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**PROGRESS TOWARDS A SYNTHESIS OF DEOXYBOUVARDIN AND
ANALOGUES; NEW SYNTHETIC METHODS**

The University of Arizona

Ph.D. 1984

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PROGRESS TOWARDS A SYNTHESIS OF DEOXYBOUVARDIN
AND ANALOGUES; NEW SYNTHETIC METHODS

by

KIM DAVID JANDA

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

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entitled Progress Towards A Synthesis Of Deoxybouvardin
And Analogues; New Synthetic Methods

and recommend that it be accepted as fulfilling the dissertation requirement
for the Degree of Doctor of Philosophy.

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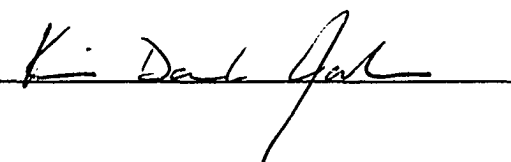
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ABSTRACT

This work involved synthetic approaches to the anti-tumor agent deoxybouvardin. Numerous reactions were explored in an attempt to build an amino acid from an aromatic aldehyde under mild conditions. From these reactions new and useful synthetic methods have been discovered for making α -acylamino alcohols and unsymmetrical imides. Some dehydroamino acids were successfully prepared from aromatic aldehydes and an N-acylphosphorylglycine ester.

Progress towards a synthesis of 5- η -thiodeoxybouvardin will also be discussed.

INTRODUCTION

Bouvardia ternifolia (cav.) Schlect (Rubiaceae)¹ was used by ancient Mexican Indians as a general curative and is still in use as a remedy for dysentery, hydrophobia, and other afflictions. The plant is locally called "trompetilla," "tlacoxochitl," "mirto," and other names [1]. As a result of the continuing search for plants possessing tumor-inhibiting constituents, Dr. Jack Cole's group in the College of Pharmacy, University of Arizona, found that the methanol extract of the stems, leaves, and flowers of Bouvardia ternifolia demonstrated inhibitory activity toward the P388 lymphocytic leukemia (PS) and B16 melanotic melanoma (B1) test systems [2] as shown in Table 1. The extract yielded three substances upon chromatography: bouvardin (1), deoxybouvardin (2), and 6-O-methylbouvardin (3), characterized in collaborative efforts with the Bates group in the Chemistry Department [3], [4]. The anti-tumor activities of each are given in Table 1.

¹The plant was collected in Coahuila, Mexico, in July, 1970. Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, U.S. Department of Agriculture, Beltsville, MD. A reference specimen is maintained by the USDA.

Table 1. Anti-Tumor Activities^a of Bouvardin (1)
Deoxybouvardin (2), and 6-O-Methylbouvardin (3)

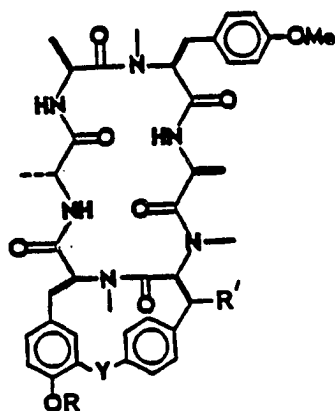
	<u>Activity,^a % T/C</u>	<u>Dose, mg/Kg</u>	<u>Test system</u>
(1)	135-217	0.02-2.0	PS
	134-152	0.12-2.0	B1
(2)	142-216	0.04-2.0	B1
	133-175	0.25-8.0	B1
(3)	134-220	0.12-2.9	PS
	132-257	0.12-2.9	PS
Natural Mixture of (1), (2) & (3)	132-167	0.12-2.0	B1
<u>KB Test System^b:</u>			
(1)	4.2 x 10 ⁻⁷	g/ml	
(2)	1.9 x 10 ⁻⁸	g/ml	
Natural Mixture of (1) & (2)	10 ⁻²	g/ml	

^aActivity in the PS and B1 test systems is defined as an increase in survival rate of test animal/control animal > 125% [5] and in the KB system as ED₅₀ < 4.0 g/ml.

^bPS P388 Lymphocytic Leukemia

B1 B16 Melanotic Melanoma

KB Adenocarcinoma of the Nasopharynx



	<u>R</u>	<u>R'</u>	<u>Y</u>
(1)	H	OH	O
(2)	H	H	O
(3)	Me	OH	O
(4)	H	H	S

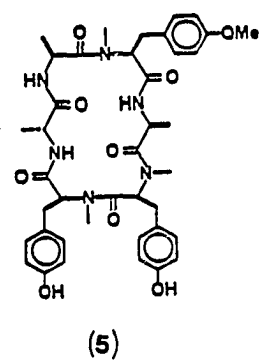
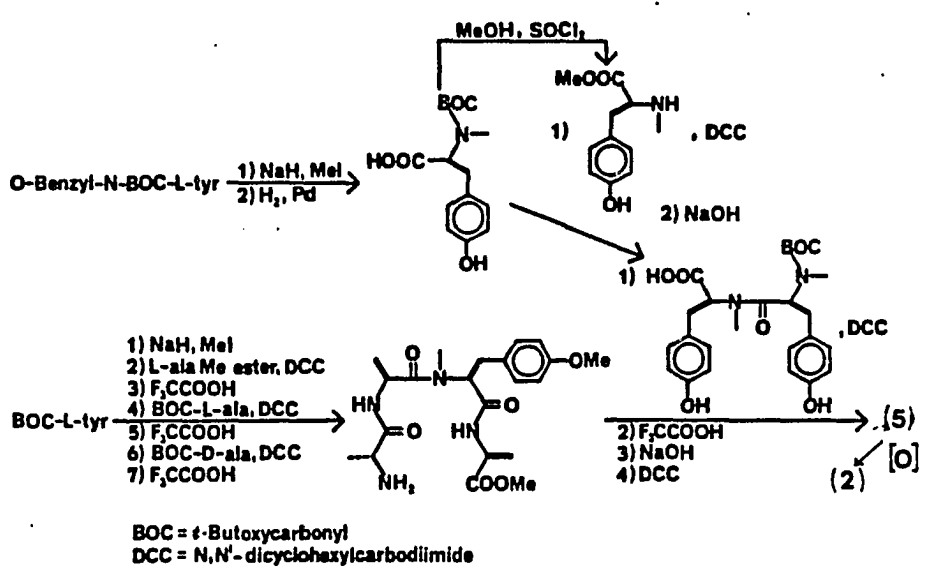
The activities of these compounds were so interesting to other researchers that Dr. Cole's group was contracted to isolate large quantities of the hexapeptides. Since the occurrence of the compounds in Bouvardia ternifolia is so small (1.1×10^{-3} and $4.4 \times 10^{-4}\%$ for (1) and (2), respectively, and much less of (3)), with resulting costs of about \$2000/gram for (1) and (2) from natural sources, investigations toward their syntheses were begun by Bates and Kriek in 1977 [6]. The major goals of the current work were to make as much further progress as possible towards syntheses of deoxybouvardin (2), the simplest member of the series, and its sulfur analog 5n-thiodeoxybouvardin (4).

The initial approach to the synthesis of deoxybouvardin (2) taken by Kriek and others in our group [6] was to prepare cyclic hexapeptide (5) and to oxidize it to (2) (Scheme I). Although (5) was obtained, many attempts to oxidize it to (2) (presumably mimicking the biogenesis of (2)) failed [7].

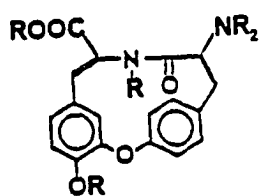
The next approaches involved as key intermediates cyclic dipeptides of type (6), which would be combined with the tetrapeptide (7) used in the synthesis of (5) to make deoxybouvardin (2).

Several efforts to make a cyclic dipeptide of type (6) from tyrosyltyrosine derivatives (8), (i.e., making the diphenyl ether linkage last) failed [8], and it was then decided to try routes involving making the diphenyl ether linkage first and the peptide bond last (i.e., via (9)). There is precedent for this approach to a 14-membered ring lactam-ether in the work of Lagarias, Houghton, and Rapoport [9].

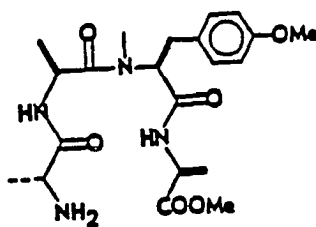
There are several methods by which diaryl ether linkages have been formed but yields are usually poor and reaction conditions are such that they would most likely racemize amino acids. The cuprous oxide catalyzed reaction of iodobenzenes with phenoxides (Ullmann reaction) gives 40-70% yield of diphenyl ethers [10] but requires refluxing in dimethylacetamide (166°C) for 24 hours which would almost certainly racemize amino acids. Though there have been improvements in the Ullmann reaction by Afzali (Eq. 1) [11] and Cava (Eq. 2) [12] these still require strong bases and high temperatures.



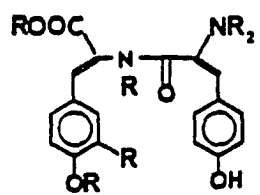
Scheme I: Initial approach to the synthesis of Deoxybouvardin (2)



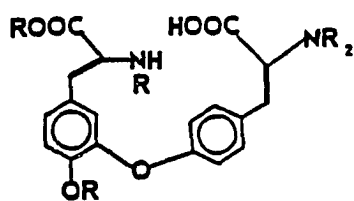
(6)



(7)



(8)

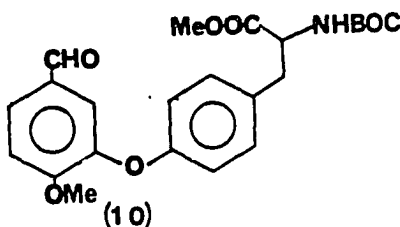
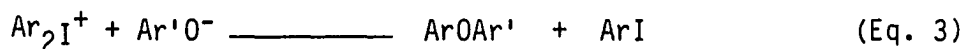


(9)



In an effort to find mild conditions for the reaction of an aryl iodide with a phenoxide, we discovered a new method for making symmetrical diphenyl ethers in high yield via a benzyne intermediate [13]. Though our procedure gives excellent yields of diaryl ethers and diaryl sulfides, it requires a strong base (potassium t-butoxide) which might be unsuitable for use with amino acids and might also have orientation problems if applied to deoxybouvardin (2).

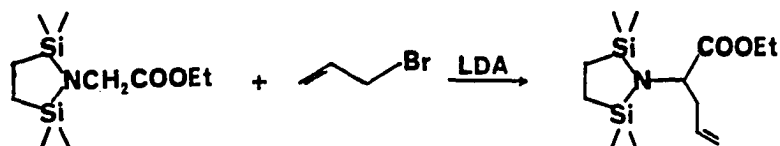
Another approach to diaryl ether synthesis, explored by Gary Linz in our group, involved reaction of diaryliodonium salts with phenoxides (Eq. 3). Attempts by Linz to make a diaryliodonium salt from a tyrosine derivative failed, but he was able to make the diaryliodonium salt from anisaldehyde in excellent yield and couple it with a phenoxide to give diaryl ether (10).



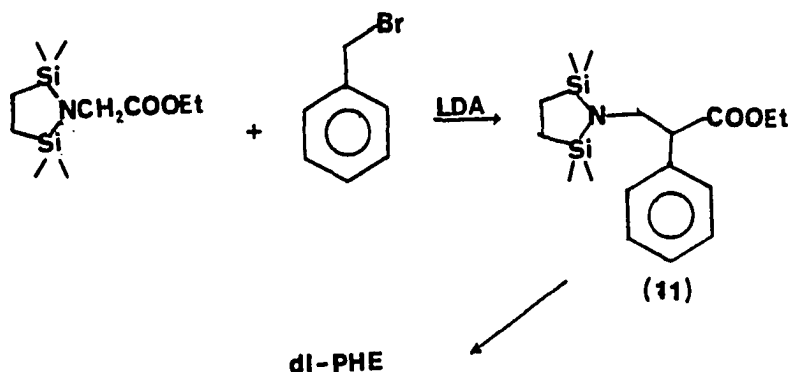
The problem now, whose solution is part of this dissertation, was to make a carboxyl-protected tyrosine grouping from the aldehyde portion of (10). There have been a number of successful syntheses of tyrosine from anisaldehyde or *p*-hydroxybenzaldehyde, but most would racemize (10) or remove the BOC grouping.

Dijuric et al. [14] showed that the reaction in Eq. 4 went in 91% yield. In earlier work [8], we tried the analogous reaction using benzyl bromide (Eq. 5), giving (11) in 70% yield. After hydrolysis of (11), a 35% yield of dl-phenylalanine resulted. Thus this route proved to give the desired amino acid, but racemic; this would also require aldehyde (10) to be reduced to the alcohol which would then be converted into a better leaving group (e.g., halogen) in order for the alkylation to proceed.

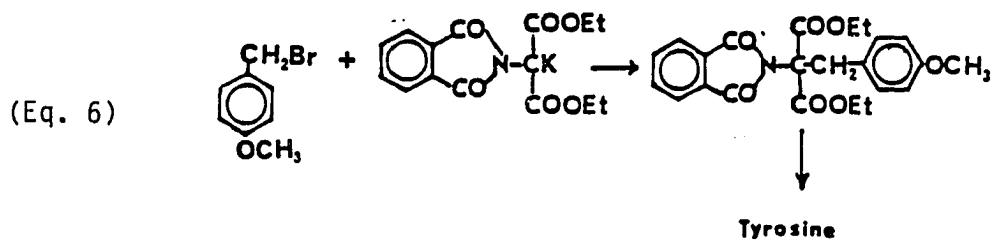
(Eq. 4)



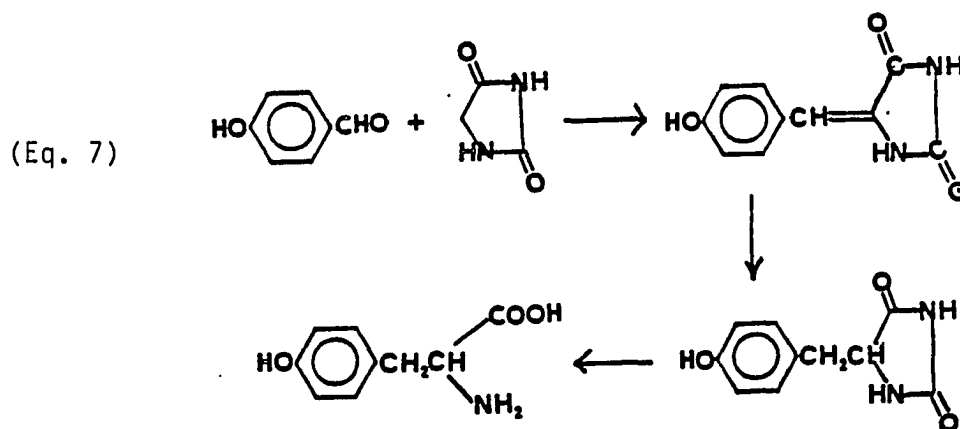
(Eq. 5)



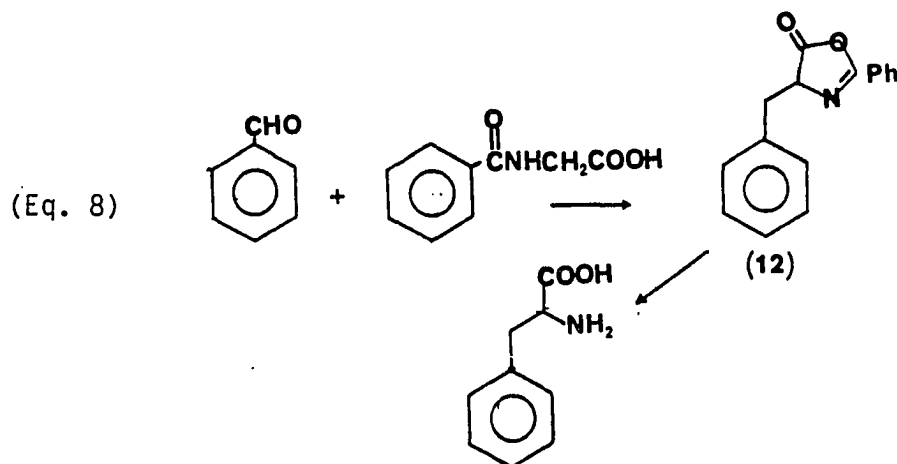
Stephen and Weizmann synthesized tyrosine in 35% yield via an initial alkylation of potassium diethyl phthalimidomalonate with *p*-methoxybenzyl bromide (Eq. 6). This route has the drawback that it requires a temperature of 145°C for 4 hours in xylene [15].



