Tetrahedron Vol. 39, No 15, pp. 2563 to 2570, 1983
Printed in Great Britain.

0040–4020/83 $3.00 + .00
Pergamon Press Ltd.

THE DIRECT CHEMICAL CONVERSION OF PEPTIDES TO β-LACTAMS

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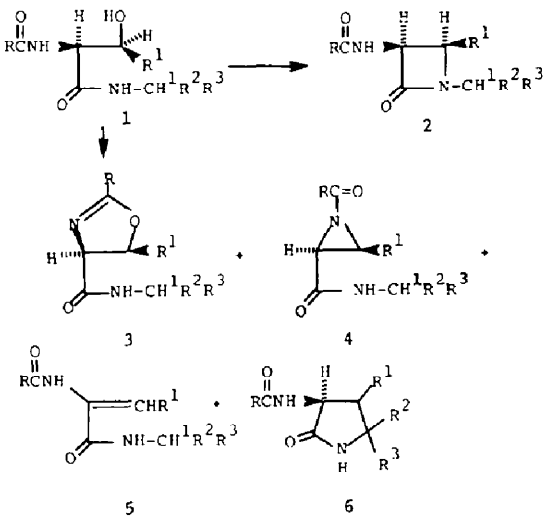
(*Received in UK 26 August* 1982)

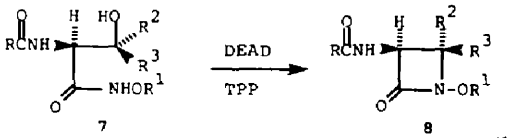
Abstract—Appropriately protected seryldipeptides which have a relatively acidic proton (H^1 of **1**) on the α′ C can be efficiently converted to β-lactams by reaction with azodicarboxylates and triphenylphosphine. Application of the same reaction conditions to serylamides which lack an acidic α′ proton provided dehydropeptides as the major product. Model reactions and potential intermediates which rationalize these results are described.

Of the many methods described for the synthesis of β-lactams, N–C_4 ring closure is of special interest because of its biosynthetic analogy and the potential for utilizing chiral amino acid and peptide derived precursors. Conceptually, the primary problem with such syntheses has been the selective ionization of the desired N–H bond and subsequent cyclization (**1**→**2**) in the presence of other acidic components which might promote the formation of undesired products (**3**, **4**, **5** or **6**, Scheme 1).



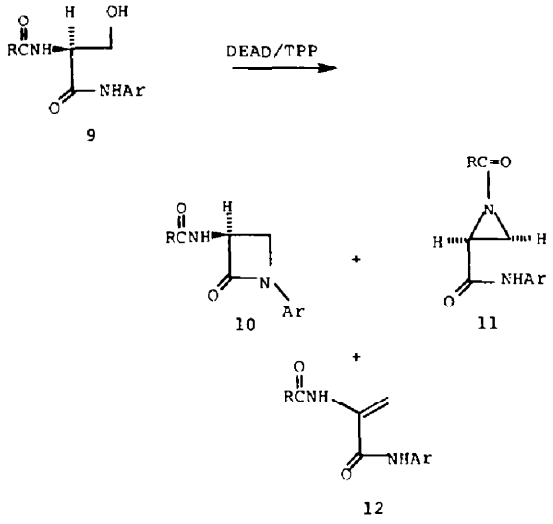
Scheme 1.

We have previously shown that the required pK differentiation can be obtained by utilizing the acidic N–H bond of amino acid hydroxamates.[2] Thus, several β-lactams were prepared by the direct reaction of protected seryl and threonyl hydroxamates with diethylazodicarboxylate (DEAD) and triphenylphosphine (TPP) (eqn. 1). Subsequently, Bose[3]



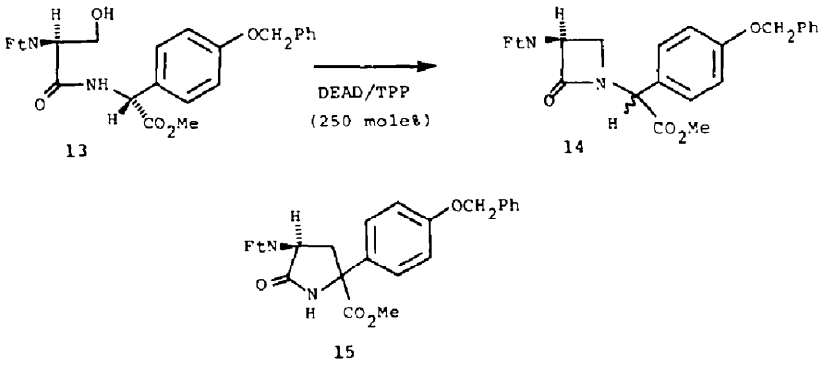
eqn (1)

has shown that N-aryl-3-amino-β-lactams, **10**, can be obtained by the cyclization of β-hydroxy-α-amino acid arylamides, **9**, using the same reagents (eqn. 2). Although concomitant aziridine, **11**, and dehydropeptide, **12**, formation was sometimes observed, the cyclization was remarkable since previous data indicated that the acidic component of the dehydrative alkylation of alcohols with DEAD/TPP should have a pKa ≤ 13.[4]



eqn (2)

Even more extraordinary was the recent finding by Townsend[5] that the protected seryl-*p*-alkoxyphenylglycine dipeptide **13** cyclized smoothly to the β-lactam **14** with DEAD/TPP (eqn. 3). This result was especially interesting since little difference might be expected in the acidity of the amide N–H bond and the α′–CH bond of **13**. Yet, no pyrrolidinone, **15**, corresponding to C-alkylation, or elimination products were reported. A clarification of this unusual result was therefore sought. Consequently, we describe here the DEAD/TPP mediated preparation of several β-lactams from seryldipeptides, serylaminomalonates, and related compounds which were anticipated to help define the scope of the reaction and provide insight into its mechanism. Although intermediates have been implicated, the detailed mechanism has not been satisfactorily elucidated.

