 0.11 mmol) and lithium hydroxide monohydrate (9.23 mg, 0.22 mmol) were dissolved in water (0.11 ml). Acetone (0.22 ml) was then added, with stirring. A soln of *p*-nitrophenylchloroacetate (28.5 mg, 0.13 mmol) in acetone (0.1 ml) was added and the mixture was stirred for 2 hr while the pH of the soln was maintained at 9.5. The mixture was diluted with water and washed twice with EtOAc. The pH was then lowered to 6 and the soln was washed twice with EtOAc. The aqueous layer was acidified to pH 1.5 with conc HCl and extracted five times with EtOAc. The combined extracts were dried (brine, Na_2SO_4) and concentrated to give 14 mg (57%) of product as a white solid: 300 MHz NMR (acetone-d_6) δ 3.47 (d of d, A of ABX, J_{AB} = 17 Hz, J_{AX} = 7.7 Hz, 1H), 3.55 (d of d, B of ABX, J_{AB} = 17 Hz, J_{AB} = 11 Hz, 1H), 4.20 (s, 2H), 4.78 (d of d, J = 8, 4 Hz, 1H), 5.15 (d of d of d, J = 4, 7.7, 17 Hz, 1H), 7.92 (br d, J = 8 Hz, 1H).

(αS,5S)-α-*Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid* (**1**)

Racemic N-chloroacetyl AT-125 (37.7 mg, 0.16 mmol) and potassium dihydrogen phosphate (4.65 mg, 0.16 mmol) were suspended in water (1 ml), and brought into soln by the addition of 1 N LiOH. The pH was adjusted to 7.0 and hog kidney acylase I (7 mg) was added. The soln was stirred for one day. The enzyme was removed by careful heating of the soln to boiling point for 1 min, followed by filtration. The pH was adjusted to 2 with conc HCl and the soln was washed five times with EtOAc. The aqueous layer was concentrated and purified by cation ion exchange to give 12 mg (84%) of **1** as white crystals: m.p. 188 ~ 196°; $[\alpha]^{20}_{578}+135°$ (C = 0.159, H_2O).

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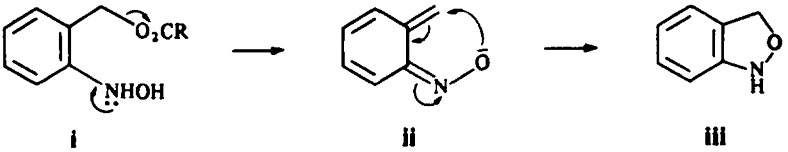

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