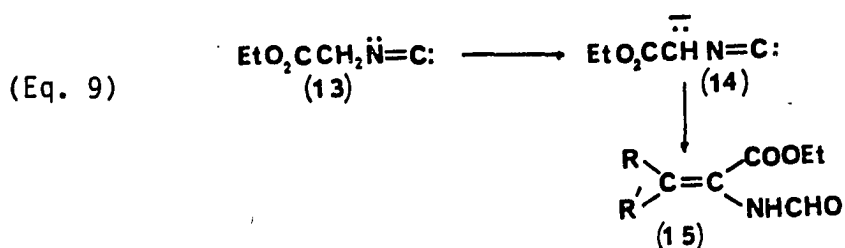
Boyd and Robson [16] effected the aldol condensation of *p*-hydroxybenzalhydantoin (Eq. 7) in the presence of diethylamine or piperidine as a catalyst. Reduction of *p*-hydroxybenzalhydantoin with ammonium sulfide, followed by alkaline hydrolysis of the *p*-hydroxybenzalhydantoin so derived, led to racemic tyrosine with an overall yield of 55%.



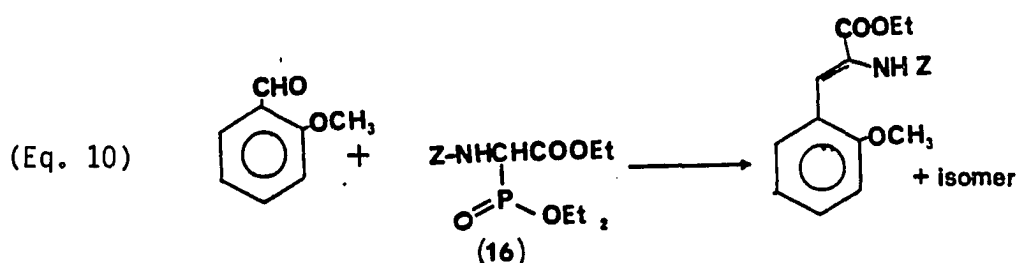
Another aldol route with milder conditions (100°C, 30 min.) was based on the synthesis of azlactone (12), Eq. 8 [17]. Hydrogenation/ hydrogenolysis of the azlactone was expected to give the amino acid, in this case phenylalanine.



Schollkopf, Gerhart and Schroder [18] have synthesized a number of β -substituted α -acylamino acrylic acids (Eq. 9). They obtained good yields (13-87%) of ethyl α -(formylamino)acrylates (15) by reacting α -metallated ethyl isocyanoacetate (14) (prepared from ethyl isocyanoacetate, (13)) with aromatic or aliphatic aldehydes or ketones. Though this appears to be an excellent method for making dehydroamino acids, it has some drawbacks; e.g., (13) is prepared using phosgene [19].

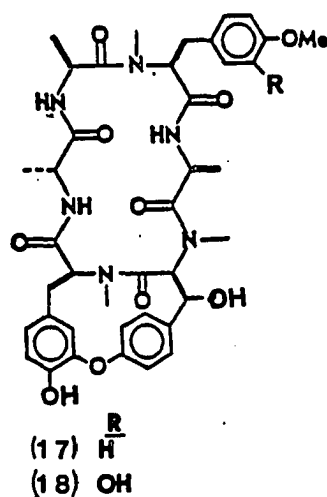


Another promising route was pioneered by Schmidt et al. [20], who aldol-condensed o-anisaldehyde with 2-benzyloxycarbonylamino-2-diethoxyphosphorylacetate (16) at room temperature (Eq. 10), giving a dehydroamino acid. This could then be hydrogenated using a chiral catalyst to give an amino acid with, in many cases, high optical induction.



The second goal in this study was to make as much progress as possible toward a synthesis of 5- η -thiodeoxybouvardin (4). Although bouvardin (1) and deoxybouvardin (2) have not been synthesized to date, some analogues have been made via microbial degradation of bouvardin (1) [21]. These analogues, (17) and (18), were found to be inactive. Thus it appears that the active end of the molecule is the upper end (as drawn), and the diphenyl ether linkage in the lower end serves to get the upper end into the right conformation. The receptor is some yet unknown site in the 80s ribosomes, where bouvardin (1) has been determined to inhibit protein synthesis [22]. This site is apparently different from that for cycloheximide and cryptopleurine, since strains resistant to these anti-tumor drugs are sensitive to bouvardin (1) [23].

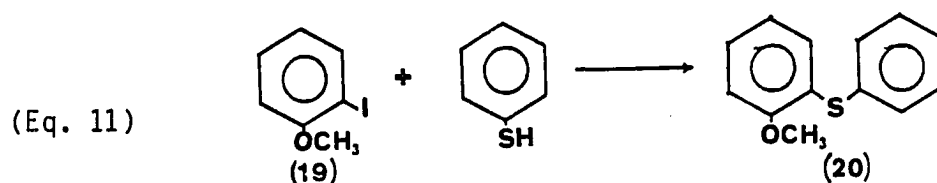
We think that 5- η -thiodeoxybouvardin (4) will have good activity, and be much easier to synthesize than deoxybouvardin (2) for two



reasons. First, the major problem with making (2) is the strain in the 14-membered ring. (3) also has a 14-membered ring, but the greater C-S bond lengths (each about 0.3 Å longer than the corresponding C-O bondlength) make a significant difference: (2) is too strained to make easily with CPK molecular models, whereas (4) is much more easily made. We expect this difference to show in the laboratory preparations as well. It should be noted that although the lower half of the molecule is less rigid in (4) than in (2), the geometry of the upper half (the active part?) appears to be very similar.

The second reason (4) should be easier to prepare is that most recipes give higher yields of diaryl sulfides than diaryl ethers. As

an extreme (and very pertinent) example, the $S_{RN}1$ synthesis of diaryl sulfides from aryl iodides and thiophenoxides in liquid ammonia goes in excellent yield, e.g., (19)----->(20) (Eq. 11) in 93% yield [24], whereas the corresponding diaryl ether synthesis fails completely.

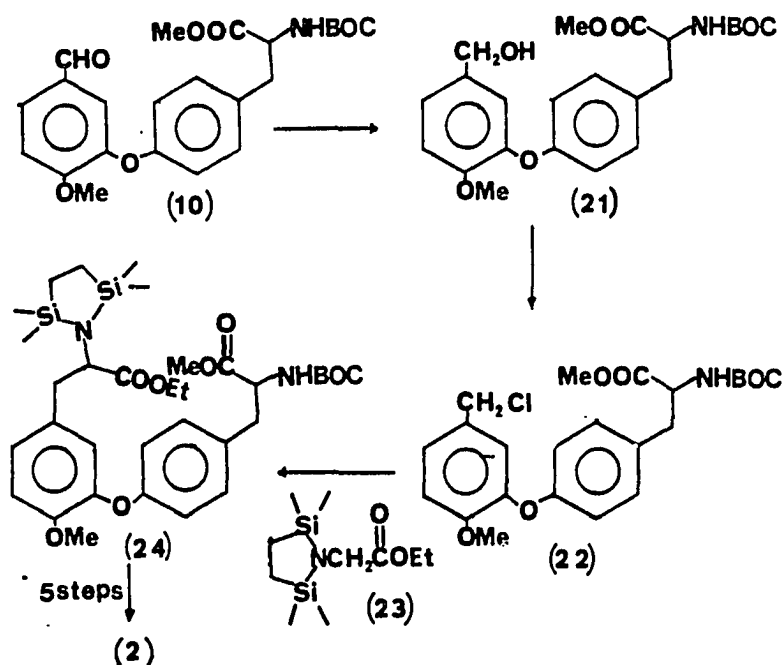


If (4) has the expected high activity, it would be very easy to make many analogues containing sulfur at the same position as an aid in determining the structure-activity relationships for these compounds.

RESULTS AND DISCUSSION

Part I: Deoxybouvardin (2): Progress Towards its Synthesis

The routes we have tried involve converting the aldehyde grouping in compound (10), synthesized by Linz in the Bates group, to a protected tyrosine grouping. In the first route (Scheme II), (10) was reduced to alcohol (21) which was then converted to the benzyl bromide (22) using a method developed by Corey [25]. However, reaction of compound (22) with the anion from (23) did not appear to give any (24), for reasons unknown at this time.

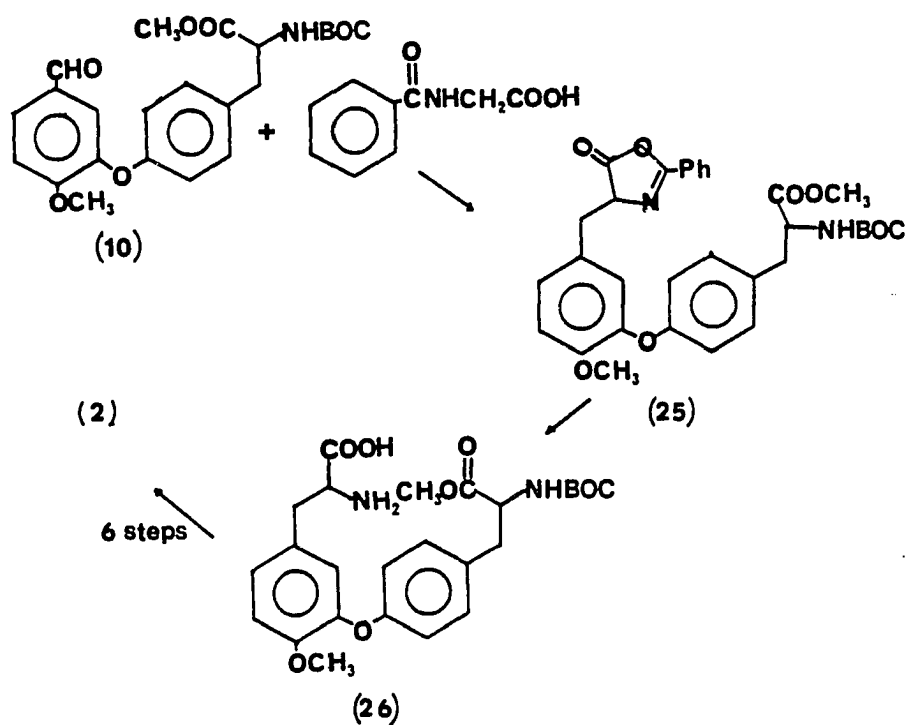


Scheme II: Stabase (23) route to Deoxybouvardin (2)

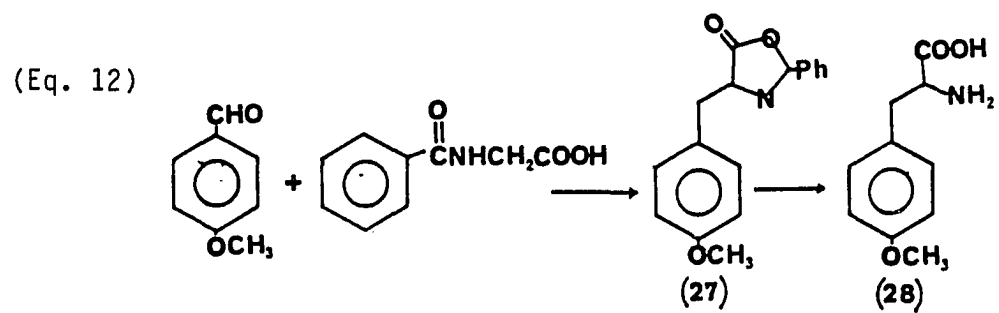
The second route we tried (Scheme III) entailed transforming aldehyde (10) into azlactone (25). Since aldehyde (10) was a valuable intermediate, we decided to work the procedure out on a model aldehyde such as benzaldehyde or anisaldehyde (Eq. 12).

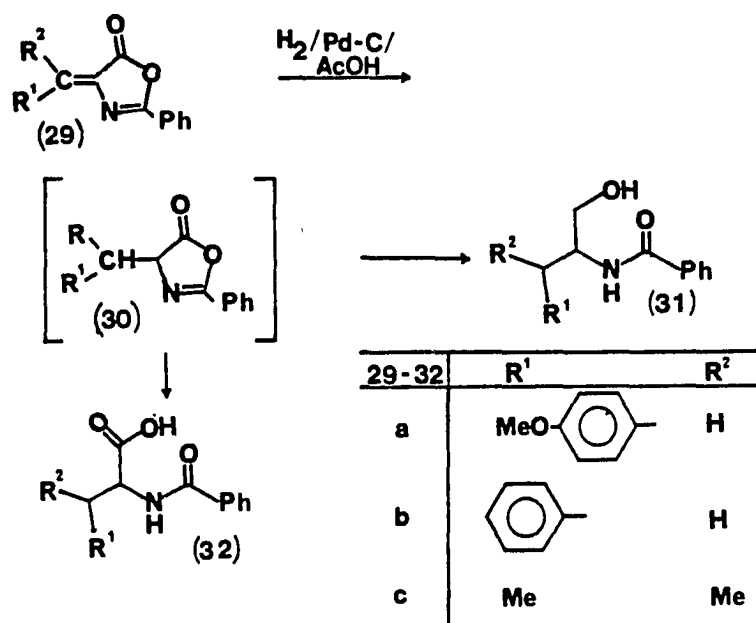
Unsaturated azlactones, e.g., (29), can easily be synthesized from any aldehyde or ketone and hippuric acid [26]. We hydrogenated (27) with palladium on carbon (10%) in acetic acid in hope of obtaining racemic tyrosine O-methyl ether (28), via reduction of the olefin and imine followed by hydrogenolysis of the benzyl ester and benzylamine [27] [28]. Instead the major product was N-[2-hydroxy-2-(4-methoxybenzyl)-ethyl]-benzamide (31a) (50%), (Scheme IV) [29]. Apparently, the lactone carbonyl group of (30a) is reduced faster than the imine group, and the resulting lactol opens to give the α -acylamino aldehyde, which is reduced to the α -acylamino alcohol (31a). The hydrogenation of the unsaturated azlactone (29a) to azlactone (30a) is precedented, but, in the past, sufficient water was present to hydrolyze (30a) to the α -acylamino acid (32) before further reduction could occur [30].