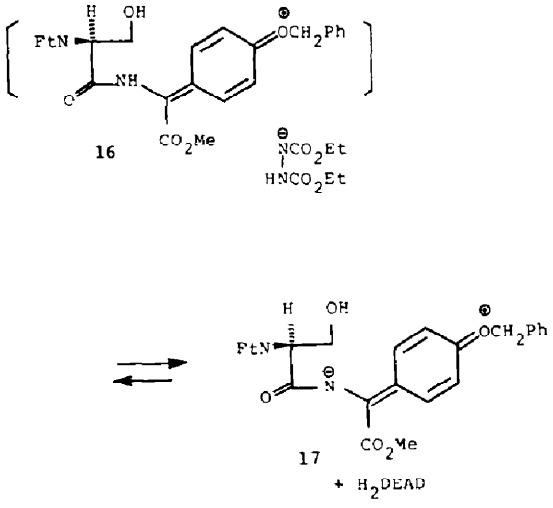


eqn (3)

RESULTS AND DISCUSSION

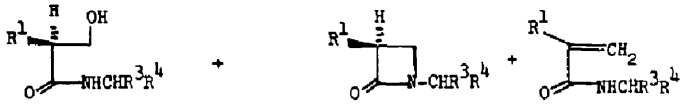
Our first consideration regarding the mechanism of the successful cyclization of **13** was that the excess of DEAD/TPP or DEAD itself promoted a reversible prior oxidation to the quinone methide intermediate, **16** (eqn. 4). Similar intermediates have been proposed to explain the unusual reactivity of the nocardicins *in vivo*.[6] The result of this transformation would be a significant decrease in the pK of the desired N–H bond. Ionization would, in fact, result in a highly resonance stabilized intermediate, **17**. Moreover, the resultant conversion of the α′–C of **13** to an sp^2 center would account for the racemization observed in the product **14**. Disturbing about this mechanism was that no loss of the benzyl protecting group of **13** was reported, as might be expected from reaction of **16** with the $HDEAD^-$ counterion.

We repeated this reaction and obtained results similar to Townsend's. However, we also noted the formation of a small amount of the dehydropeptide, 18 (11%, Table 1). The cyclization was even more



eqn (4)

Table 1.



	R^1	R^3	R^4	#	(%)	#	(%)
13	FtN	CO_2Me	$C_6H_4OCH_2Ph$	14	(87[b], 93[c])	18	(11[b], 0[c])
19	FtN	CO_2Me	Ph	20	(30[b], 81[c])	21	(0[bc])
22	FtN	CO_2Me	H	23	(50, 22[d])	24	(30)
25	FtN	CH_2PhOCH_3	H	26	(9)	27	(38)
28	FtN	CH_2Ph	H	29	(26)	30	(26)
31	FtN	CO_2Et	CO_2Et	32	(82, 52[d])	33	(18)

[a] Yields are based on chromatographed mixtures of β-lactam and dehydropeptide except where noted.

[b] Excess DEAD/TPP.

[c] 100 mole % DEAD/TPP

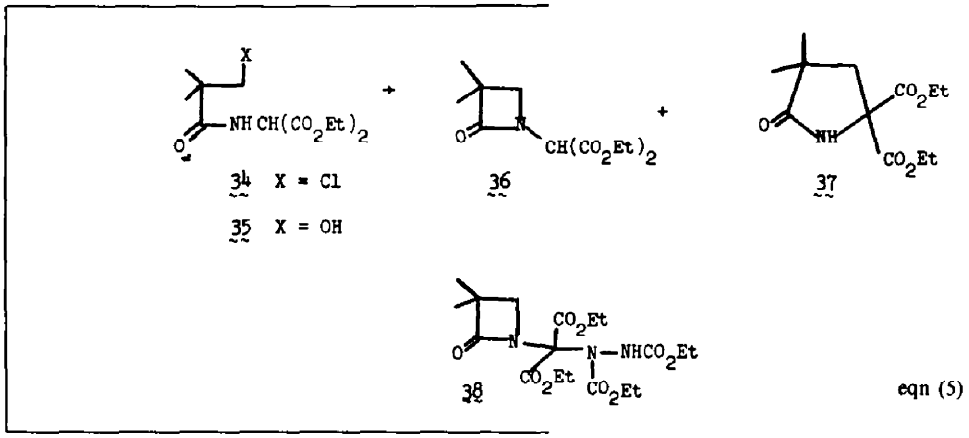
[d] Recrystallized yield.

efficient when only 100 mole % of the dehydrating reagents were used, rather than the reported 250 mole %. The diastereomeric mixture, **14a, b** was isolated in 93% yield with no trace of 18. If the quinone methide mechanism was operative in this cyclization, the unsubstituted serylphenyl-glycine, **19**, which lacks the *p*-alkoxy group, would not be expected to cyclize to the corresponding β-lactam. However, this was not the case.

When **19** was subjected to excess DEAD/TPP a complex mixture was obtained. After repeated chromatography, a diastereomeric mixture of β-lactams **20** was isolated in 30% yield. Repeating the reaction with only 100 mole % of DEAD/TPP improved the yield of the diastereomeric mixture of **20** to 81%. As determined by NMR and HPLC, recovered starting material **19** showed no loss of chirality at the α′C–H position. However, whether the recovered **19** had ever reacted in an equilibrium sense with the DEAD/TPP complex was not known. When the diastereomers of **20** were separated and resubjected to the reaction conditions, reequilibration to the original diastereomeric mixture was rapid. Thus, epimerization of the exocyclic chiral center could occur in the reaction medium after cyclization. These results are consistent with the observations of base induced epimerization made by Cooper[7] and Wasserman[8] during their syntheses of 3-aminonocardicinic acid. While these preliminary studies suggested that the quinone methides like **16** were not likely intermediates during the cyclization (**13**→**14**), they do not preclude an intermediate in which the α′-C is sp^2 hybridized. Thus, we decided to further explore the scope of this reaction.

Consequently, a series of seryldipeptides was subjected to the DEAD/TPP reaction. As shown in Table 1, serylglycine, **22**, and the serylbenzylamides **25**, and **28** reacted to give mixtures of β-lactam and dehydropeptide in poor yield. Unlike the cyclization of **13** or **19**, these reactions were relatively slow and yielded mixtures which were difficult to separate. However, the serylaminomalonate **31** reacted quantitatively to give the β-lactam **32** and dehydropeptide **33** in a ratio of 4.5:1. After a simple chromatography and selective recrystallization compound **32** was isolated in 52% yield.

