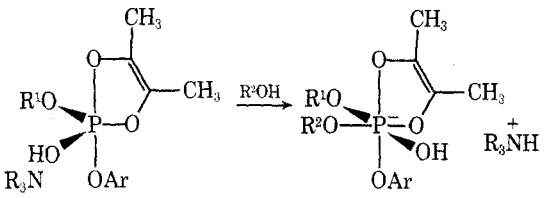
$$X{=}P(O)OAr + R^1OH \rightarrow X{=}P(O)OR^1 + ArOH \quad (1)$$

$$X{=}P(O)OR^1 + R^2OH \rightarrow CH_3COCH(CH_3)OP(O)(OR^1)(OR^2) \quad (2)$$

Alcohol R^1OH reacts much faster with $X{=}P(O)OAr$ than with the product $X{=}P(O)OR^1$, and, therefore, the symmetrical phosphates, $CH_3COCH(CH_3)OP(O)(OR^1)_2$, are not formed in any appreciable extent. Moreover, the phenols with electron-withdrawing substituents are much less reactive than alcohols toward both $X{=}P(O)OAr$ and $X{=}P(O)OR^1$, and hence the corresponding aryl phosphates are not produced.

The effective catalysis of reaction 2 by the phenol salts [e.g., a factor of ~140 in the reaction of i-C_4H_9OH with $X{=}P(O)O$-c-C_5H_9 by p-$N_2C_6H_4{}^-O(C_2H_5)_3NH^+$ in 0.2 M $CDCl_3$ at 25°] could involve 5- and 6-coordinate phosphorus intermediates[4] **4** and **5**; the latter, **5**, is analogous to



4 **5**

compounds isolated from the reaction of stable pentaoxyphosphoranes, phenols and tertiary amines.[4,5]

These results may have a bearing on the mechanism of action of enzymes that catalyze the reactions of phosphates and pyrophosphates, since the presence of tyrosine, lysine, arginine, and histidine residues could facilitate the addition of nucleophiles to 4-coordinate phosphorus by analogous mechanisms.

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(1) F. Ramirez, J. F. Marecek, and I. Ugi, *Synthesis*, 99 (1975).
(2) F. Ramirez, J. F. Marecek, and I. Ugi, *J. Am. Chem Soc.*, **97**, 3809 (1975).
(3) The elemental analyses of all new compounds agree with the calculated values. ^1H NMR signals are in parts per million vs.TMS = 10 (τ); ^{31}P NMR signals are in parts per million vs. H_3PO_4 = 0.
(4) For a recent discussion with the pertinent literature see F. Ramirez, V. A. V. Prasad, and J. Marecek, *J. Am. Chem. Soc.*, **96**, 7269 (1974).
(5) See also H. R. Allcock and E. C. Bissell, *J. Chem. Soc., Chem. Commun.* 676 (1972).

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Synthesis of DL-γ-Carboxyglutamic Acid Derivatives[1]

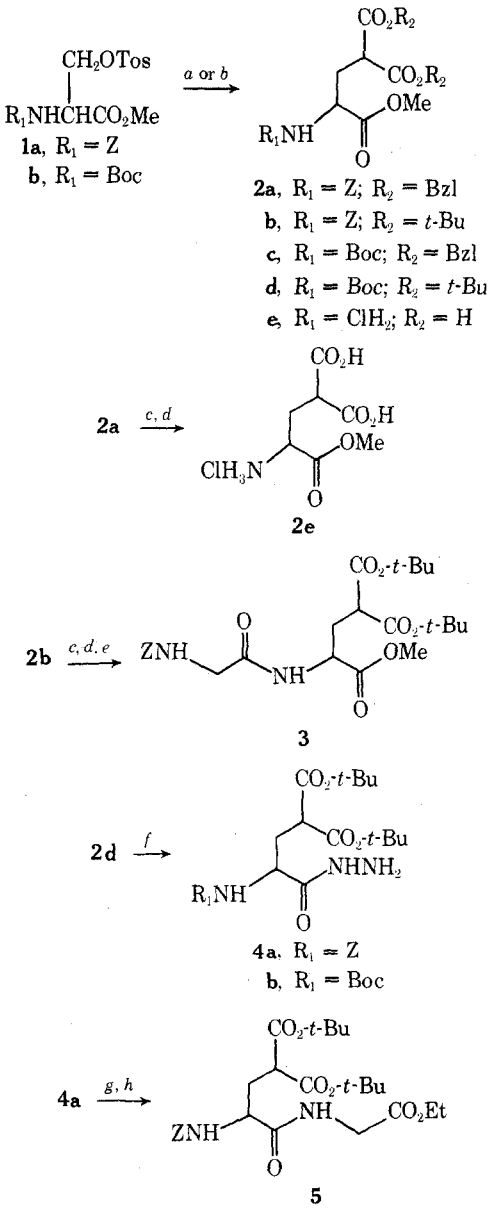
Summary: A method of synthesis of DL-γ-carboxyglutamic acid derivatives has been developed involving the reaction between *O*-tosyl serine derivatives and esters of malonic acid.