Though we were unable to prepare (26), we felt the reaction of (29) to (31) was interesting and we decided to look at its scope. The analogous phenylalanine and valine derivatives (31b) and (31c), respectively, were prepared similarly in 60% yields. Thus, α -acylamino alcohols (31) can be readily prepared in two steps from aldehydes or ketones and hippuric acid via azlactones (29).



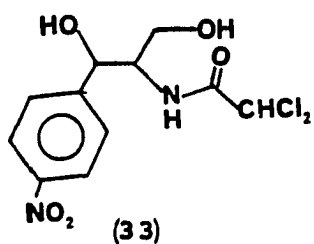
Scheme III: Azlactone route to Deoxybouvardin



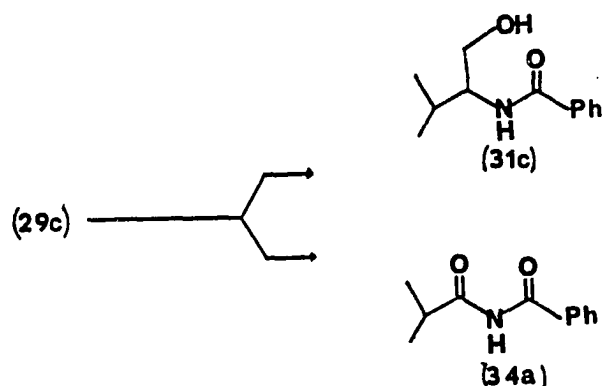


Scheme IV: Synthesis of α -acylamino alcohols from azlactones

Since these compounds were new and had a strong resemblance to the antibiotic chloramphenicol (33) [31], we submitted them for testing to the National Cancer Institute. All three compounds were accepted for testing but were found to be inactive in a leukemia screen (3PS31) [32].



In the course of the isolation of α -amino alcohol (31c) we isolated an unexpected by-product (34a) in 2% yield (Scheme V). Compound (34a), an unsymmetrical acyclic imide, was an unusual product in that a carbon atom has been lost and it was not at all apparent how it was formed from (29a). (34a) was identified by x-ray analysis because it was a highly crystalline substance and we were unable to establish with certainty by NMR (^1H or ^{13}C) the arrangement of atoms between the isopropyl group and the phenyl group.



Scheme V: Unexpected by-product from azlactone reduction

This compound is apparently the first acyclic imide to be studied by x-ray [33]. Unlike the imides in 5- and 6-membered rings, where the oxygens must be at the ends of a "W" conformation, the oxygens in acyclic imides have a choice, and in this structure adopt a twisted "U" conformation. The gradual twist about the system is

indicated by torsion angles of 10.4 and 12.0° about C(9)-C(8)-N-C(7) and C(8)-N-C(7)-C(1), respectively, and a 24.3° angle between the least squares planes formed by N-C(7)-O(7)-C(1) and the benzene ring (continuing the twist in the same direction). The O-C-N and C-N-C angles are all greater than 120°, presumably to give a greater distance between the oxygen atoms with the partial negative charges. The isopropyl group is rotated to put C(11) almost halfway between O(8) and HN, with C(1) close to O(8) (C(10)-C(9)-C(8)-O(8) = 25.9°) and HC(9) close to HN.

As can be seen in Fig. 1, the molecules in the crystal are held together by an infinite series of bifurcated hydrogen bonds (dotted lines) in the b direction from the NH of one molecule to the two carbonyl oxygens of the next molecule. HN thus fulfills a role played by a metal in metal acetylacetonates. The distances and angles observed are typical of a bifurcated system [34]: N-O(7), 2.92 Å; N-O(8), 3.15 Å; HN-O(7), 2.10 Å; HN-O(8), 2.28 Å; N-H-O(7), 137°; N-H-O(8), 144°. Fig. 2 depicts the final bond lengths and angles, Table 2 lists the final positional parameters and isotropic thermal parameters, and the unit cell contents are shown in Fig. 1.

Available methods for the synthesis of unsymmetrical acyclic imides suffer from low yields, high temperatures, numerous steps, or scrambling of the groupings to give symmetrical imides [35-38]. Thus when we found imide (34c) as a 2% by-product during a reduction of azlactone (29c) with hydrogen over Pd/C [29], we decided to vary the conditions to see if the yield of imide (34c) could be improved.

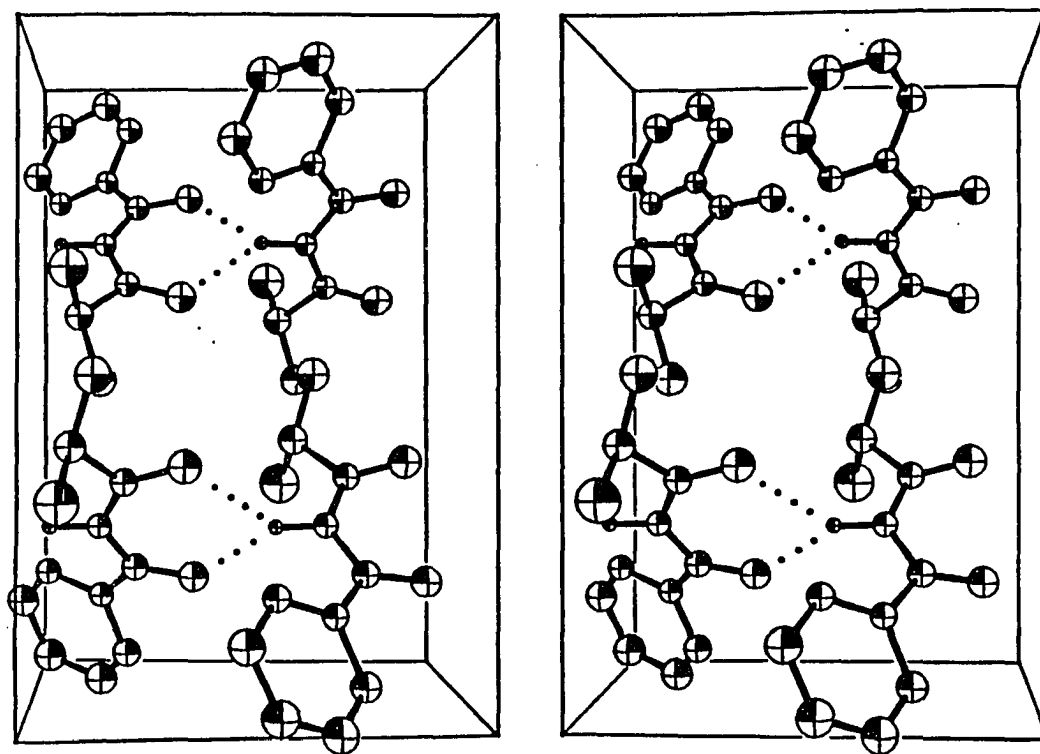


Figure 1. Stereoscopic illustration of a unit cell, b horizontal, c vertical, with 30% probability thermal spheres.

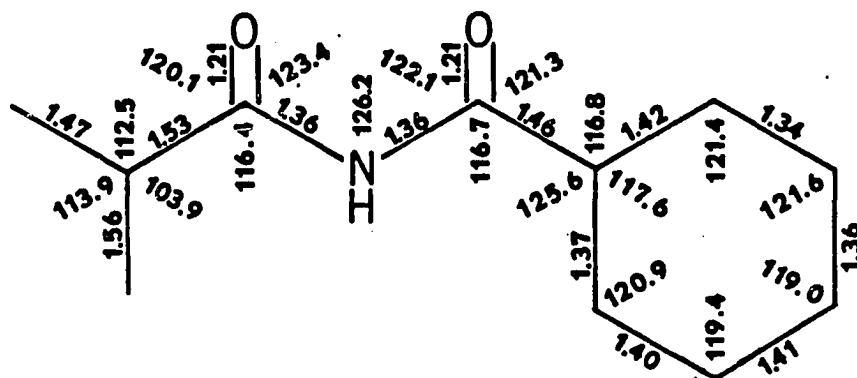


Figure 2. Bond lengths (Å) and angles (°). E.s.d.'s in bond lengths are 0.02-0.03Å, and in angles 0.9-1.2°.

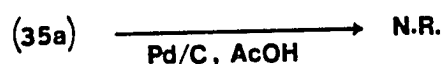
Table 2. Final Atomic Positional Parameters ($\times 10^3$) and Isotropic Thermal Parameters for Non-H Atoms with e.s.d.'s in Parentheses

Temperature factors are of the form $\exp[-B(\sin^2\theta/\lambda^2)]$.

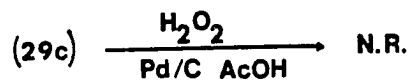
	<u>x</u>	<u>y</u>	<u>z</u>	<u>B</u> (\AA^2)
C(1)	35(1)	835(1)	666	3.4(4)
C(2)	-11(2)	929(1)	724(2)	4.6(5)
C(3)	-121(2)	982(1)	661(2)	6.1(6)
C(4)	-192(1)	950(1)	535(2)	6.5(6)
C(5)	-148(2)	858(1)	472(2)	6.1(6)
C(6)	-34(2)	803(1)	539(2)	3.8(4)
C(7)	155(2)	784(1)	745(2)	3.9(5)
C(8)	337(2)	650(1)	721(2)	3.9(4)
C(9)	438(2)	596(1)	608(2)	5.1(5)
C(10)	480(2)	496(1)	658(3)	6.7(6)
C(11)	574(2)	668(1)	587(3)	9.4(7)
N	238(1)	718(1)	665(2)	3.3(3)
O(7)	177(1)	798(1)	876(2)	5.0(3)
O(8)	343(1)	628(1)	852(2)	5.9(4)

We did not know the reaction mechanism, but we felt oxygen was somehow involved. Eq. 13 and Eq. 14 were our first experimental attempts at solving the mystery. These both proved unsuccessful so we decided to use the exact conditions used on the hydrogenation of the azlactones (29) to α -acylamino alcohols (31), except we substituted O_2 for H_2 and did not do the reaction under 3 atm (i.e., O_2 was bubbled into the solution (Eq. 15). This gave a 21-fold increase in the yield of the imide. Thus the reaction appeared to be a Pd/C catalyzed oxygenation. To prove the need for oxygen, we ran the reaction without oxygen (Eq. 16) and no reaction was observed.

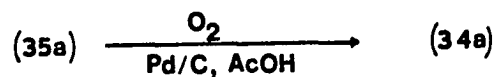
(Eq. 13)



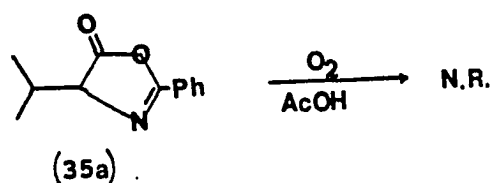
(Eq. 14)



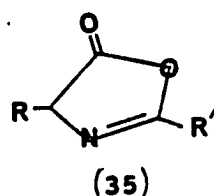
(Eq. 15)



(Eq. 16)



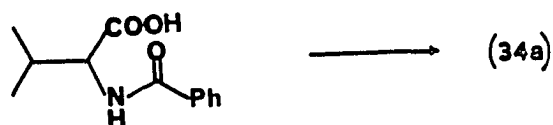
Unsaturated azlactones such as (35) are easily prepared from N-acylglycines and aldehydes or ketones via unsaturated azlactones, from α -amino acids $\text{RCH}(\text{NH}_2)\text{COOH}$ and anhydrides $(\text{R}'\text{CO})_2\text{O}$, or from α -amino acids $\text{RCH}(\text{NHCOR}')\text{COOH}$ and Ac_2O [26].



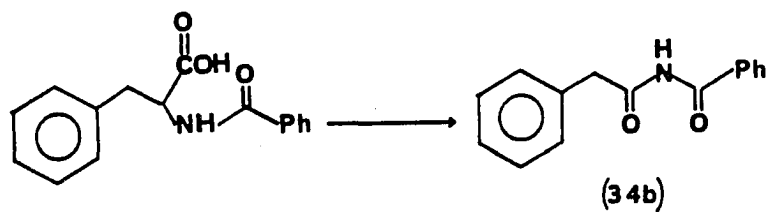
As in (Eq. 15) the unsaturated azlactone was isolated and then subjected to oxidative conditions. We found that the azlactone (35) need not be isolated but could be oxidized directly in the acetic anhydride-acetic acid solution in which it was prepared. Thus in one pot, N-benzylvaline was converted into imide (34a) in 50% yield (Eq. 17)

[39]. Similarly, N-benzylphenylalanine was converted to imide (34b) in 60% yield (Eq. 18), and phenylalanine was converted to imide (34c) in 55% yield (Eq. 19).

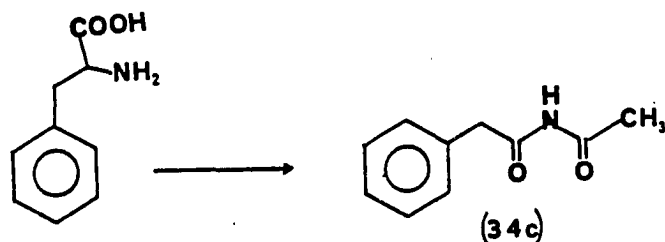
(Eq. 17)



(Eq. 18)

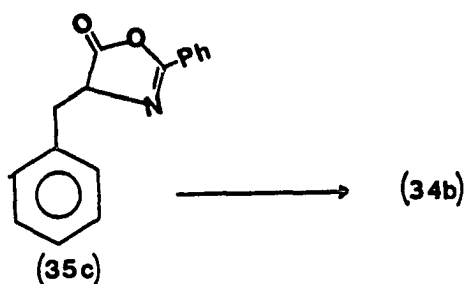


(Eq. 19)



Though 50-60% yields of the imides via one pot conversions was good, we thought it might be possible to increase the yields by varying the solvent. By changing to benzene the yield dropped to 10%, but with Me₂SO the yield of (34b) rose to 82% (Eq. 20).

(Eq. 20)

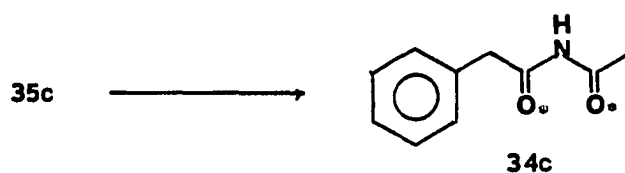


In experiments designed to narrow the mechanistic possibilities, we ruled out mechanisms involving decarbonylation of (35) to imine (36) (Eq. 21) by oxidizing (35c) with $^{18}\text{O}_2$ to (34c) containing to ^{18}O 's (Eq. 22), and mechanisms involving singlet O_2 by recovering 9,10-diphenylanthracene unchanged under the reaction conditions (Eq. 23) [40].