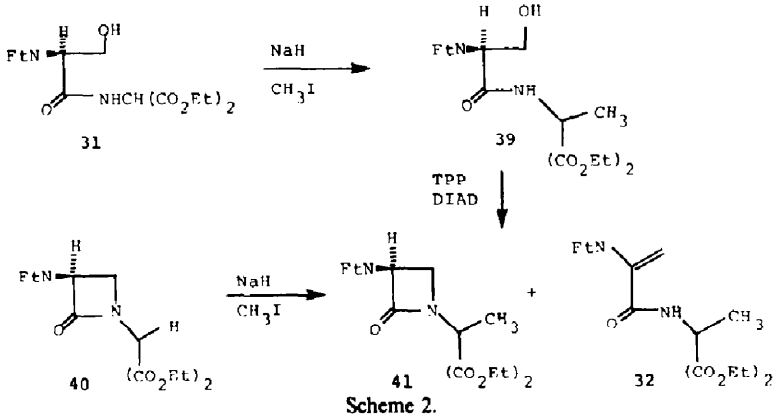
The trend in these studies indicated that increased acidity of the α′-CH bond of the amide increased the relative amount of β-lactam formed and the ease of the reaction. Thus, the question of how the amide nitrogen becomes activated in the presence of a more acidic α′-CH position became even more intriguing. One might expect that in cases such as **13**, **19** and **31**, deprotonation and alkylation would occur at the α′C position. In fact, when the model β-chloroamide, **34** was treated with NaH in DMF/CH_2Cl_2 (1:4) the expected pyrrolidinone **37** was obtained in 49% recrystallized yield (eqn 5). No β-lactam was detected by NMR or IR of the crude reaction mixture. However, when the analogous β-hydroxyamide **35** was treated with DEAD/TPP, no pyrrolidinone was obtained. Only β-lactam **36** (49%) and the DEAD adduct **38** (35%) were isolated after chromatography and recrystallization. In control reactions, treatment of the isolated β-lactam **36** with DEAD/TPP or with DEAD plus a catalytic amount of Et_3N provided similar mixtures **36** and **38**. Thus, the adducts may be formed by a direct competitive Michael type addition of the β-lactam, as it is generated, to DEAD. The formation of the azodicarboxylate adducts was subsequently avoided by the slow addition of only 100 mole % of the more hindered diisopropylazodicarboxylate (DIAD) to THF solutions of the β-hydroxyamide substrate and TPP.



eqn (5)

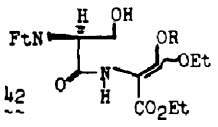
The model studies shown in eqn (5) indicated that the DEAD/TPP mediated reaction cannot be proceeding through the straightforward pathway in which the most acidic position is alkylated. In order to further substantiate this thought we prepared diethyl N-phthaloyl-L-serylamino-(2 methyl)-malonate **39** by treatment of **31** with NaH followed by CH_3I (Scheme 2). As expected and by analogy to the Sorensen amino acid synthesis,[9] no N-alkylated material was detected. Reaction of **39** with diisopropylazodicarboxylate (DIAD)/TPP provided an 18:1 mixture of dehydropeptide **40** and β-lactam **41**. The formation of only minor amounts of β-lactam in this case again indicated that an acidic α′-CH position facilitates the azodicarboxylate/TPP mediated cyclization. For characterization and comparison purposes, the methylated β-lactam **41** was also prepared by alkylation of lactam **32**.

These results are also consistent with the azodicarboxylate/TPP mediated cyclization proceeding through an intermediate in which the α′-carbon is sp^2 hybridized. One such possible intermediate is the enol **42**. If R = H in **42**, cyclization to the β-lactam would probably require formation of an



Scheme 2.

intermediate dianion. Alternatively, if in **42** R = $Ph_3\overset{+}{P}$

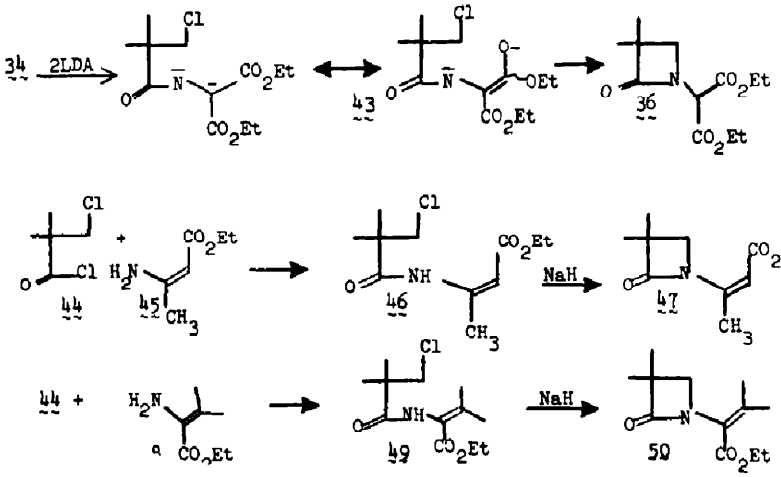


(derived from reaction with the DEAD/TPP complex in a reversible fashion), the pK of the NH bond should be significantly reduced relative to that of the starting material **31**. As indicated earlier,[2] such a pK reduction would also be expected to promote the desired cyclization. Analogies to both of these possibilities were studied in model systems.

Treatment of the chloride **34** with 220 mole% of LDA at −78° to generate the *dianion* **43** and then warming to room temperature produced the β-lactam **36** in 84% yield (eqn 6). None of the pyrrolidinone **37**, previously formed by the reaction of **34** with 100 mole% of base (eqn 5), was detected. As expected, the enamides **46** and **49** (prepared by acylation of ethyl 3-amino-crotonate **45** and dehydrovaline **49** with β-chloropivaloylchloride **44**) cyclized cleanly to the β-lactams **47** and **48** upon treatment with one equivalent of NaH (Scheme 3).

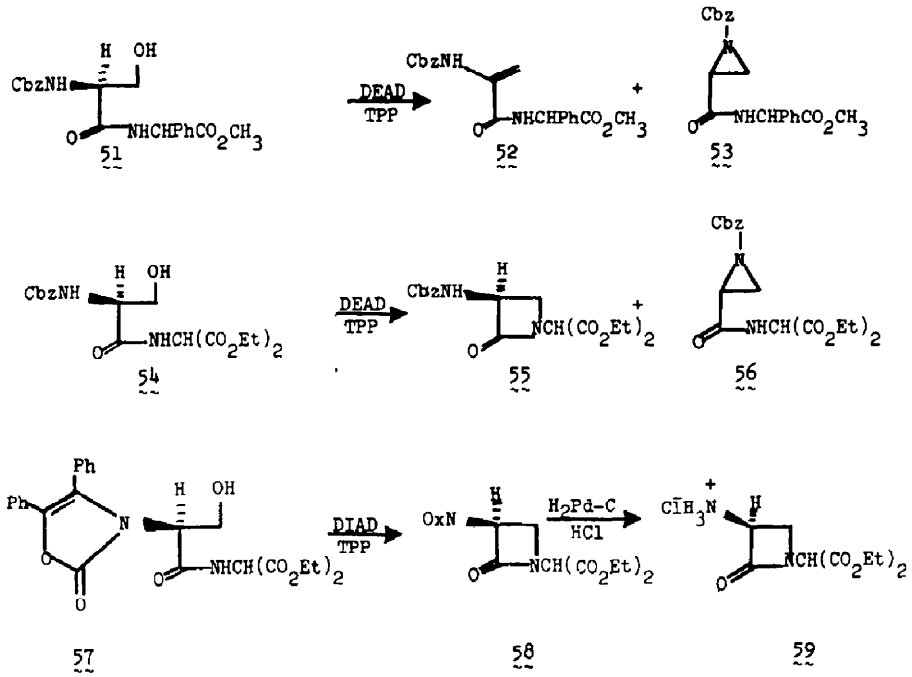
Further studies related to the mechanism of formation of β-lactams by the reaction of serylaminomalonates and related compounds with azodicarboxylates and TPP are being carried out. However, worthy of mention is the finding that the TPP/CCl_4/Et_3N system, which readily converts serylhydroxamates to β-lactams,[2] is not effective for the cyclization of β-hydroxyamides (e.g. **19**→**20**).