Sir: We wish to report the synthesis of derivatives of γ-carboxyglutamic acid (Gla),[1b] a new amino acid recently identified in prothrombin[2] and factor X,[2e] two of the four vitamin-K-dependent blood clotting factors. The success of the preparation of side chain protected cysteine[4,5] derivatives by displacement reactions on corresponding serines and alanines, and the DL-glutamic acid synthesis of Wieland et. al.[6] suggested the sequence of reactions outlined below for the preparation of Gla derivatives.[7]

Compounds **2a** and **2d** were prepared by the tosylate displacement[8] shown; yields and physical data are listed in Table I. Hydrolysis of aliquots of each reaction mixture followed by amino acid analysis[9] indicated the presence of glutamic acid in all cases.

Attempts to achieve SN2 displacement of the tosylate group were unsuccessful under a variety of conditions.[10] *Rather, the reaction seems to proceed in a stepwise fashion:* elimination to a dehydroalanine derivative, followed by conjugate addition of the malonate anion to the α,β-unsaturated ester. The optical rotations for the Gla derivatives obtained via this procedure were usually between +1 and +2°, indicating probable racemization. This was confirmed by acidic hydrolysis of **2c** to glutamic acid, which was shown to be totally racemized.

That appropriately protected Gla derivatives could be selectively deprotected and incorporated into peptides at either the α-amino or the α-carboxyl positions was shown



1a, $R_1 = Z$
b, $R_1 = Boc$

2a, $R_1 = Z$; $R_2 = Bzl$
b, $R_1 = Z$; $R_2 = t$-Bu
c, $R_1 = Boc$; $R_2 = Bzl$
d, $R_1 = Boc$; $R_2 = t$-Bu
e, $R_1 = ClH_2$; $R_2 = H$

2e

3

4a, $R_1 = Z$
b, $R_1 = Boc$

5

[a] $Li^+ {}^-CH(CO_2R_2)_2$, THF. [b] $Na^+ {}^-CH(CO_2R_2)_2$, DMF. [c] H_2, Pd/C, HOAc. [d] HCl/Et_2O. [e] Z-Gly-OH, THF, isobutyl chloroformate, *N*-methylmorpholine. [f] Hydrazine hydrate, methanol, 3 hr. [g] HCl/THF, *n*-butyl nitrite, −23°, 15 min. [h] Et_3N, H-Gly-OEt, THF, 0°, 2.5 hr.

Table I
Yields and Physical Data for Gla Derivatives[a]

Compd	Yield, %[b]	Mp, °C[c]
2a	82	Oil
2b	30	Oil
2c	60	82–83.5
2d[d]	56	Oil
2e[e]	43	122.5–123.5 dec[e]
3	63[f]	91.5–93
4a	75[g]	108.5–110
4b	73	82–83
5[e]	80[h] (60[g])	97.5–99[e]

[a] All new compounds gave satisfactory NMR spectra and combustion analysis, except as noted. [b] Isolated yields of purified products; not maximized. [c] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. [d] Combustion analysis was not obtained for this compound; the substance was characterized as the hydrazide, 4b. [e] Characterized as the monohydrate. [f] Overall yield from 2b. [g] Overall yield from 1a, without purification of 2b. [h] Overall yield from 4a.

in the following manner: hydrogenation of **2b,** followed by coupling to *N*-benzyloxycarbonylglycine using the mixed anhydride procedure,[11] afforded dipeptide **3** in 63% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate to the dipeptide derivative was 53%. Selective hydrazinolysis of either methyl ester **2b** or **2d** provided the corresponding hydrazides, **4a** and **4b,** and thus a convenient means of coupling at the COOH terminus. Conversion of **4a** to the acyl azide, and reaction with ethyl glycinate using a modified Honzl–Rudinger[12] procedure, afforded the dipeptide **5** in 80% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate was 60%.