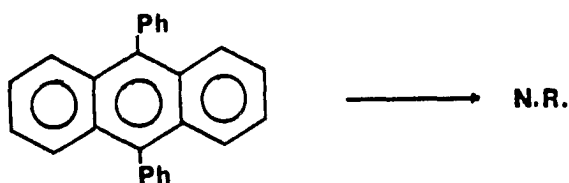


The reaction (Scheme VI) apparently involves autoxidation of (35) to (37) ($\text{R}'' = \text{H}$) and/or (38) by triplet oxygen, tautomerization of (37) ($\text{R}'' = \text{H}$) and/or (38) to (39), and fragmentation (not necessarily concerted) of (39) to (34) and CO_2 . Pd/C is involved in the first (i.e., autoxidation) step, as (35) was recovered unchanged in

(Eq. 22)

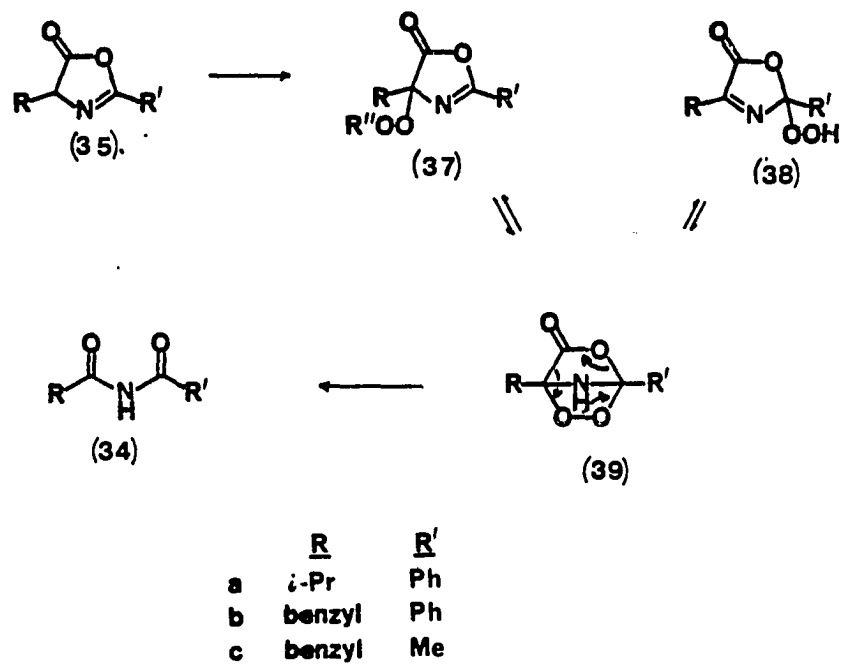


(Eq. 23)



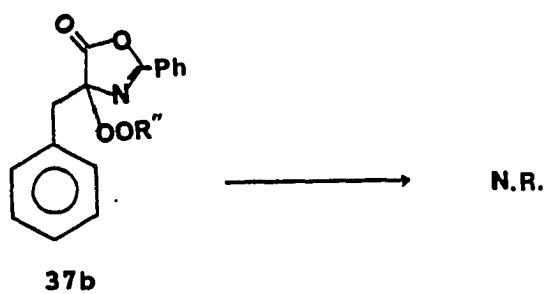
its absence. The yield was lowered somewhat when acetic anhydride was present by the trapping of some of the hydroperoxide (37b) ($R'' = H$) as the perester (37b) ($R'' = Ac$) in 22% yield during the preparation of (34b) in acetic anhydride-acetic acid. An attempted selective aminolysis of perester (37b) ($R'' = Ac$) to hydroperoxide (37b) ($R'' = H$) with morpholine gave no imide (34b) (Eq. 24), probably because of attack on the lactone carbonyl group.

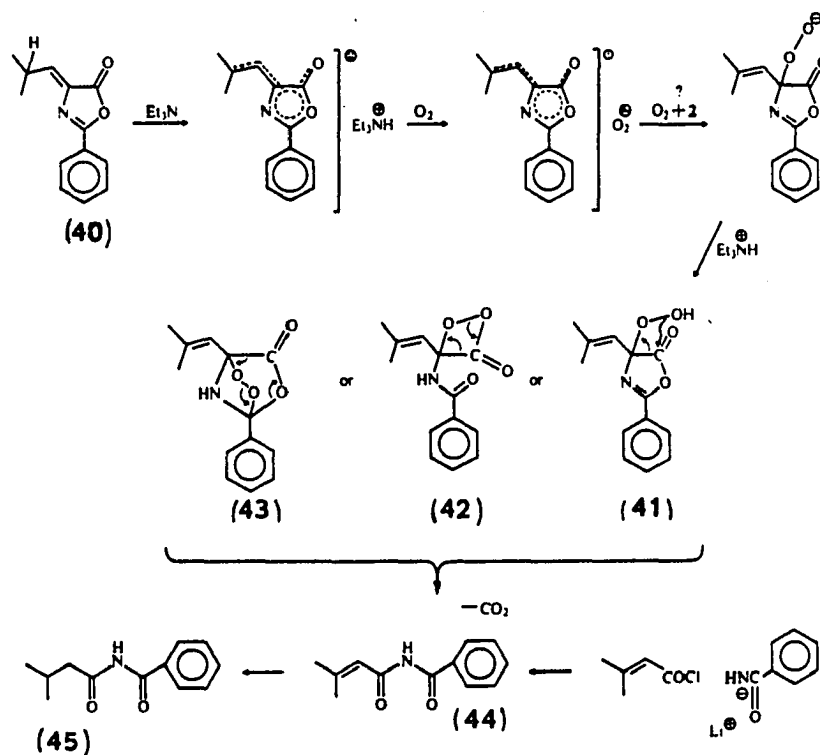
The mechanism which we have proposed is analogous to that postulated independently by Bisson and Warnhoff [41] (Scheme VII), who found that when isobutylidene azlactone (40) was allowed to react with



Scheme VI: Synthesis of unsymmetrical acrylic imides from azlactones

(Eq. 24)





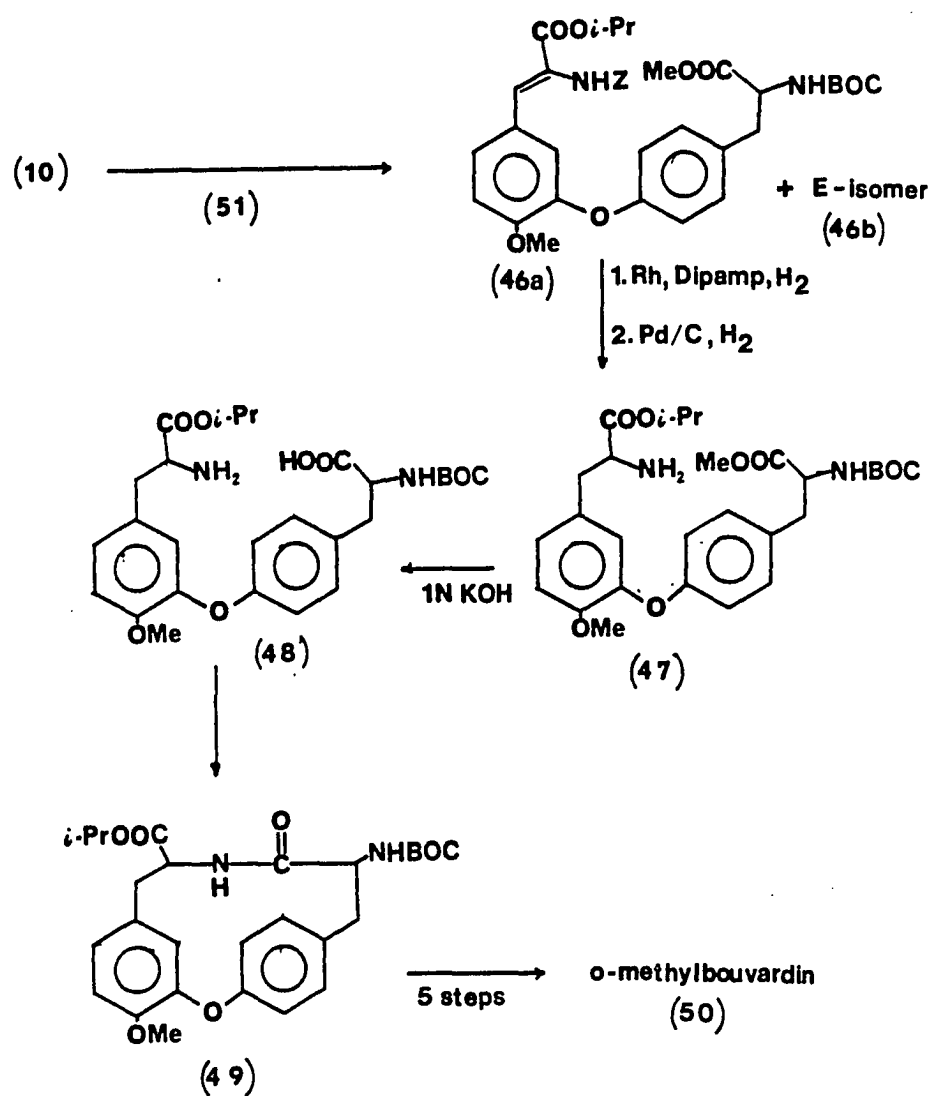
Scheme VII: Bisson's proposed mechanisms of unsymmetrical imide formation

triethylamine in acetonitrile solution, β,β -dimethylacrylyl imide (44) was isolated in 50% yield. This was then hydrogenated to give imide (45). They postulated possible hydroperoxide (41) and peroxide (42) and (43) intermediates, none of which were isolated.

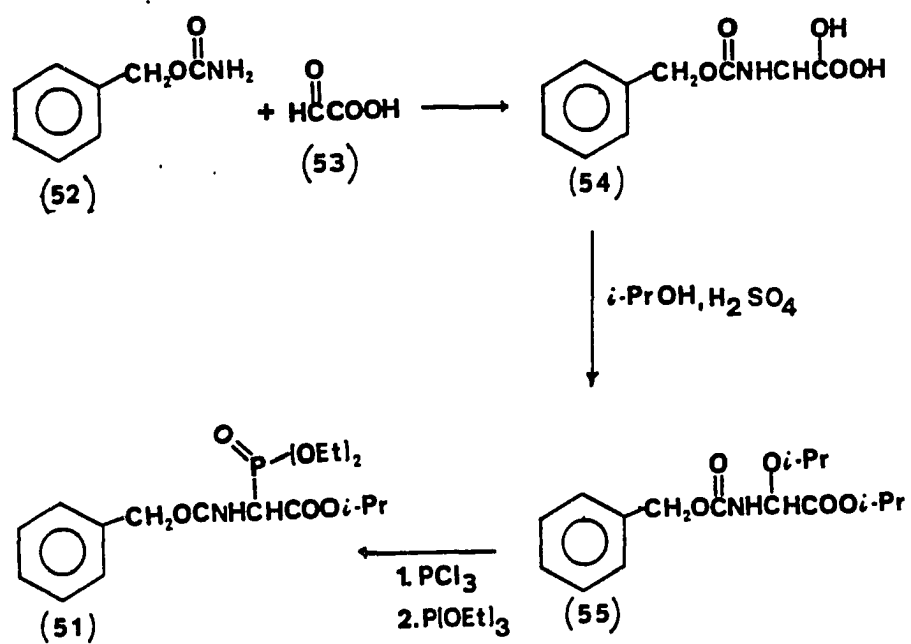
The third and final route tried (Scheme VIII), which we feel will ultimately lead to deoxybouvardin (2), involved making a dehydro-amino acid ester (46a).

The synthesis of the suitably protected dehydroamino ester (46a) was based on a method by Schmidt [20]. Schmidt reacted an *N*-acylphosphorylglycine ester (16) with *o*-anisaldehyde to get *N*-benzyloxycarbonyl-*O*-methoxyphenyl-dehydroalanine ethyl ester in 82% yield. We already had a methyl ester on the right half of compound (10), which we wanted to saponify selectively in the (47) ---->(48) step, and since the rate constant for saponification of a methyl ester is only about twice that of an ethyl ester whereas it is about 15 times that of an isopropyl ester, we decided to make the isopropyl ester (51). This was done as shown in (Scheme IX).

Glyoxylic acid (53) was condensed with benzyl carbonate (52) to give α -hydroxy-*N*-benzyloxy-carbonylglycine (54) [42]. This was then reacted with isopropanol with a catalytic amount of H_2SO_4 to give isopropyl α -isopropoxy-*N*-benzyloxycarbonylglycinate (55). (55) was next reacted with phosphorous trichloride and triethyl phosphite to give the desired isopropyl 2-benzyloxycarbonylamino-2-diethoxyphosphorylacetate (51). (51) was metallated with NaH in THF and reacted with (10), in a Wadsworth-Emmons (Horner) modification of the



Scheme VIII: Synthesis of O-methyldeoxybouvardin via dehydroamino acid route

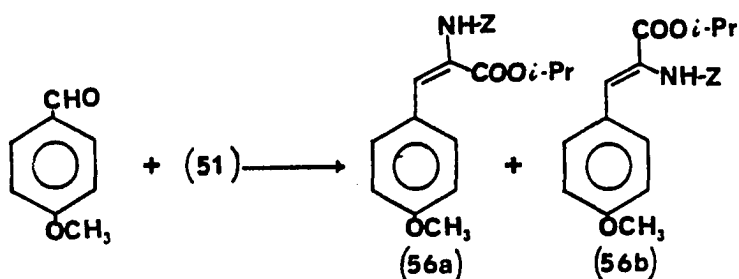


Scheme IX: Synthesis of N-Acylphosphorylglycine ester (5)

Wittig reaction [43-44], to give the optically active N-benzyloxycarbonyldehydroamino acids (46a) and (46b) in 62% yield.

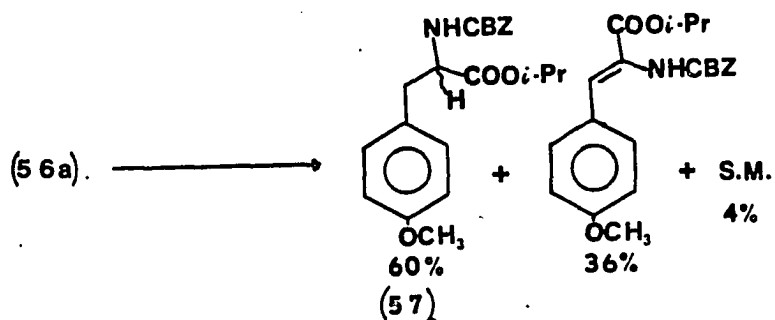
Since (46a) and (46b) were valuable and in short supply, we decided to do some hydrogenations using model compounds (56a) and (56b). These dehydroamino acids were synthesized analogously to (46a) and (46b) by metallating isopropoxy-N-benzyloxycarbonylglycinate (51) in THF with *p*-anisaldehyde (Eq. 25).

(Eq. 25)

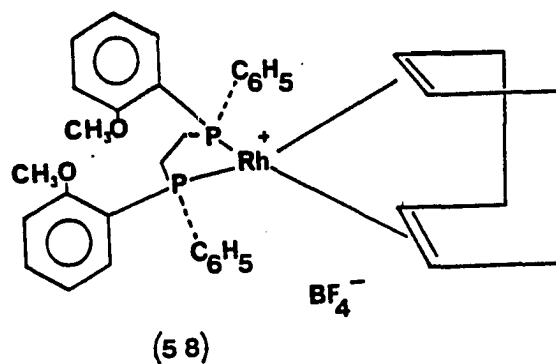


To learn the properties of the reduced materials with a cheaper catalyst than rhodium/DIPAMP, 100% E (56a) was hydrogenated using PtO₂ in methanol for 2 hours at room temperature. Unexpectedly, the Z isomer (56b) was obtained along with the expected hydrogenated product (57) (Eq. 26). These results led us to believe the mixture of (46a) and (46b) obtained from the reaction of (10) + (51) might not have to be separated, but could be isomerized to the equilibrium mixture of 90% Z and 10% E, which could then be reduced quite selectively to the desired stereoisomer of (47).