Since all of these studies indicated that β-lactam formation from serylaminomalonates is facile, we also sought to improve the practical utility of the sequence. Needed was a N-protecting group which could be more easily removed than phthaloyl (Ft) and which would further diminish dehydroamino acid formation. The Cbz group seemed to be a logical choice. When N–Cbz serylphenylglycine methyl ester **51** was treated with DEAD/TPP, unfortunately, a mixture of dehydropeptide **52** and aziridine **53**, but no β-lactam, was formed (eqn 7). When the N-Cbz-serylaminomalonate **54** was treated similarly, β-lactam (**55**) formation was competitive with that of aziridine (**56**, eqn 8), but still not efficient. The 4, 5-diphenyl-4-oxazoline-2-one (Ox)[10] derivative proved to be quite suitable. When the Ox-serylaminomalonate **57** (Scheme 4) was treated with DIAD/TPP, the desired β-lactam **58** was obtained in 96% isolated yield. The Ox group was subsequently removed by catalytic hydrogenation to provide the free 3-amino-N-substituted-2-azetidinone **59** in 82% recrystallized yield. Thus, with appropriate amino protection, the direct DIAD/TPP mediated cyclization of serine containing dipeptides appears to be an efficient and practical route to useful functionalized β-lactams.



eqn (6)

Scheme 3.



Scheme 4.

EXPERIMENTAL

General comments. M.ps were taken on a Thomas–Hoover m.p apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 727b spectrometer. NMR spectra were obtained in $CDCl_3$ with TMS as a reference, unless otherwise stated, on a Varian EM390, XL-100 or Nicolet NB300 Spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus 902 or Dupont DP102 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. High pressure LC was performed using a Beckman/Altex Model 332 chromatograph. Medium pressure chromatography was executed with the Michel–Miller system packed with Silica Gel 60 (40–63 μ).

General procedure for the synthesis of seryldipeptides

(A) (L)-N-phthaloylserine[11] (2 g, 8.5 mmol), 2.3 g (17 mmol) N-hydroxybenztriazole (HBT), 9.35 mmole of the amine hydrochloride and 1.2 ml (8.5 mmole) Et_3N were dissolved in 50 ml CH_2Cl_2 or DMF. Dicyclohexylcarbodiimide (DCC), (1.9 g, 9.35 mmole) was added and the reaction was stirred for 4–20 hr. The usual workup involved first filtering off the precipitated dicyclohexylurea (DCU) then taking the supernatant up in 100 ml ether or EtOAc. The soln was washed with 10% Na_2CO_3 (3 × 50 ml), 0.1 N HCl (3 × 20 ml), water (3 × 50 ml, only when DMF was the solvent), brine (2 × 50 ml), and dried over $MgSO_4$. The product was isolated after evaporation, chromatography (where necessary) and recrystallization.

(B) Alternatively, the water and CH_2Cl_2 soluble carbodiimide, 1-cyclohexyl-3(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich) was used instead of DCC. Since the urea produced was water soluble, no chromatographic purification was necessary.

Methyl(L)N$^{\alpha}$ - phthaloylseryl - (D) - p - benzyloxyphenylglycinate **13**. Methyl(D)-*p*-benzyloxyphenyl glycine hydrochloride was prepared by a method adapted from Cooper *et al.*[7] Thus, 10 g (60 mmole) of (D)-*p*-hydroxyphenylglycine (Sigma) in 300 ml THF/water (1:1) with 8.3 ml of Et_3N was treated with 13.1 g (60 mmole) di-t-butyl-dicarbonate for 16 hr at room temp. The apparent pH of the soln was 8 at the completion of the reaction. The mixture was extracted with EtOAc (250 ml), then acidified to pH 3 and extracted with EtOAc again (6 × 100 ml). The acidic extracts were washed with brine and dried over $MgSO_4$. After evaporation and recrystallization 11.5 g (43 mmole) of the t-BOC derivative was isolated, mp. 200° (dec. starts at 137°). A second crop of crystals (m.p. 200°) amounted to 4.4 g (total yield 98%). MS (CI with methane) *m/e* 166 (M-101). NMR ($DCCl_3$/d_6DMSO) 1.43 (9H, s), 4.9–5.1 (1H, br), 6.65–7.2 (4H, m), 5.8–6.2 (1H, br).

This compound decomposes over the course of 2 months at room temp.

The BOC derivative (4.4 g, 16 mmole) was treated with 200 mole% NaH in 75 ml DMF. Benzylchloride (1.8 ml, 16 mmole) was added whereupon the mixture solidified. On standing overnight the reaction again became homogenous and was poured into 100 ml water—the apparent pH was 8. The soln was extracted with 200 ml of EtOAc which was discarded. After acidifying to pH 3 the soln was extracted with EtOAc (5 × 100 ml). The combined extracts were washed with water (3 × 150 ml, pH 5), then dried over $MgSO_4$ and evaporated.

The mixture was dissolved in 100 ml of MeOH and was saturated with HCl. After stirring for 2 hr at R.T., the soln was concentrated to 25 ml and the product was precipitated with ether. Methyl (D)-*p*-benzyloxyphenylglycine hydrochloride was isolated, 1 g (3.3 mmole, 20%), m.p. 212–213°; $[\alpha]_D$ – 94.4 (*c* = 1.6, MeOH), NMR (d_6DMSO) 3.7 (3H, s), 5.13 (3H, s), 7.0–7.6 (9H, m), 9.2 (3H, br s).

Methyl (L)-N$^{\alpha}$-phthaloylseryl-(D)-p-benzyloxyphenylglycinate **13**. This was prepared by coupling procedure A. Compound **13** was isolated in 62% yield after 2 recrystallizations from EtOAc and hexanes, m.p. 188.5–191° (lit. 189–190°).[5] $[\alpha]_D$ – 121° (*c* = 1.77, $CHCl_3$)(lit. – 118°). NMR 3.7 (3H, s), 4.0–4.5 (3H, m), 5.03 (2H, s), 5.5 (1H, d), 6.8–8.0 (14H, m).

Methyl (L)-N$^{\alpha}$-phthaloylseryl-(D)-phenylglycine **19**. Methyl (D)-phenylglycine hydrochloride was prepared from (D)-phenylglycine (Aldrich) in methanolic HCl (3 hr, R.T.). Upon concentration to half the original volume, the addition of ether precipitated the product in 87% yield, m.p. 223° (lit. 222–223°).[13] $[\alpha]_D$ – 133° (*c* = 2.48, MeOH) (lit. – 119°, H_2O). MS *m/e* 166 (M-35). NMR (d_6DMSO) 3.77 (3H, s), 5.0 (1H, s), 7.4–7.6 (5H, s), 9.1–9.5 (3H, br).