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References and Notes

(1) (a) The following abbreviations have been used in the text: Gla,[1b] γ-carboxyglutamic acid; Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; *t*-Bu, *tert*-butyl; Tos, *p*-toluenesulfonyl. (b) There is no international symbol for this entity; both Glx[2b,c] and Gla[2d,3] have been used previously.
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(8) Displacement reactions were run under similar conditions: 15 ml of solvent, ambient temperature, 20 hr. Sodium malonates were formed by adding 1 equiv of the malonic ester to a stirred suspension of sodium hydride in dimethylformamide. Lithium malonates were generated by reaction of 1 equiv of lithium diisopropylamide (prepared by *n*-butyllithium and diisopropylamine in THF) with the malonic ester in THF. The metal malonate (2 equiv) was then added dropwise to stirred solutions of the tosylate in the same solvent. Starting tosylates were prepared according to published procedures.[4,5]
(9) Beckman Model 116 amino acid analyzer; Beckman custom spherical ion exchange resin, type VR-30.
(10) Reaction of *N*-benzyloxycarbonyl-*O*-tosyl-L-serine methyl ester under any of the following conditions results largely in elimination: diisopropylamine, THF, 20 hr; sodium malonate (1 equiv), methanol, 20 hr; sodium malonate (1 equiv), DMF, 20 hr; diethylamine, 50:50 ether–ethyl acetate, 7 hr or 20 hr; lithium malonate (1 equiv), THF, 20 hr.
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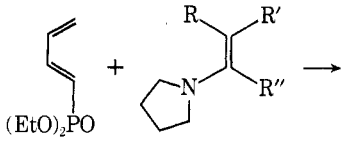
Cycloaddition Reactions of Enamines and Diethyl 1,3-Butadienephosphonate. The Formation of β-Aminophosphonates via a Mannich Reaction[1,2]

Summary: Cycloaddition of 1-diethylphosphinyl-1,3-butadiene and enamines proceeds in good yield to give β-aminophosphonates which deaminate to yield cyclohexadienephosphonates.

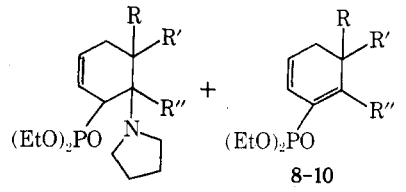
Sir: We wish to report the first observed cycloaddition reaction of a phosphonate activated butadiene to an enamine.

The diene **1** was prepared from triethyl phosphite and 1,4-dichloro-2-butene in two steps, with an overall yield of 74%, by using a procedure for the formation of diethyl vinylphosphonate.[3] The reaction of 0.1 mol of diene **1** with an equal amount of 1-pyrrolidinocyclohexene(**2**), 1-pyrrolidino-2-methylpropene (**3**), or 1-pyrrolidinopropene (**4**) was carried out under nitrogen in a solution containing 100 ml of benzene and refluxed for 24–48 hr. Water was added to the refluxing solution, in the work-up, to hydrolyze any enamine. The major products were β-aminophosphinates (**5, 6,** or **7**) and the cyclohexadienyl phosphonates (**8, 9,** or **10**). The yields of the cyclohexadienephosphonates were increased at the expense of the β-aminophosphonates by further heating of the reaction mixture. The latter were never completely transformed. The products were separated and isolated from the organic layer with dilute hydrochloric acid solution. The acid layer was neutralized to recover the amine.



1 2-4

2 (R = H; R′R″ = $-CH_2CH_2CH_2CH_2-$)
3 (R, R′ = CH_3; R″ = H)
4 (R = CH_3; R′, R″ = H)



5-7 8-10

Products	
5	8
6	9
7	10