(Eq. 26)



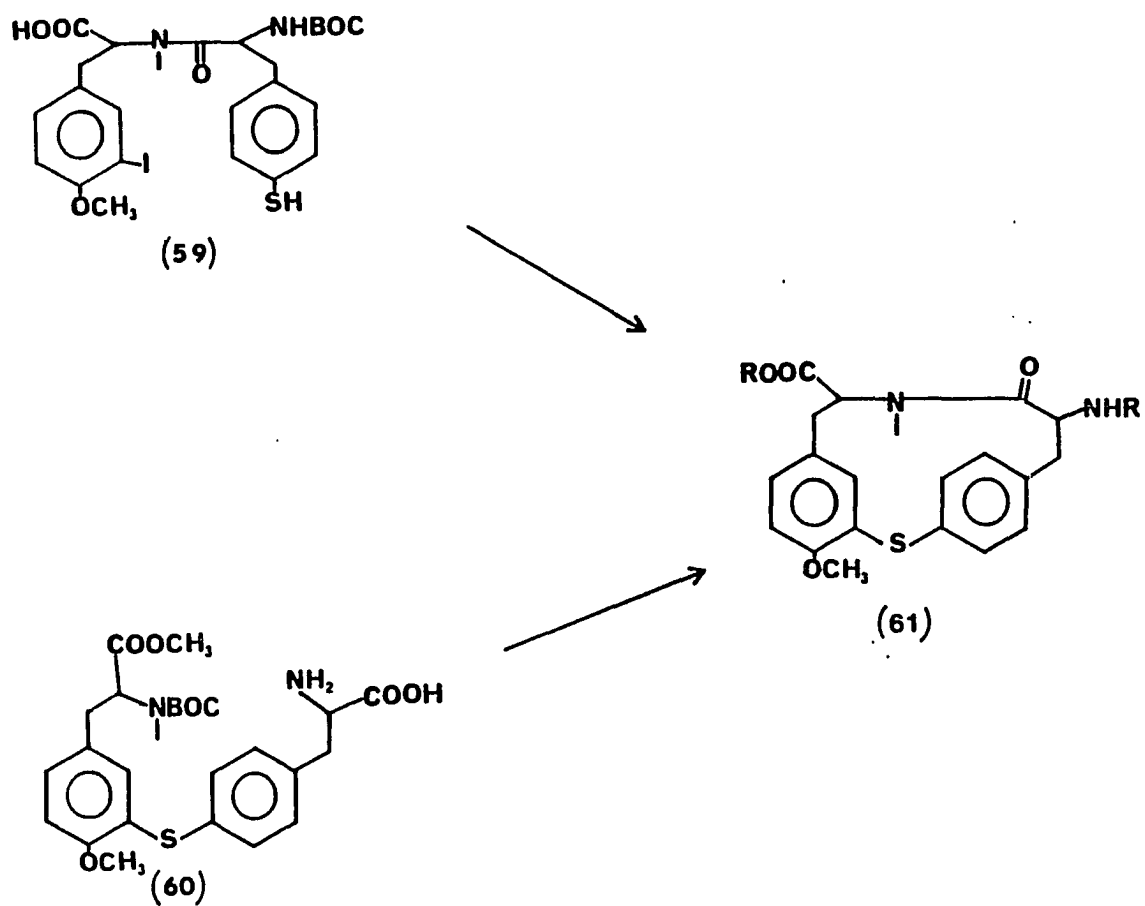
This is as far as the synthesis has been taken. The next four steps to get to the 14-membered ring (49) are only proposed at this point (Scheme VIII). The dehydroamino acid (46a) will be hydrogenated with the chiral rhodium catalyst DIPAMP [45] (58), then hydrogenated with Pd/C to remove the carbobenzyloxy group to give (47). Removal of the methyl ester using potassium hydroxide (1N) in methanol for 15 minutes followed by acidification should give (48). This is now ready to be closed to the 14-membered ring (49). Reactions closely analogous to the last five steps have all been performed previously so no trouble is anticipated here.



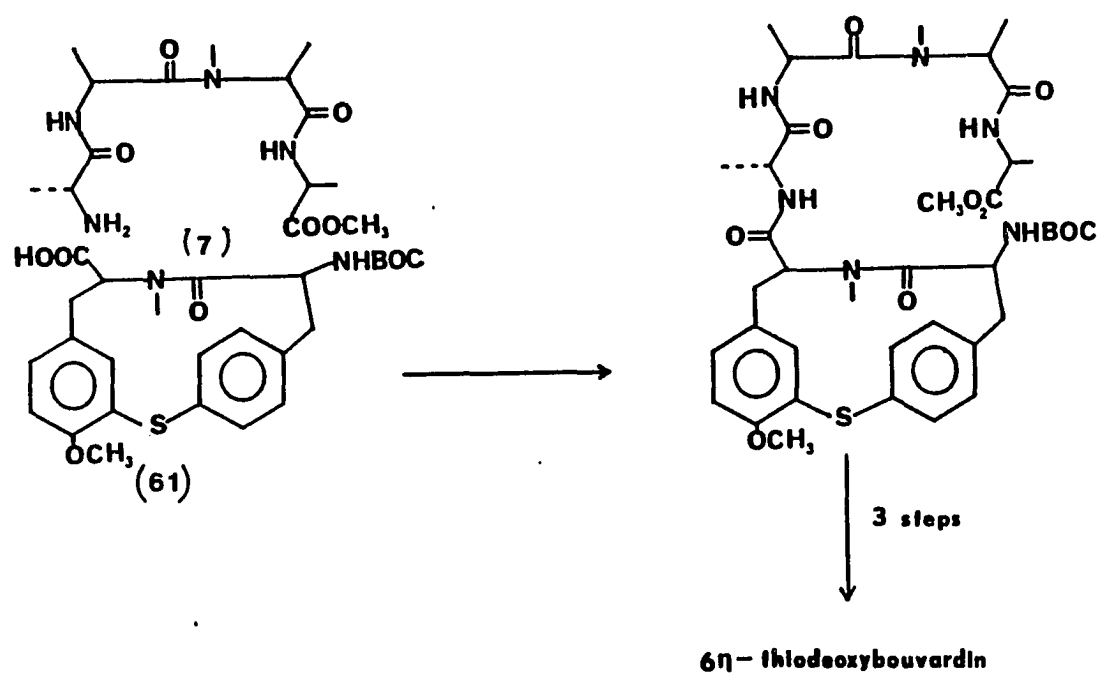
Part II: 5 η -Thiodeoxybouvardin (4):
Progress Towards its Synthesis

Bouvardin (1) went through complete preclinical testing before it was decided it did not have sufficiently broad activity to warrant the expense of clinical testing. Cassady and Douros in 1980 concluded a discussion of bouvardin (1) with ". . . it is a unique chemical entity which merits attention in terms of analogue synthesis especially since no work on analogues has been reported to date." [46]

The first analogue we decided to synthesize was 5 η -thiodeoxybouvardin (4). Again, as with deoxybouvardin (2), the main problem was to synthesize the 14-membered ring. We wanted to try two possible routes to do this (Scheme X). Once the 14-membered ring was formed it could be combined with tetrapeptide (7) (already made for the hexapeptide (5) synthesis) (Scheme XI).

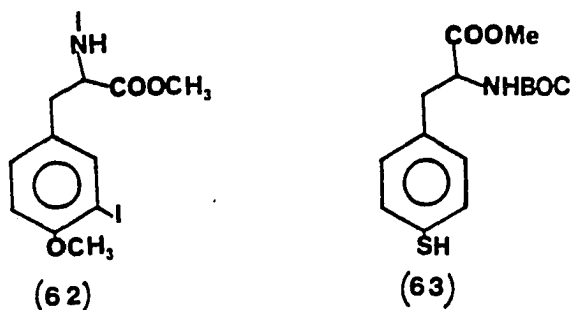


Scheme X: Possible routes to 14-membered ring of 5n-thiodeoxybouvardin (4)

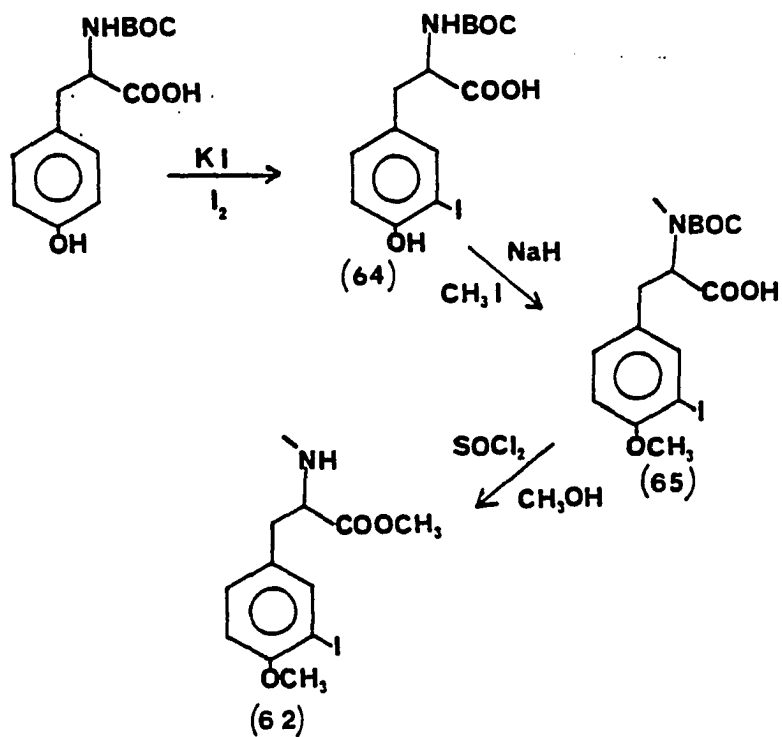


Scheme XI: Synthesis of 5η-thiodeoxybouvardin (4)

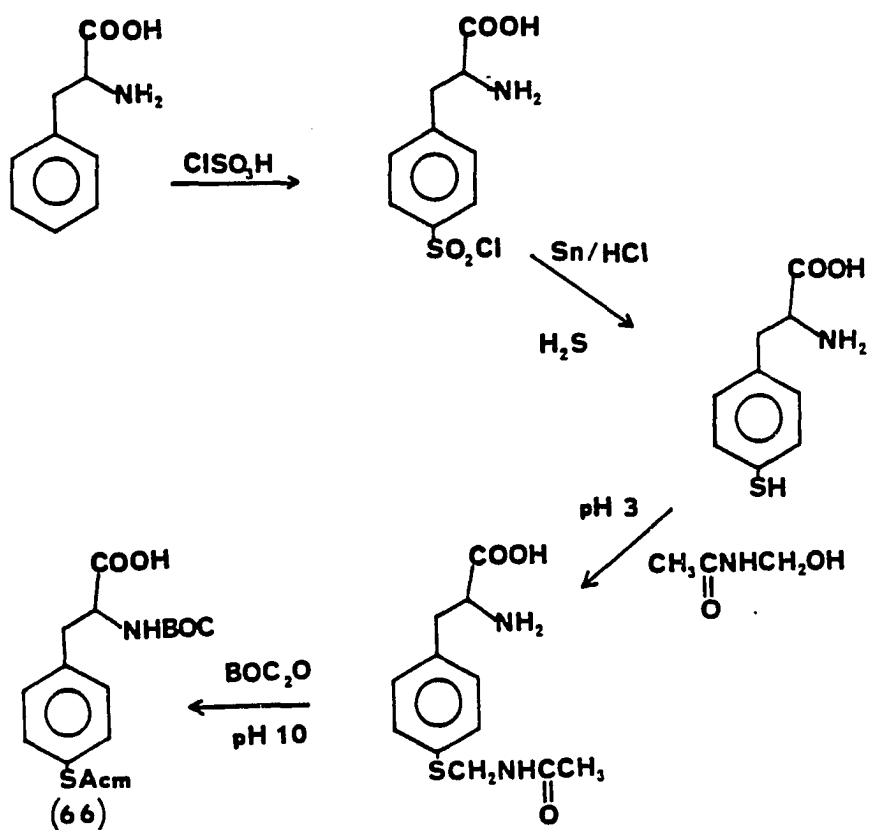
The first route we tried was to synthesize dipeptide (59). The dipeptide was broken up into the left half (62) and the right half (63). The left half was made in the following manner (Scheme XII). Boc-tyrosine was treated with KI and I_2 to give 3-iodo-Boc-tyrosine (64). This was then methylated using NaH and methyl iodide to give (65). Thionyl chloride in methanol removed the Boc group, along with forming the methyl ester, giving the left half (62).



The right half of dipeptide (59) was synthesized using the method of Escher [47] (Scheme XIII). L-Phenylalanine was treated with chlorosulfonic acid, yielding 4-chlorosulfonylphenylalanine. This was reduced with tin and H_2S to give 4-mercaptophenylalanine. The thiol group was protected using N-(hydroxymethyl)acetamide (=ACM), and the nitrogen protected with Boc via Boc_2O , giving (66).



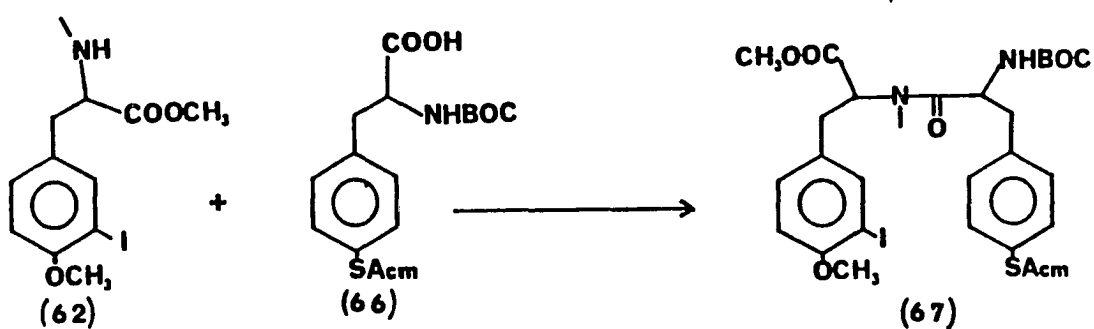
Scheme XII: Synthesis of left half of dipeptide (59)



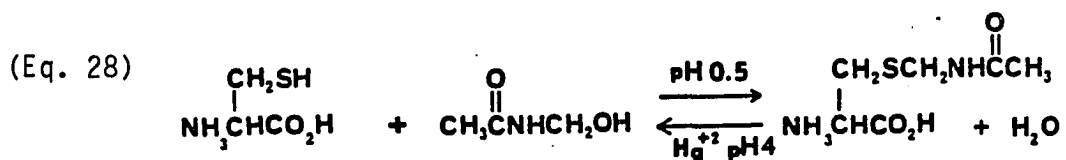
Scheme XIII: Synthesis of right half of dipeptide (59)

(62) and (66) were coupled (Eq. 27) using the water soluble DCC coupling reagent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), giving dipeptide (67).