Coupling with (L)-N-phthaloylserine by method A resulted in the isolation of **19** in 62% yield, m.p. 154–155° (EtOAc and hexanes). MS *m/e* 323 (M-77), 305 (M-77). $[\alpha]_D$ −89.5° (*c* = 2.56, methanol). Homogenous by HPLC [10 μ silica, 80/20 EtOAc and hexanes]. NMR 3.19–3.3 (1H, m), 3.7 (3H, s), 3.8–4.5 (3H, m), 4.89–5.03 (1H, m), 5.53–5.6 (1H, d), 7.4 (5H, s), 7.7–8 (4H, m). (Found: C, 63.00; H, 4.94; N, 7.37. Calc for $C_{20}H_{18}N_2O_6$: C, 62.83; H, 4.71; N, 7.33).

Methyl (L)-M^{α}-*phthaloylserylglycinate* **22**. This was prepared from (L)-N-phthaloylserine and methyl glycine by method A in 50% yield and isolated as a foamy residue which was homogenous by TLC [75/25 EtOAc and hexanes]. NMR 3–3.4 (1H, br), 3.73 (3H, s), 3.84–4.6 (3H, m), 4.9–5.06 (1H, m), 7.6–8.0 (5H, m).

N-p-*Methoxybenzyl*-(L)-N^{α}-*phthaloylserylamide* **25**. This was prepared (method A) in 69% yield, m.p. 103–106° (EtOAc and hexanes). NMR 3.7 (3H, s), 3.8–4.2 (3H, m), 4.3–4.4 (2H, d), 4.8–4.9 (1H, m), 6.77–7.23 (5H, m), 7.6–7.9 (4H,m).

N-*Benzyl*-(L)-N^{α}-*phthaloylserylamide* **28**. This was prepared (method A) in 35% yield, m.p. 106–108°. Homogenous by HPLC. NMR 3.7–4.27 (3H, m), 4.3–4.4 (2H, d), 4.8–4.9 (1H, m), 7.26 (5H, s and 1H, br) 7.6–7.8 (4H, m).

Diethyl (L)-N-*phthalolyseryl-aminomalonate* **31**. This was prepared (method A) in 64% yield, m.p. 103–105° (EtOAc and hexanes). NMR 1.17–1.37 (6H, dt), 3.1–3.3 (1H, m), 4.0–4.5 (6H, m), 4.93–5.07 (1H, m), 5.12–5.2 (1H, d), 7.6–8 (5H, m). (Found: C, 54.97; H, 5.22; N, 7.12. Calc for $C_{18}H_{20}N_2O_8$: C, 55.1; H, 5.1; N, 7.12).

Diethyl N-(β-*chloropivaloyl*)-*aminomalonate* **34**. Diethyl aminomalonate hydrochloride (1 g, 4.7 mmole) was dissolved in 5 ml of dry pyridine and cooled to 0°. β-Chloropivaloylchloride[15] (0.72 g, 4.7 mmole) was added dropwise under N_2. The mixture warmed to room temp and stirred for 2 hr at which time 50 ml anhyd ether was added. The ppt was filtered off and the supernatant washed with 0.1NHCl (4 × 25 ml), 5% $NaHCO_3$ (25 ml), brine (50 ml) and dried over $MgSO_4$. On evaporation, 1.35 g (4.6 mmole, 98%) of the oily product was isolated. NMR 1.16–1.33 (12H, m), 3.63 (2H, s), 4.13–4.36 (4H, q), 5.06–5.13 (1H, d), 6.8–6.9 (1H, bd).

Diethyl N-(β-*hydroxypivaloyl*)-*aminomalonate* **35**. This was prepared (method B) from β-hydroxy pivalic acid[14] and diethyl aminomalonate in 88% yield. The compound was isolated as an oil. NMR 1.13–1.3 (12H, m), 3.5 (2H, br s), 4.16–4.4 (4H, q), 5.1–5.16 (1H, d), 7.6–7.7 (1H, d).

Ethyl N-(β-*chloropivaloyl*)-3-*aminocrotonate* **46**. This was prepared in 42% yield from β-chloropivaloylchloride and ethyl 3-aminocrotonate (Aldrich) by the procedure used for **34**, m.p. 76–77.5° (after recrystallization from hexanes); IR (KBr) 1705, 1675 cm^{-1}; ^{1}HNMR δ 1.06–1.23 (9H, m), 2.3 (3H, s), 3.6 (2H, s), 4.0–4.23 (2H, q) 6.7 (1H, s), 6.8–7.1 (1H, br). (Found: C, 53.10; H, 7.20; N, 5.73. Calc for $C_{11}H_{18}NO_3Cl$: C, 53.44; H, 7.29; N, 5.67).

Ethyl N-(β-*chloropivaloyl*)-*dehydrovaline* **49**.[16] This was prepared in 20% yield by the procedure used for compounds **34** and **36**, m.p. 111–113°; IR (KBr) 1715, 1640; ^{1}HNMR δ 1.13–1.36 (3H, t and 6H, s), 1.83 (3H, s), 2.2 (3H, s), 3.67 (2H, s), 4.1–4.3 (2H, q), 6.9–7.2 (1H, br s). (Found: C, 55.02, H, 7.65; N, 5.47. Calc for $C_{25}H_{20}NO_3Cl$: C, 55.17; H, 7.66; N, 5.36).

Methyl (L)-N^{α}-*Cbz-seryl*-(D)-*phenylglycine* **51**. This was prepared by method B using N-Cbz-(L)-serine (Chemical Dynamics Co.) and methyl (D)-phenylglycine in 87% yield, m.p. 140–142° EtOAc and hexanes). NMR 3.73 (3H, s), 3.6–3.8 (1H, m), 4.0–4.5 (3H, m), 5.13 (2H, s), 5.5–5.6 (1H, d), 5.9–6.0 (1H, d), 7.4 (10 H, s). (Found: C, 62.04; H, 5.86; N, 7.37. Calc for $C_{20}H_{22}N_2O_6$: C, 62.18; H, 5.70; N, 7.25).

Diethyl (L)-N^{α}-*Cbz-serylaminomalonate* **54**. This was prepared (method B) from (L)-N-Cbz-serine and diethyl aminomalonate in 75% yield, m.p. 85–88° (dec). NMR 1.1–1.3 (6H, m), 3.6–4.5 (8H, m), 5.06 (2H, s), 5.13–5.23 (1H, d), 7.3 (5H, s and 1H, br.). (Found: C, 54.50; H, 6.04; N, 7.15. Calc for $C_{18}H_{24}N_2O_8$: C, 54.54; H, 6.06; N, 7.07).