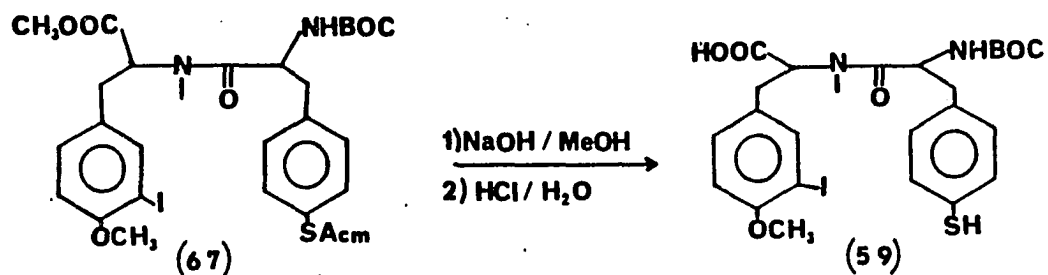
(Eq. 27)



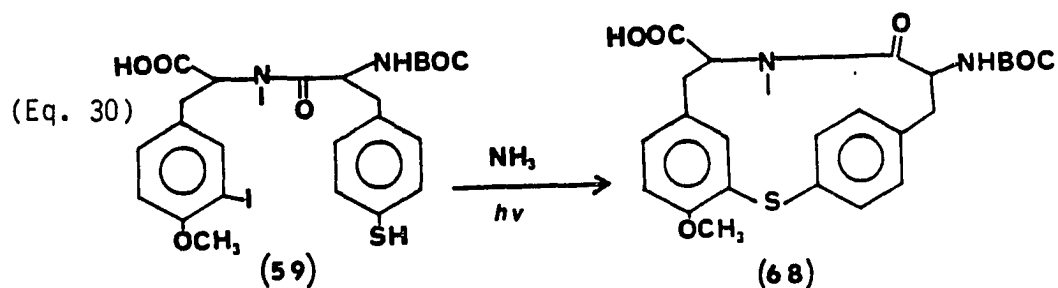
The ACM protecting group is normally removed using mercuric acetate [48] (Eq. 28). In our case this was not possible since the dipeptide (67) was not water soluble. Instead we were able to remove the acetamidomethyl protecting group using 2N NaOH in methanol and then upon acidification obtain the thiol group (59) (Eq. 29).



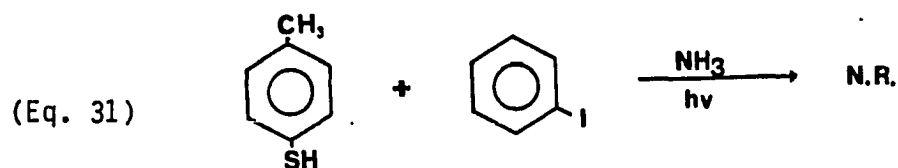
(Eq. 29)



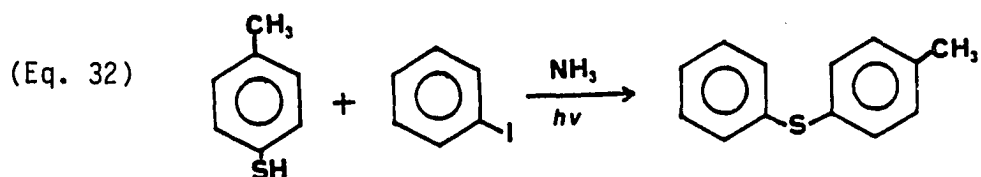
The attempted photolysis of (59) a number of times in liquid NH₃ gave no 14-membered ring (68) (Eq. 30), and thus the second route was tried.



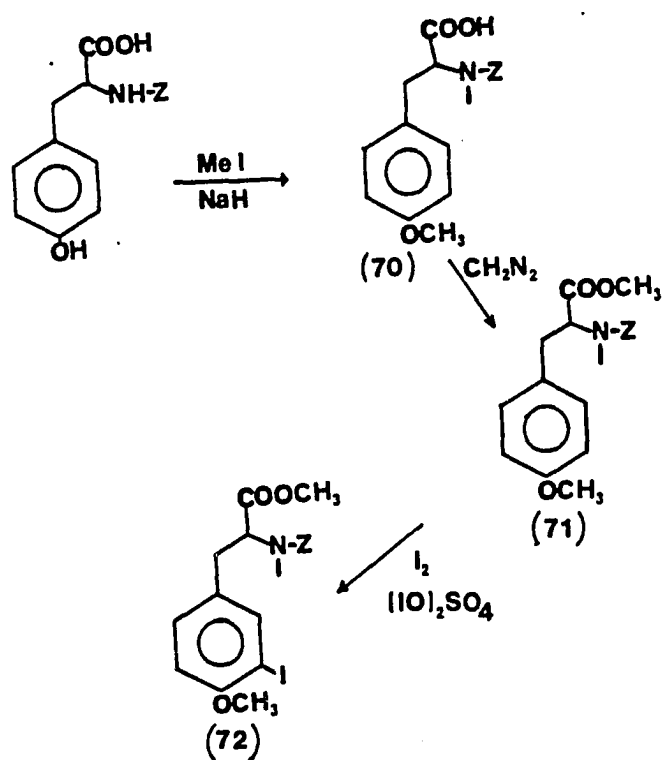
Before we tried another photolysis we decided to try a model compound to be sure conditions were right for diaryl sulfide synthesis. Professor J. F. Bunnett reported that the reaction in Eq. 31 was tried by a former student of his without any success.



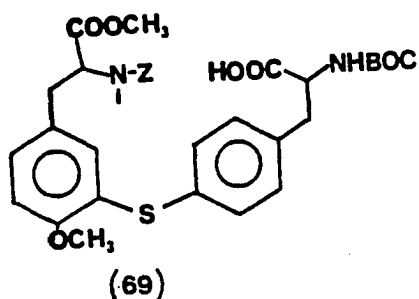
Since this was a very pertinent reaction for us, we decided to try it ourselves using *p*-thiophenol and iodobenzene (Eq. 32). Since after photolysis and workup the thioether was obtained in 65% yield, we decided to proceed with our synthesis.



Again we broke the target compound (69) into two halves. The right half (63) had already been synthesized and hence only the left half of the molecule (72) needed to be made (Scheme XIV). *N*-Z-L-tyrosine was methylated using methyl iodide to yield (70), which was treated with diazomethane to give (71). Iodine and iodyl sulfate gave the desired left half (72).



Scheme XIV: Synthesis of left half of target compound (69)



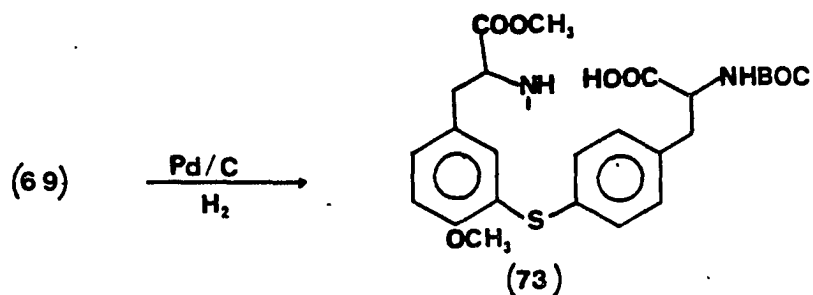
Photolysis of (72) and (63) gave the desired protected thioether (69) in 43% yield (Eq. 33).



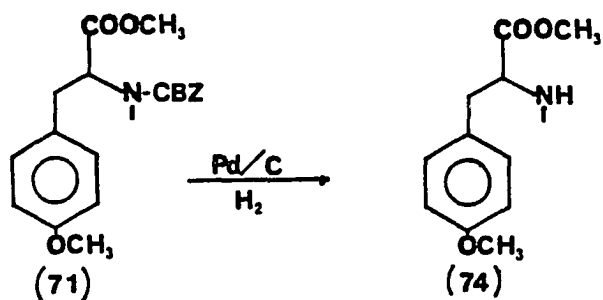
Four attempts to remove the carbobenzyloxy protecting group using hydrogen and palladium on carbon proved unsuccessful (Eq. 34). A model compound (71) was tried to see if our catalyst was bad (Eq. 35), but the desired amine (74) was obtained in quantitative yield, so the catalyst was good. Therefore, it appears the sulfur in (69) is poisoning the catalyst.

A way which would avoid the sulfur poisoning of the catalyst was to leave the carbobenzyloxy group off and use a compound previously made in the dipeptide synthesis (62). The combination of (62) with (63) would give a compound (73) which in one step could be closed to the fourteen membered ring (Eq. 36). Unfortunately, two attempts to

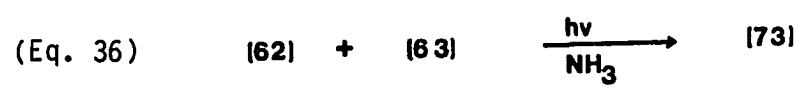
(Eq. 34)



(Eq. 35)



bring this reaction about did not succeed; only small amounts (if any) of (73) were formed, with the major products being (74) and (63). At this time compound (73) has not been successfully prepared. A likely route to it is removal of the benzyl group of (69) by some method other than H_2/Pd , e.g., Royer's method using palladium-poly(ethylenimine) "ghosts" [49], or with Na/NH_3 .



EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-360L, or Bruker WM-250 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS). Infrared (IR) spectra were run on a Perkin-Elmer 983 infrared spectrophotometer. Elemental analyses were performed by the University Analytical Center. All melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected.

4-Methoxybenzyl Alcohol

NaBH_4 (0.0147 mole) was stirred with 50 ml of dry methanol for 5 min. Anisaldehyde (0.0147 mole) in 10 ml of methanol was added dropwise over 15 min as the solution boiled vigorously. After stirring 6 h at room temperature, the solution was quenched with 25 ml of water and extracted 2 x 100 ml of 50/50 ethyl acetate/benzene. The organic layer was dried over MgSO_4 and evaporated under reduced pressure, leaving 4-methoxybenzyl alcohol as a clear liquid (1.80g, 90% yield); ^1H NMR (CDCl_3): δ 7.22 (~d, $J = 8.1$ Hz, 2H), 6.84 (~d, $J = 8.1$ Hz, 2H), 4.51 (s, 2H), 3.76 (s, 3H), 2.81 (bs , 1H).

4-Methoxybenzyl Chloride

To a stirred solution of 7.5 mmole of N-chlorosuccinimide in 40 ml of anhydrous methylene chloride under nitrogen was added

dropwise at 0°C 7.5 mmole of dimethyl sulfide. After cooling to -20°C, 7.5 mmole of 4-methoxybenzyl alcohol in 5 ml CH_2Cl_2 was added gradually over a few min. The solution was warmed to 0°, stirred for 1h, and poured into 30 ml of ice - NaCl. After shaking and separating the mixture, the aqueous phase was extracted with two 40 ml portions of ether. The combined organic phases were washed with five 25 ml portions of cold brine solution and dried (MgSO_4). Evaporation of solvents gave 90% yield of 4-methoxybenzyl chloride; ^1H NMR (CDCl_3): δ 7.24 (~d, J = 8.0 Hz, 2H), 6.79 (~d, J = 8.0 Hz, 2H), 4.46 (s, 2H), 3.66 (s, 3H).

(21), Reduction Product of Aldehyde (10)

NaBH_4 (0.23 mmole) in 5 ml of dry methanol was stirred for 5 min and (10) (0.23 mmole) in 5 ml of MeOH was added dropwise over 15 min as the solution bubbled vigorously. After 6 h stirring at room temperature the solution was quenched with 5 ml of water and extracted 2 x 30 ml of EtOAc. The EtOAc solution was dried over MgSO_4 , filtered, and evaporated under reduced pressure, giving (21) as a clear oil in 85% yield; ^1H NMR (CDCl_3): δ 7.67 (dd, J = 8.4, 1.9 Hz, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.09 (~d, J = 8.7 Hz, 2H), 6.90 (~d, J = 8.7 Hz, 2H), 5.02 (d, J = 8.1 Hz, 1H), 4.49 (s, 2H), 4.57 (dd, J = 12.6, 4.7 Hz, 1H), 3.95 (s, 3H), 3.72 (s, 3H), 3.06 (m, 2H), 1.43 (s, 9H).

(22), Chlorination of Benzyl Alcohol (21)

To a stirred solution containing 0.175 mmole of N-chlorosuccinimide in 4 ml of anhydrous methylene chloride under nitrogen was added dropwise at 0°C 0.175 mmole of dimethyl sulfide. After cooling to -20°C, 0.175 mmole (21) in 2 ml CH₂Cl₂ was added over a few min. After warming to 0°C, stirring for 1 h and pouring into 10 ml of ice - NaCl, the aqueous phase was extracted with two 20 ml portions of ether. The combined organic layers were washed with five 15 ml portions of cold brine solution and dried (MgSO₄). Filtration and evaporation of solvents left a 90% yield of (22); ¹H NMR (CDCl₃): δ 7.69 (dd, J = 8.5, 1.9 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.00 (~d, J = 8.7 Hz, 2H), 6.90 (~d, J = 8.7 Hz, 2H), 5.05 (d, J = 8.3 Hz, 1H), 4.57 (dd, J = 12.8, 4.5 Hz, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.71 (s, 3H), 3.06 (m, 2H), 1.44 (s, 9H).

Azlactone (29a)

Anisaldehyde (6.25 mmole), hippuric acid (5.5 mmole), fused sodium acetate (0.0305 mmole), and 8 ml of acetic anhydride were heated on a steam bath for 15 min. The yellow precipitate which formed on cooling was filtered and washed with cold glacial acetic acid, leaving (29a), mp 153-154°C, 65% yield; ¹H NMR (CDCl₃): δ 8.18 (~d, J = 8.7 Hz, 2H), 8.15 (~t, J = 6.0 Hz, 2H), 7.59 (~t, J = 7.0 Hz, 2H), 7.52 (~t, J = 7.4 Hz, 1H), 7.21 (s, 1H), 6.98 (~d, J = 8.9 Hz, 2H), 3.89 (s, 3H).

Azlactone (29b)

Benzaldehyde (0.028 mole), hippuric acid (0.018 mole), fused sodium acetate (0.017 mole), and 40 ml of acetic anhydride were heated on a steam bath for 15 min. The yellow precipitate was filtered and washed with cold glacial acetic acid, leaving (29b), mp 140-141°C, 63% yield; $^1\text{H NMR}$ (CDCl_3): 8.23-8.15 (m,4H), 7.65-7.36 (m,6H), 7.23 (s,1H).

Azlactone (29c)

Hippuric acid (0.067 mole), fused sodium acetate (0.0073 mole), and 30g of acetone (2.01 mole) were refluxed 6 h at 110°C. The orange solution was chilled and poured over 200 ml of ice water. The orange precipitate was filtered and dissolved in 100 ml ether. This solution was washed with Na_2CO_3 (3 x 50 ml), dried over MgSO_4 , and evaporated under reduced pressure, giving (29c) (30% yield, mp 94-97°C); $^1\text{H NMR}$ (CDCl_3): δ 8.05 (dd, $J = 6.9$ Hz,2H), 7.55-7.44 (m,3H), 2.41 (s,3H), 2.35 (s,3H).

 α -Acyllamino Alcohols from Azlactones

Azlactones (29a-c) (1.5g) in dry acetic acid (50 ml) containing 10% palladium on activated carbon (1.2g) were shaken for 10 h under 3 atm hydrogen. Filtration, evaporation at room temperature, and chromatography over silica gel with hexane/ethyl acetate (6/4) gave (31a-c) with details as follows:

α -Acylamino Alcohol (31a)

(31a), mp 104-106°C, 50% yield, was identified by high resolution MS: M/e 285.140 (M+.); calc. for (M+.) 285.144. ^1H NMR (CDCl_3): δ 7.66 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.3 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 7.5 Hz, 1H), 4.3 (m, 1H), 3.76 (dd, J = 11.6, 3.8 Hz, 1H), 3.66 (dd, 1H, J = 11.6, 5.0 Hz, 1H), 3.3 (bs, 1H), 2.91 (d, J = 7.1 Hz, 2H).

 α -Acylamino Alcohol (31b)

(31b), mp 133-134°C, 60% yield, Anal. calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$: C, 75.29; H, 6.67; N, 5.49. Found: C, 75.29; H, 6.97; N, 5.35. ^1H NMR (CDCl_3): δ 7.67 (~d, J = 8.4 Hz, 2H), 7.55-7.25 (m, 8H), 6.5 (bd, J = 7.5 Hz, 1H), 4.36 (m, 1H), 3.76 (dd, J = 11.2, 3.7 Hz, 1H), 3.69 (dd, J = 11.2, 5.0 Hz, 1H), 2.99 (d, J = 7.2 Hz, 2H).

 α -Acylamino Alcohol (31c)

(31c), mp 75-77°C, was obtained in 60% yield, Anal. calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$: C, 69.56; H, 8.21; N, 6.76. Found: C, 69.16; H, 8.11; N, 6.92. ^1H NMR (CDCl_3): δ 7.75 (~d, J = 8.4 Hz, 2H), 7.39 (~t, J = 7.6 Hz, 1H), 7.29 (~t, J = 8.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 1H), 4.49 (bs, 1H), 3.86 (m, 1H), 3.68 (d, J = 3.6 Hz, 2H), 1.95 (octet, J = 7.0 Hz, 1H), 0.91 (d, J = 6.7 Hz, 6H).

Unsymmetrical Imide (34b)

After N-Benzoyl-DL-phenylalanine (1.0g) in acetic anhydride (20 ml) was heated at 100°C for 30 min and the mixture was cooled to 25°C, 10% Pd/c (0.1g) was added and the mixture was stirred overnight while oxygen was bubbled through. After the mixture was filtered through Celite, washed with 3 x 30 ml of ether, and the ether evaporated, the residual oil was subjected to LC (silica). Elution with ethyl acetate-hexane gave (34b) in 60% yield; mp 132-133°C; ^1H NMR (CDCl_3): 9.06 (bs, 1H), 7.84 (dd, $J = 7.0, 1.5$ Hz, 2H), 7.58 (tt, $J = 7.4, 1.2$ Hz, 1H), 7.45 (dd, $J = 6.5, 1.3$ Hz, 2H), 7.34 (m, 5H), 4.34 (s, 2H). Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.02; H, 4.31; N, 4.35.

Unsymmetrical Imide (34a)

The above procedure with N-benzoyl-DL-valine (500 mg, 2.26 mmole) gave (34a) (216 mg, 50%); mp 149-150°C; ^1H NMR (CDCl_3): 8.5 (bs, 1H), 7.86 (~d, $J = 7.9$ Hz, 2H), 7.60 (~t, $J = 7.3$ Hz, 1H), 7.50 (~t, $J = 7.4$ Hz, 2H), 3.66 (heptet, $J = 6.8$ Hz, 1H), 1.26 (d, $J = 6.8$ Hz, 6H); MS: M/e 191(M+.), 122, 105, 77, 70. Anal. calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$: C, 68.90; H, 6.85; N, 7.32. Found: C, 68.90, H, 7.00; N, 7.31. A crystal of (34a), grown by diffusion of pentane into chloroform solution, with crystal dimensions 0.4 x 0.1 x 0.1 mm, was subjected to x-ray analysis. Syntex P2 four-circle diffractometer. Cell constants from 25 reflections with $7 \leq 2\theta \leq 14^\circ$. No

absorption correction. $2 \theta_{\max} = 45^\circ$. Range of hkl: 0-9, 0-9, 0-14. Three check reflections collected after every 200 data points showed no appreciable crystal decay. 385 of 746 reflections with $I > 3 \sigma(I)$ used in F^2 refinement. $R_{\text{int}} = 0.048$. Structure solved by Multan 80 (Main et al., 1980) [50] using 180 highest E values; 11 non-H atoms found in first E map; other 3 non-H atoms found in first E map; other 3 non-H atoms put in calculated positions. Refinement of non-H atoms with isotropic temperature factors gave $R = 0.102$, final refinement (126 parameters) was of non-H atoms with anisotropic temperature factors; $wR = 0.054$, $S = 2.0$, weighting scheme of Corfield, Doedens & Ibers (1967) [51], with $p = 0.04$. $(\Delta/\sigma)_{\max} = 0.007$. $\Delta\rho = -0.3 - 0.3 \text{ e\AA}^{-3}$. Atomic scattering factors from International Tables for X-ray Crystallography (1962) [52]. Least squares refinement program NUCLS (Doedens and Ibers, 1967) [53], plotter program ORTEP (Johnson, 1965) [54] (Tables 3-5).

Table 3. Final Atomic Positional Parameters ($\times 10^3$) and Isotropic Thermal Parameters for H Atoms

	<u>x</u>	<u>y</u>	<u>z</u>	<u>B(A²)</u>
HC(2)	41	- 953	823	4.6
HC(3)	-161	-1048	703	6.2
HC(4)	-274	- 990	481	6.5
HC(5)	-204	- 828	383	6.1
HC(6)	1	- 741	491	3.8
HC(9)	393	- 581	509	5.1
H(1)C(10)	547	- 450	592	6.7
H(2)C(10)	536	- 497	758	6.7
H(3)C(10)	385	- 452	679	6.7
H(1)C(11)	642	- 629	519	9.4
H(2)C(11)	539	- 733	545	9.4
H(3)C(11)	628	- 683	685	9.4
HN	227	- 719	554	3.3

Table 4. Anisotropic Temperature Factors ($\times 10^3$) of the Form
 $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$

	<u>β_{11}</u>	<u>β_{22}</u>	<u>β_{33}</u>	<u>β_{12}</u>	<u>β_{13}</u>	<u>β_{23}</u>
C(1)	13(2)	7(1)	9(2)	-2(1)	0(2)	-1(1)
C(2)	14(2)	8(1)	17(2)	2(1)	0(2)	0(2)
C(3)	16(3)	7(1)	21(2)	3(2)	-3(2)	-1(2)
C(4)	19(3)	9(1)	19(3)	5(2)	-2(3)	-2(2)
C(5)	18(2)	16(2)	14(2)	0(2)	9(2)	-4(2)
C(6)	18(2)	4(1)	16(2)	2(1)	4(2)	1(1)
C(7)	16(2)	5(1)	12(2)	2(1)	-1(2)	1(1)
C(8)	15(3)	7(1)	9(2)	0(1)	-2(2)	-1(1)
C(9)	22(3)	9(1)	11(2)	-1(2)	-2(2)	5(1)
C(10)	38(3)	5(1)	34(4)	8(2)	-5(4)	2(2)
C(11)	20(3)	17(2)	36(4)	4(2)	-7(3)	6(3)
N	14(2)	6(1)	9(1)	1(1)	0(2)	0(1)
O(7)	25(2)	8(1)	10(1)	4(1)	2(1)	1(1)
O(8)	19(1)	9(1)	11(1)	4(1)	0(1)	-1(1)

Table 5. Structure Factors

L	K	FO	FC	L	K	FO	FC	L	K	FO	FC	L	K	FO	FC
***	H = 0	***													
0	2	306	312	0	7	145	151	7	2	76	75	5	1	61	67
0	3	72	78	0	8	82	93	7	5	98	94	5	2	100	100
0	4	78	38	0	9	75	86	7	8	43	61	5	3	125	123
0	5	401	411	0	10	92	79	8	1	71	66	5	4	66	58
0	6	306	293	0	11	75	60	8	2	61	68	5	5	97	97
0	7	346	337	0	13	59	80	8	3	75	85	5	6	64	52
0	9	164	158	1	1	218	220	8	4	66	74	5	6	104	104
0	14	91	98	1	2	923	926	8	6	156	140	5	9	54	34
2	0	801	844	1	3	99	99	8	8	75	63	5	10	55	63
2	1	182	180	1	4	175	181	9	1	67	83	6	0	101	112
2	2	273	270	1	5	288	285	9	4	66	62	6	1	74	78
2	3	266	263	1	7	203	201	***	H = 2	***		6	3	139	141
2	4	269	284	1	9	91	72	0	0	144	143	6	5	75	80
2	5	263	266	1	10	57	56	0	1	133	134	6	6	98	91
2	6	88	91	2	1	569	585	0	2	386	380	6	9	57	34
2	7	234	248	2	2	76	75	0	3	379	380	7	0	79	62
2	8	50	65	2	3	137	137	0	4	68	51	7	1	91	89
2	9	110	120	2	4	131	135	0	6	93	99	7	3	79	85
2	12	73	80	2	5	73	65	0	7	80	88	7	4	139	142
2	14	68	71	2	6	376	370	0	12	125	123	7	5	70	71
4	0	294	288	2	7	81	96	1	0	426	422	7	7	86	95
4	1	318	319	2	8	133	140	1	1	418	418	7	8	57	41
4	2	46	44	2	11	66	61	1	2	516	534	7	9	63	58
4	3	101	105	2	13	79	62	1	3	567	569	8	3	95	99
4	4	102	108	3	1	141	143	1	4	236	244	8	5	75	79
4	5	217	219	3	2	117	110	1	5	183	185	8	6	99	98
4	6	135	137	3	3	230	227	1	8	152	155	9	0	87	74
4	7	148	147	3	4	121	125	1	10	57	70	9	2	60	54
4	8	65	68	3	5	50	45	1	11	75	71	9	3	64	61
4	9	95	99	3	7	107	100	2	0	521	508	***	H = 3	***	
4	10	85	89	3	8	56	65	2	1	324	324	0	1	244	244
4	12	57	59	3	9	71	78	2	2	444	460	0	3	267	272
6	0	314	319	4	1	267	263	2	3	362	361	0	4	178	179
6	1	70	72	4	2	48	50	2	4	158	155	0	6	142	147
6	2	123	124	4	3	140	142	2	5	302	299	0	7	101	94
6	5	98	104	4	4	144	141	2	6	167	161	0	11	87	93
6	6	93	88	4	5	74	66	2	7	152	159	0	12	62	55
6	7	236	237	4	6	56	44	2	9	79	85	1	1	96	93
6	8	80	84	4	7	50	57	2	10	76	98	1	2	195	197
6	9	118	111	4	8	82	79	2	12	78	79	1	3	477	464
6	11	64	72	4	10	85	77	3	C	89	87	1	4	314	318
8	0	95	91	5	1	167	181	3	2	166	163	1	5	252	251
8	1	79	87	5	2	101	104	3	4	268	261	1	7	82	65
8	3	82	84	5	3	61	65	3	5	140	130	1	8	105	111
8	4	146	155	5	4	68	68	3	6	120	117	1	9	142	143
8	5	66	68	5	5	90	87	3	9	83	86	1	10	130	133
8	6	56	43	5	6	110	112	3	10	84	67	1	11	117	112
8	7	107	105	5	7	50	61	4	0	47	49	2	1	152	154
8	8	60	56	5	8	68	76	4	1	124	127	2	2	152	147
***	H = 1	***		5	9	80	76	4	2	274	267	2	3	196	188
0	1	727	715	6	1	160	155	4	3	118	111	2	4	274	275
0	2	580	550	6	2	99	97	4	4	71	77	2	5	157	149
0	3	416	403	6	4	74	80	4	6	59	61	2	6	82	82
0	4	241	244	6	5	108	109	4	8	60	59	2	7	71	59
0	5	107	104	6	6	88	95	4	10	71	60	2	8	68	62
0	6	202	190	6	8	89	91	4	12	69	71	3	1	98	98
				6	10	76	75	5	0	103	103	3	2	312	311

Table 5. -- Continued

L	K	FD	FC	L	K	FD	FC	L	K	FD	FC
3	3	141	138	3	5	123	121	8	2	59	47
3	4	180	183	3	6	93	100	***	H = 6	***	
3	5	55	64	3	8	75	70	0	0	240	243
3	6	77	68	4	0	47	41	0	1	90	90
3	7	97	98	4	1	96	91	0	3	101	92
3	11	85	85	4	2	96	90	0	4	73	70
4	2	62	56	4	3	93	95	0	5	109	106
4	3	105	101	4	5	110	106	0	7	190	191
4	4	143	134	4	9	62	80	1	0	73	83
4	5	115	106	5	2	66	75	1	6	97	100
4	7	65	54	5	3	62	70	1	7	111	111
5	2	131	127	5	4	117	115	2	0	171	180
5	3	76	83	6	C	67	70	2	1	87	93
5	5	52	51	6	1	94	90	2	2	107	112
5	7	94	49	6	2	112	127	2	3	69	72
6	2	57	65	6	3	85	80	2	4	53	45
6	3	51	36	6	4	56	53	2	5	53	59
6	4	68	66	7	0	84	80	2	7	111	113
6	5	77	74	7	1	89	89	3	0	69	59
6	9	58	56	7	3	106	107	3	1	89	87
7	1	120	128	7	5	60	71	3	4	65	53
7	2	105	113	8	0	117	114	4	0	97	107
7	3	131	118	8	2	93	91	4	4	63	48
7	4	189	184	***	H = 5	***		5	C	149	158
8	2	66	70	0	1	120	114	5	1	100	101
9	2	58	46	0	2	129	126	6	0	106	109
***	H = 4	***		0	4	63	47	***	H = 7	***	
0	0	46	38	0	6	227	236	J	4	85	79
0	1	46	39	0	8	285	291	0	5	97	85
0	3	191	194	1	1	175	172	J	6	80	71
0	4	153	152	1	2	116	115	1	2	82	72
0	5	259	255	1	3	75	57	1	5	92	92
0	6	80	79	1	4	66	62	2	1	90	95
0	8	113	111	1	9	71	75	2	5	63	55
0	9	186	195	2	1	183	190	2	6	81	79
0	10	63	46	2	2	82	79	3	2	85	88
1	0	116	114	2	3	86	91	3	3	65	63
1	1	220	223	2	6	84	79	3	5	54	43
1	2	105	98	2	8	121	126	4	1	62	57
1	3	207	210	2	9	57	54	4	2	74	69
1	4	197	199	3	1	84	85	4	5	61	39
1	5	76	82	3	2	63	56	4	7	57	57
1	6	136	128	3	5	51	61	5	2	68	71
1	8	97	90	3	6	81	77	***	H = 8	***	
1	10	151	144	3	7	56	71	0	4	60	49
2	0	262	261	4	1	143	145	1	3	88	90
2	1	109	112	4	3	61	65	2	0	58	58
2	2	191	190	4	5	74	76	2	4	56	62
2	3	136	140	5	2	90	99	3	0	56	39
2	4	63	69	5	3	72	73	3	5	60	62
2	5	196	187	5	4	53	41	4	0	78	83
2	7	98	96	5	5	59	58	***	H = 9	***	
2	9	135	141	6	1	183	178	1	4	64	63
3	0	86	79	6	2	73	77				
3	1	95	88	6	3	73	72				
3	2	172	175	6	6	64	69				
3	3	173	179	8	1	74	74				

Unsymmetrical Imide (34c)

After DL-phenylalanine (5g, 30.3 mmole) in 50 ml of Ac₂O was heated at 100°C for 10 min with stirring, the solution was oxidized directly as above, yielding (34c) (2.93 g, 55%); mp 124-126°C; IR (CH₂Cl₂) 1711, 1735 cm⁻¹; ¹H NMR (CDCl₃): δ 8.4 (bs, 1H), 7.22 (~s, 5H), 3.76 (s, 2H), 2.32 (s, 3H); MS: M/e 177 (M+.), 118.91. Anal. calcd for C₁₀H₁₁NO₂: C, 67.79; H, 6.21; N, 7.91. Found: C, 67.49; H, 6.17; N, 8.18.