Diethyl N^{α}-*ox*-L-*serylaminomalonate* **57**. This was prepared in 59% yield by method B using N-Ox-L-serine DCHA salt[10] and diethyl aminomalonate. M.p. 104–105° (after recrystallization from EtOAc–hexanes); NMR δ 1.1–1.35 (6H, m), 4.0–4.35 (8H, m), 5.1–5.2 (1H, d), 7.3 (5H, s), 7.5 (5H, s), 8.1–8.15 (1H, brd); $[\alpha]_D^{23}$ = 13.4 (*c* = 0.73, CH_3OH). (Found: C, 61.89, H, 5.48, N, 5.87. Calc for $C_{25}H_{26}N_2O_8$: C, 62.24; H, 5.39; N, 5.81).

Procedures for the DEAD/TPP cyclizations

Cyclization of compound **13**. Compound **13** was treated with DEAD/TPP under Townsend's conditions (2.5 equiv of reagents for 10 min, followed by a water quench)[5] and resulted in a 98% yield of a mixture of **14a,b** and the dehydropeptide, **18**. (5:3:1). The dehydropeptide was not apparent in the prechromatography NMR of the mixture [δ 5.83, 6.27, *J* = 4.2 Hz].

Repeating the reaction using only 1 equiv of the reagents resulted in a 93% yield of **14a,b** only.

Cyclization of compound **19**. Compound **19** (0.5 g, 1.3 mmole) (3.25 mmole) of TPP were dissolved in 20 ml THF and treated with 0.51 ml of DEAD. Within 5 min the soln began to turn a yellowish brown, and it continued to darken over the 4.5 hr of the reaction, whereupon the reaction was quenched with water. The products **20a,b** were isolated in a 4:3 ratio after repeated chromatography. 0.1618 g (0.44 mmole, 29.5%).

Repeating the reaction on the same scale with 1 equiv of reagents for 2.5 hr led to an 81% yield of the desired products. Chromatography [silica, 5% ether, 95% CH_2Cl_2] gave partial separation of **20a** and **20b**. Fraction 1 was enriched in compound **20b** (0.22 g): NMR 3.8 (3H, s), 3.4–4.2 (2H, m), 5.27–5.4 (1H, m, J = 4.17), 5.7 (1H, s), 7.39 (5H, s), 7.6–7.9 (4H, m). Fraction 2 was almost exclusively compound **20a**: NMR 3.39–3.49 (1H, dd, J = 4Hz), 3.87 (3H, s), 3.9–4.03 (1H, t, J = 6Hz), 5.48–5.58 (1H, dd, J = 4Hz), 5.83 (1H, s), 7.53 (5H, s), 7.6–7.9 (4H, m).

Epimerization of compound **20b**. The sample enriched in compound **20b** (0.22 g, 0.6 mmole) was treated with 0.12 g (0.6 mmole) TPP and 70 μl (0.6 mmole) DEAD in 10 ml THF. The reaction was followed by HPLC. [10 μ silica, 2.50 × 3.2 mm, 0.4% IPA in CH_2Cl_2, 5 ml/min, 0.5 cm/min, Rt **20a** 4.34 min, Rt **20b** 6.7 min.] Within 5 min a new equilibrium had been reached which was the same as seen in the cyclization reaction.

Cyclization of compound **22**. Compound **22** (0.66 g, 2.16 mmole) was treated with 0.57 g (2.18 mmole) of TPP and 0.34 ml (2.16 mmole) of DEAD in 30 ml of THF for 3 hr NMR of the crude mixture showed compounds **22**, **23** and **24** in a ratio of 2:5:3. Chromatography [silica, 80/20 hexanes and EtOAc] gave two fractions containing the products. From fraction 2 was crystallized 75.4 mg (0.26 mmole) of **23**, m.p. 178–180°. IR ($HCCl_3$) 1785 (sh), 1770, 1750, 1720. MS *m/e* 290 (M + 1). Homogenous by HPLC [10 μ sulica, 250 × 3.2 mm, 0.4% IPA in methylene chloride, 5 ml/min, 0.25 cm/min, Rt 9.6 min.] NMR 3.83 (3H, s), 3.86–3.98 (2H, m), 3.99 4.5 (2H, q. J_{CH_2} = 16.5), 5.53–5.6 (1H, dd), 7.6–7.9 (4H, m). (Found: C, 58.31, H, 4.05; N, 9. 67. Calc for $C_{14}H_{12}N_2O_5$: C, 58.13; H, 4.15; N, 9.69). Fraction 3 contained a mixture of **23** and **24** and was rechromatographed on a TLC column [80/20/0.8 CH_2Cl_2, hexanes, IPA]. 63 mg (0.22 mmole) of **23** was isolated, but **24** composed on the column. The total yield of **23** was 22%.

Cyclization of **25**. Compound **25** (0.448 g, 1.3 mmole) and 0.361 g (1.4 mmole) of TPP were dissolved in 15 ml THF. DEAD (0.02 ml, 1.4 mmole) was added dropwise under N_2. After 12 hr the reaction was quenched with water, evaporated and chromatographed [silica, CH_2Cl_2 and ether]. Compounds **26** and **27** co-eluted along with another unidentified component. After evaporation, 0.28 g (65% mass recovery) of the mixture was isolated. The mixture (0.125 g) was applied to a prep TLC plate (silica, 2 mm) and eluted 4 times with EtOAc–hexanes. 92 mg (0.28 mmole, 22%) of mixture of 26 and 27 was isolated in a ratio of 1:4. Compound **26**: IR 1780. NMR 3.5–3.7 (2H, m), 3.83 (3H,

s), 4.43–4.53 (2H, d), 5.34–5.5 (1H, m), 6.9–7.4 (4H, q), 7.7–8.0 (4H, m). Compound **27**: IR 1750, 1720. NMR 3.83 (3H, s), 4.46–4.53 (2H, d), 5.8 (1H, s), 6.2 (1H, s), 6.2–6.4 (1H, b), 6.9–7.3 (4H, m), 7.7–8 (4H, m).

Cyclization of **28**. Compound **28** (0.3 g, 9.3 mmole) and 0.26 g (1 mmole) of TPP were dissolved in 10 ml of THF. DEAD (0.19 ml, 1 mmole) was added dropwise under N_2. After 12 hr the reaction was quenched with water and evaporated. Chromatography [silica, CH_2Cl_2 and ether] resulted in the isolation of 0.24 g (83% mass recovery) of a three component mixture containing compounds **29** and **30**. 135 mg of the mixture was applied to a prep TLC plate (silica, 2 mm) and eluted 4 times with ether and hexanes (2:1). 85.6 mg (0.27 mmole, 29%) of a 1:1 mixture of **29** and **30** were isolated. IR (mixture): 1780, 1760, 1725. Compound **29**: NMR 3.46–3.66 (2H, m) 4.46 = 4.6 (2H, d) 5.4–5.5 (1H, m), 7.43 (5H, s), 7.7–8.0 (4H, m). Compound **30**. NMR 4.5–4.56 (2H, d), 5.76 (1H, s), 6.17 (1H, s), 7.3 (5H, s), 7.7–8.0 (4H, m).

Cyclization of **31**. Compound **31** (0.5 g, 1.28 mmole) was treated with 0.34 g (1.28 mmole) TPP and 0.20 ml (1.28 mmole) DEAD in 40 ml of THF for 1.5 hr. The reaction was followed by HPLC and TLC, and shown to be complete in 15 min. Compounds **32** and **33** co-eluted on silica gel chromatography [9:1 CH_2Cl_2 and ether]. Compound **32** crystallized selectively from EtOAc and hexanes to give 0.2473 g (0.67 mmole, 52%), m.p. 149–150°. IR (KBr) 1780, 1760, 1730. MS (CI with methane) *m/e* 375 (M + 1). NMR 1.19–1.39 (6H, dt) 4.03–4.47 (6H, m), 5.37 (1H, s), 5.47–5.57 (1H, m), 7.6–7.9 (4H, m). ^{13}C NMR: 15.81, 48.2, 55.8, 58.52, 64.3, 125.3, 133.4, 136.0, 165.9, 166.3, 166.9, 168.2. Single peak by HPLC [10 μ silica, 250 × 3.2 mm, 5 ml/min, 0.25 cm/min, Rt 6.48 min., 898:100:2 methylene chloride, hexanes, IPA]. (Found: C, 57.44; H, 5.04; N, 7.38. Calc for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.81; N, 7.49).

The supernatant from the crystallization was enriched in **33**, but it could not be crystallized selectively. HPLC conditions the same as for **32**: Rt 6 min. NMR 1.19–1.39 (6H, dt), 4.0–4.4 (4H, m), 5.17–5.27 (1H, d), 5.93 (1H, m), 6.3 (1H, m), 7.0–7.2 (1H, br d), 7.6–7.9 (4H, m).

Cyclization of compound **34**

(A) (*With* 100 *mole % of base*). Compound **34** (0.5 g, 1.7 mmole) was treated with 75 mg (1.7 mmole) of pre-washed 50% NaH in 10 ml of DMF/CH_2Cl_2 (1:4) for 15 hr under N_2. The reaction was quenched in 0.1 N HCl and extracted with EtOAc (100 ml). The organic phase was then washed with 0.1 N HCl (25 ml), H_2O (2 × 25 ml), brine (25 ml) and dried over $MgSO_4$. Evaporation, followed by recrystallization from hexanes gave a total of 0.203 g (0.70 mmole, 46%) of **37**, m.p. 94–95°. The filtrate contained **34** and **37** in a 1:1 ratio. Data for **37**: IR (KBr) 1720, 1700; NMR 1.13–1.3 (12H, m), 2.53 (2H, s), 4.0–4.4 (4H, m), 6.6 (1H, b). (Found: C, 56.18; H, 7.56; N, 5.45. Calc for $C_{12}H_{19}NO_5$: C, 56.03; H, 7.39; N, 5.45).

(B) *With* 220 *mole % of base*. Compound **34** (155 mg, 0.53 mmole) was dissolved in 6 ml THF and cooled to −78° under N_2. LDA (220 mole % from 0.167 ml, 1.2 mmole, diisopropyl amine and 1 ml of 1.3 M n-BuLi in 3 ml of THF was added. The light yellow soln of the dianion of **34** was allowed to warm slowly to room temp over 4–5 hr. After continued stirring for 12 hr, the soln was diluted with 75 ml ether and washed with 25 ml of 0.1 N HCl, 25 ml 5% $NaHCO_3$, and 25 ml brine. Drying over $MgSO_4$, filtering, and evaporation yielded 114.4 mg (0.45 mmole, 84%) of **36** which was identical to that prepared from **35**.

Cyclization of compound **35**. Compound **35** (0.5 g, 1.8 mmole) and 0.5 g (1.9 mmole) of TPP were dissolved in 20 ml of THF. 0.33 ml (1.9 mmole) DEAD was added dropwise under N_2. After 1 hr the mixture was concentrated and chromatographed (silica, CH_2Cl_2 and hexanes) to yield 0.499 g of an oil. Crystallization from hexanes gave 0.27 g (0.64 mmole, 35%) of **38**, m.p. 68–69°. IR 1760, (shoulders at 1740, 1720). NMR 1.16–1.4 (18H, m), 3.6 (2H, bs), 4.06–4.43 (8H, overlapping quartets), 7.1–7.3 (1H, bs). (Found: C, 50.08; H, 6.70; N, 9.73. Calc for $C_{18}H_{24}N_3O_9$: C, 50.1; H, 6.70; N, 9.7).

The mother liquid contained exclusively **36**, which was isolated as an oil IR (neat) 1780, 1740. NMR 1.16–1.36 (12H, singlet overlapping a triplet), 3.4 (2H, s), 4.13–4.4 (4H, q), 5.16 (1H, s).

Formation of adduct **38** *directly from β-lactam* **36**. Compound **36** (36.3 mg, 0.14 mmole) was dissolved in 5 ml of THF. Et_3N (2 μl, 0.014 mmole) and DEAD (22 μl, 0.14 mmole) were added. After stirring at room temp for 1 hr, all the DEAD had been consumed (TLC) and the mixture was evaporated to dryness. An NMR of the crude mixture showed a 1:1 ratio of the **38** and starting **36**. After chromatography (silica gel, 1:1 EtOAc-hexanes) 38.8 mg of **36** and **38** were isolated.

Attempted cyclization of **39** *to* **41**. Compound **39** (72.2 mg, 0.17 mmole) was dissolved with 63 mg (0.24 mmole) of TPP in 10 ml THF and 35 μl (0.17 mmole) DIAD in 5 ml of THF was added dropwise over 10 min. After stirring for 1 hr, TLC revealed the presence of some starting material so 10 μl more of DIAD was added. After a total of 2 hr, the reaction was quenched with water and evaporated. A mixture of **40**, **41** was isolated in 58% yield after chromatography (silica gel, $CH_2Cl_2Et_2O$). Normal phase HPLC and the 90 MHz ^1H NMR spectrum failed to distinguish the two components. At 300 MHz, however, the Me peaks of **40** and **41** appeared at 1.821 and 2.019 ppm respectively and in a ratio of 18.1:1. Reverse phase HPLC (C-18, 10 μ silica, 250 × 4.6-mm col, 45:55 CH_3CN–H_2O) also effectively separated the two components. For the major component **40**: ^1H NMR (90 MHz) δ 1.16–1.33 (6H, t); 1.82 (3H, s), 4.06–4.36 (4H, q), 5.83 (1H, d, J = 1.5Hz), 6.23 (1H, d, J = 1.5 Hz), 7.4 (1H, br s), 7.36–8.0 (4H, m). The minor product, **41**, was identical to that formed by the alkylation of **32** with CH_3I. ^1H NMR (300 MHz) 1.23–1.4 (6H, overlapping triplets), 2.02 (3H, s), 3.85–3.9 (1H, dd, J = 3.75 Hz, 7.1 Hz), 3.95–4.0 (1H, t, J = 7.5 Hz), 5.425–5.45 (1H, dd, J = 3.75 Hz, 7.1 Hz), 7.7–7.9 (4H, m). IR (thin film in CH_2Cl_2) 1770, 1740, 1720 cm^{-1}.

Cyclization of **46** *to β-lactam* **47**. This was accomplished by treatment of 209 mg (0.84 mmole) of **46** with 64.5 mg (1.3 mmole) of NaH in 5 ml of DMF–CH_2Cl_2 (1:4) for 3 hr at room temp. The mixture was poured into 75 ml of ether and washed with two 25 ml portions of water, 25 ml brine, dried over $MgSO_4$, filtered and evaporated to yield 177 mg (0.84 mmole, 100%) of **47** as an oil IR (neat) 1770, 1705 cm^{-1}; ^1H NMR δ 1.16–1.33 (9H, m), 2.63 (3H, s), 3.26 (2H, s), 4.03–4.26 (2H, q), 5.2 (1H, s).

Cyclization of **49** *to β-lactam* **50**. This was prepared in the same manner as for the preparation of **47**. β-lactam **50** was obtained as oil in 83% yield. IR (thin film in $CDCl_3$) 1760, 1740, 1720 cm^{-1}. ^1H NMR δ 1.23–1.37 (3H, t and 6H, s); 1.93 (3H, s), 2.23 (3H, s), 3.3 (2H, s), 4.09–4.3 (2H, q).

Cyclization of compound **51**. Compound **51** (0.5 g, 1.29 mmole) and 0.34 g (1.29 mmole) of TPP in 30 ml THF were treated with 0.2 ml (1.29 mmole) of DEAD for 30 min. The resulting mixture was chromatographed (silica, CH_2Cl_2/ether) yielding 25.5 mg (0.07 mmole, 5%) of **52**, [NMR 3.7 (3H, s), 5.06 (2H, s), 5.16 (1H, m), 5.53–5.6 (1H, d), 6.1 (1H, m), 7.6 (10H, m)] 273 mg (0.74 mmole) of **53**, m.p. 68–71°. IR (KBr) 3400, 1730 (1715), 1650. NMR 2.4–2.5 (1H, m), 3.03–3.13 (1H, dd), 3.65 (3H, s), 5.1 (2H, s), 5.13–5.2 (1H, d), 7.36 (10H, s). ^{13}C NMR: 33.8, 38.5, 54.5, 57.9, 70.51, 162.7, 168.4, 172.4.

Cyclization of compound **54**. Compound **54** (0.5 g, 1.2 mmole) and 0.33 g (1.2 mmole) of TPP in 30 ml THF were treated with 0.2 ml (1.29 mmole) of DEAD for 1 hr at R.T. The mixture was chromatographed as above, yielding 0.29 g (63% mass recovery) of a mixture of **55** and **56**. 105 mg of the mixture was prep TLC'd (silica, 2 mm, ether/hexanes, 4 times). Compound **55** eluted first. After evaporation, 64.1 mg (0.18 mmoles, 15%) of **55** was isolated as an oil. IR (neat) 1770, 1750, 1715. NMR 1.13–1.33 (6H, m), 3.56–3.7 (2H, m), 4.0–4.4 (4H, m), 4.6–4.8 (1H, m), 5.1 (3H, 2 overlapping singlets), 5.8–6 (1H, m), 7.4 (5H, s). Compound

56: 39.5 mg (0.1 mmole, 8.7) IR (neat) 1760, 1730. NMR 1.16–1.33 (6H, t), 2.4–2.6 (2H, dd), 3.06–3.16 (1H, dd), 4.1–4.4 (4H, dq), 4.5–4.8 (1H, b), 5.06–5.1 (1H, d), 5.13 (2H, s), 7.4 (5H, s).

Cyclization of **57** *to β-lactam* **58**. To 25 ml dry of THF was added 1.1 g (2.5 mmole) of **57** and 0.78 g (3 mmole) of TPP. While stirring at room temp, a soln of 0.5 ml (2.5 mmole) of DIAD in 25 ml of THF was added dropwise over 1 hr. Immediately after completion of the addition, the colorless soln was concentrated and chromatographed (silica gel, CH_2Cl_2) to provide 1.1 g (2.45 mmole, 96%) of **58**, m.p. 94–95° (after recrystallizing from EtOAc-hexanes); $[\alpha]_D^{23} = -70.2°$ ($c = 0.97$, CH_3CH_2OH); ^1H NMR δ 1.17–1.40 (6H, m), 3.87–4.4 (6H, m), 4.87–5.0 (1H, dd), 5.17 (1H, s), 7.26 (5H, s), 7.47–7.60 (5H, m); IR (KBr), 1730–1790 cm^{-1} (br, C = 0). (Found: C, 65.28; H, 5.35; N, 6.07. Calc for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.17; N, 6.03).

Diethyl-3(S)-amino-1-malonyl-2-azetidinone, **59**. This was prepared by catalytic hydrogenation of 324 mg (0.72 mmole) of **58** in 15 ml of EtOH containing 0.6 mL of 1.2 N HCl over 80 mg of 10% Pd–C at 35 psi for 4.5 hr. The mixture was then filtered through Celite. The Celite was washed with 50 ml of EtOH and the combined filtrate was evaporated. The residue was recrystallized from EtOH–ether to give 165.4 mg (0.59 mmole, 82%) of **59**, m.p. 137–141° (d); $[\alpha]_D^{23} = -33.8$ ($c = 0.4$, EtOH); ^1H NMR δ 1.16–1.37 (6H, t), 3.93–4.4 (6H, m), 4.67–4.9 (1H, m), 5.3 (1H, s), 8–10 (3H, br). IR (KBr) 1780–1730 cm^{-1} (br C = 0). (Found: C, 42.88; H, 6.16; N, 10.07. Calc for $C_{10}H_{17}N_2O_5Cl$: C, 42.86; H, 6.07; N, 10.0).

Acknowledgements—We gratefully acknowledge support of the National Institutes of Health and Eli Lilly and Company. The 300 MHz NMR system used was obtained by grants from NIH and the University of Notre Dame.

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