Using Schlenk line techniques, a reaction on 1/10 the above scale was carried out with oxidation by stirring for 4 days under 100 ml 99% ¹⁸O at 0.5 atm. The imide (34c) obtained (0.134g, 25%) had an NMR spectrum identical with that above but had MS values of M/e 181 (M+.), 120, and 91.

Saturated Azlactone (35b), from
N-Benzoyl-DL-phenylalanine

The literature procedure [26] was used except the crude product was chromatographed (LC) on silica. Elution with ethyl acetate-hexane gave (35b) in 75% yield; ¹H NMR (CDCl₃): δ 7.9-7.7 (m, 2H), 7.5-6.9 (m, 8H), 3.9 (m, 1H), 2.1 (~d, J = 6.9 Hz, 2H).

Saturated Azlactone (35a), from
N-Benzoyl-DL-valine

N-Benzoyl-DL-valine (100 mg) was heated with 3 ml acetic anhydride on a steam bath for 30 min. Most of the acetic acid was removed

with argon, leaving a thick syrup, which was dissolved in 50 ml of ether and extracted 2 x 30 ml with sodium bicarbonate. Evaporation left (35a) as a viscous oil in 55% yield; ^1H NMR (CDCl_3): δ 8.1-7.9 (m,2H), 7.55-7.10 (m,3H), 4.35 (d, J = 8.0 Hz,1H), 2.10 (m,1H), 1.1 (d, J = 6.6 Hz,6H).

Saturated Azlactone (35c), from DL-Phenylalanine

The literature procedure [26] gave (35c) in 80% yield; ^1H NMR (CDCl_3): δ 7.10 (~s,5H), 3.20 (m,1H), 2.10 (d, J = 6.5 Hz,2H), 1.91 (s,3H).

Unsymmetrical Imide (34c), from
Saturated Azlactone (35c)

Oxygen was bubbled overnight through a vigorously stirred mixture of 3.2g (35 c) and 320mg of Pd/C giving after chromatography (silica, ethylacetate-hexane) imide (34c) in 15% yield.

Unsymmetrical Imide (34a), from
Saturated Azlactone (35a)

Oxygen was bubbled overnight through a vigorously stirred mixture of 500mg (35a), 15 ml acetic acid, and 200mg of Pd/C. After filtering through Celite, washing 3 x 30 ml ether, and evaporating, the residual oil was subjected to LC (silica). Elution with ethyl acetate-hexane gave (34a) in 44% yield.

Unsymmetrical Imide (34b), from
Saturated Azlactone (35b)

Saturated azlactone (35b) (200 mg) treated similarly gave (34b) in 55% yield. From the LC fractions just before those containing (34b) was obtained perester (37b) as a viscous oil with an NMR spectrum similar to that of azlactone (35b); ^1H NMR (CDCl_3): δ 7.88 (dd, $J = 6.7, 1.4$ Hz, 2H) 7.55 (tt, $J = 7.4, 1.4$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 2H), 7.20 (m, 5H), 3.48 (d, $J = 13.2$ Hz, 1H), 3.28 (d, $J = 13.2$ Hz, 2H), 7.20 (m, 5H), 3.48 (d, $J = 13.2$ Hz, 1H), 3.28 (d, $J = 13.2$ Hz, 1H), 2.14 (s, 3H). Anal. calc for $\text{C}_{18}\text{H}_{15}\text{NO}_5$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.02; H, 4.31; N, 4.35.

With benzene as solvent the yield of (34b) dropped to 10%.
With DMSO, it rose to 82%.

^{18}O Labelled Product (34c), from
Saturated Azlactone (35c)

Azlactone (35c) was dissolved in 5 ml acetic anhydride and heated at 100° for 10 min. with stirring. The solution was allowed to cool at room temperature, then degassed and 50 mg of Pd/C was added. Using standard Schlenk Line techniques the oxidation was carried out using 100 ml of 99% $^{18}\text{O}_2$ at 0.5 atm while stirring for 4 days. The imide (34c) obtained (0.234g, 25%) had an NMR spectrum identical with that of the unlabeled (34c) but had MS values of M/e 181 (M+) and 120 instead of 179 (M+) and 118.

N-Benzoyloxycarbonyl-p-methoxyphenyldehydroalanine
Ethyl Ester

2-Benzoyloxycarbonylamino-2-(diethoxyphosphoryl) ethyl ester ((51), 1.53 mmole dissolved in 0.75 ml THF) was added dropwise to a solution of 1.53 mmole of NaH with stirring in 1 ml THF. After the gas evolution ceased, 1.53 mmole of anisaldehyde dissolved in 0.75 ml THF was added dropwise to the solution. After stirring under argon overnight, the solution was diluted with 30 ml CHCl_3 and evaporated, giving a dark yellow syrup which was redissolved in 100 ml CHCl_3 and washed with 30 ml H_2O giving an emulsion which was partially broken up using NaCl solution. Evaporation of the organic layer and LC (silica, eluting with 70/30 hexane/ethyl acetate) gave 107 mg of E isomer, then 234 mg of Z isomer; $^1\text{H NMR}$ (CDCl_3): Z isomer: δ 7.50 (d, J = 8.7 Hz, 2H), 7.34 (s, 1H), 7.35 - 7.27 (bs, 5H), 6.84 (d, J = 8.4 Hz, 2H), 6.30 (bs, 1H), 5.12 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H): E isomer: δ 7.41 - 7.31 (m, 6H), 7.22 (d, J = 8.7 Hz, 2H), 6.91 (bs, 1H), 6.82 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H).

Isopropyl α -Isopropoxy-N-
benzyloxycarbonylglycinate (55)

α -Hydroxy-N-benzyloxycarbonylglycine (54) [54] (2.71 mmole) was dissolved in 25 ml of 2-propanol and cooled to 0°C. Sulfuric acid (0.1 ml) was added slowly to the solution which was then stirred at room temperature for 65h and poured over 50 ml saturated NaHCO_3 , dried over MgSO_4 , filtered, and evaporated, leaving (55) as a liquid

(70% yield); ^1H NMR (CDCl_3): δ 7.35 (s, 5H), 6.01 (bd, $J = 9.6$ Hz, 1H), 5.38 (d, $J = 9.6$ Hz, 1H), 5.19 (d, $J = 12.7$ Hz, 1H), 5.12 (d, $J = 12.7$ Hz, 1H), 5.05 (heptet, $J = 6.1$ Hz, 1H), 3.99 (heptet, $J = 6.1$ Hz, 1H), 1.26 (d, $J = 6.1$ Hz, 6H), 1.21 (d, $J = 6.1$ Hz, 3H), 1.19 (d, $J = 6.1$ Hz, 3H).

Isopropyl 2-Benzyloxycarbonylamino-2-diethoxyphosphorylacetate (51)

To (55) (1.84 mmole) in 10 ml of distilled benzene, 0.20 ml of PCl_3 was added dropwise with stirring. After heating for 18h at 70°C , triethyl phosphite (0.32 ml) was added dropwise and the reaction was stirred for another 3h at 70°C . The solution was evaporated, 100 ml ether was added and the ether solution was washed 4 x 30 ml sodium bicarbonate. The organic layer was dried over MgSO_4 , filtered and evaporated, leaving 0.622g (87.6% yield) of (51); ^1H NMR (CDCl_3): δ 7.35 (s, 5H), 5.63 (bd, $J = 9.0$ Hz, 1H), 5.13 (d, $J = 2.4$ Hz, 2H), 5.10 (heptet, $J = 6.2$ Hz, 1H), 4.85 (dd, $J = 22.0$ Hz, 9.2 Hz, 1H), 4.15 (m, 4H), 1.30 (m, 12H).

Dehydroamino Acids (56a) & 56b)

Sodium hydride (3.5 mmole, from 50% dispersion in mineral oil washed with pentane) was stirred in THF (3 ml) as (51) (3.5 mmole) in 2.5 ml THF was added dropwise. After gas evolution ceased, 0.423 ml of anisaldehyde in 1 ml of THF was added and the solution was stirred

overnight. The solvent was evaporated, leaving 1.18 g of an orange oil which was subjected to LC (silica) eluting with ethyl acetate/hexane 0-70% gradient. The fractions containing (56a) and (56b) were rechromatographed on MPLC (silica, eluting with 35% Et₂O/petroleum ether), giving first 226 mg (18%) of (56a), then 383 mg (30%) (56b) and a small amount of aldehyde (10). ¹H NMR (CDCl₃): Z isomer (56b): δ 7.49 (d, J = 8.8 Hz, 2H), 7.32 - 7.30 (s, 5H), 7.31 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.3 (bs, 1H), 5.13 (s, 2H), 5.12 (heptet, J = 6.3 Hz, 1H), 3.09 (s, 3H), 1.28 (d, J = 6.2 Hz, 6H). E isomer (56a): δ 7.57 (bs, 1H), 7.40 - 7.31 (m, 6H), 7.20 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 5.02 (heptet, J = 6.2 Hz, 1H), 3.81 (s, 3H), 1.08 (d, J = 6.3 Hz, 6H).

Dehydroamino Acids (46a) and 46b)

Sodium hydride (0.37 mmole, from 50% dispersion in mineral oil washed with pentane) was stirred in THF (0.4 ml) as (51) (0.37 mmole) in 0.6 ml THF was added dropwise. After evolution of gas ceased, (0.37 mmole) of (10) in 0.4 ml THF was added dropwise and the solution was stirred overnight. The solvent was evaporated, giving a syrupy orange solution which was dissolved in 100 ml CHCl₃ and extracted with water; saturated NaCl solution was added to break up the emulsion. The organic layer was dried over MgSO₄ and evaporated, giving 193 mg (46a) and (46b) which was separated by LC (silica, eluting with ethyl

acetate/hexane gradient to 70% ethyl acetate); this gave 74 mg of (46b), then 86 mg of (46a). A very pure product was obtained using MPLC (silica, eluting with ethyl acetate/hexane, 60:40); ^1H NMR (CDCl_3): E isomer (46b): δ 7.37 (s, 5H), 7.15 - 6.90 (m, 3H), 7.02 (d, J = 8.6 Hz, 2H), 6.93 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.15 (s, 2H), 5.03 (bs, 1H), 4.99 (heptet, J = 6.3 Hz, 1H), 4.54 (q, J = 7.4 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.04 (m, 2H), 1.41 (s, 9H), 1.09 (d, J = 6.3 Hz, 6H). Z isomer (46a): δ 7.40 - 7.21 (M, 2H), 7.31 (bs, 5H), 7.16 (s, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 5.07 (s, 2H), 5.05 (m, 1H), 5.03 (bs, 1H), 4.54 (q, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.04 (m, 2H), 1.40 (s, 9H), 1.27 (d, J = 6.2 Hz, 6H).

4-Methylphenyl Phenyl Sulfide

Approximately 50 ml of NH_3 was condensed into a flask containing 0.375g p-thiocresol and 0.275 ml iodobenzene under nitrogen and it was photolyzed using a Hanovia lamp for 3h. Every 15 min the reaction was stopped and the reaction vessel was washed down with isopropanol to remove the ice which had formed. After the ammonia was blown off, the residue was dissolved in 100 ml ether, extracted 4 x 30 ml of 2N NaOH, dried over MgSO_4 , and evaporated, leaving 4-methylphenyl phenyl sulfide as a light yellow oil, 65% yield; ^1H NMR (CDCl_3): δ 7.29 (d, J = 8.2 Hz, 2H), 7.27 - 7.15 (m, 5H), 7.12 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H).

3-Iodotyrosine Derivative (62)

To (65) (0.0883g) in 5 ml of methanol stirred and cooled in an ice/methanol bath, thionyl chloride (0.21 ml) was added dropwise over 5 min. After refluxing overnight and evaporating the volatiles, the residual oil was washed 2 x 10 ml ether and dissolved in 20 ml chloroform. Ammonia was bubbled into the solution for 5 min. The mixture was filtered through Celite and the solution evaporated, leaving 69.9 mg (62) (99% yield); ^1H NMR (CDCl_3): δ 7.5 (d, $J = 3.0$ Hz, 1H), 7.10 (dd, $J = 8.0, 3.0$ Hz, 1H), 6.70 (d, $J = 8.3$ Hz, 1H), 3.18 (s, 3H), 3.64 (s, 3H), 3.40 (m, 1H), 2.90 (d, $J = 6.6$ Hz, 2H), 2.25 (s, 3H), 1.7 (bs, 1H).

Sulfur Dipeptide (67)

To (62) (22 mg, 0.062 mmole) and (25 mg, 0.068 mmole) (66) in 5 ml acetonitrile, DMF was added dropwise until a homogeneous solution resulted. After 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.068 mmole) had been added to this solution and it had been stirred for 2 days, it was washed successively with water (2 x 20 ml), dilute HCl (0.5 M, 2 x 20 ml), and water (20 ml). The dried solution was evaporated under reduced pressure, giving (67) as a foam in 66% yield; ^1H NMR (CDCl_3): δ 7.56 (d, $J = 2.1$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.03 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 6.15 (bs, 1H), 5.20 (d, $J = 6.4$ Hz, 1H), 5.16 (dd, $J = 9.8, 3.0$ Hz, 1H), 4.71 (dd, $J = 8.4, 2.8$ Hz,

1H), 4.62 (t, J = 5.5 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.3 - 2.8 (m, 4H), 2.75 (s, 3H), 1.94 (s, 3H), 1.39 (s, 9H).

N-Boc-L-(4'-SH)-Phenylalanine

N-Boc-L-(4'-S'ACM) Phenylalanine ((66), 14.4 mg) was dissolved in 2 ml of degassed methanol and 2 ml of degassed 2N NaOH was added dropwise under argon at 0°C. The solution was stirred overnight and diluted with 3 ml of water. Acidification to pH 2 using 3N NaHSO₄ gave a white precipitate which was quickly extracted with ethyl acetate (3 x 30 ml), dried with Na₂SO₄, filtered and concentrated under reduced pressure giving 9.6 mg of (63); ¹H NMR (CDCl₃): δ 7.20 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 4.98 (vbd, 1H), 3.34 (s, 1H), 3.15 (m, 1H), 2.06 (d, J = 12.5 Hz, 2H), 1.42 (s, 9H).

Photolysis of (72) + (63); Diaryl Sulfide (69)

(63) (0.136 mmole) and (72) (0.136 mmole) were placed in a 2-neck 50 ml round bottom and approximately 40 ml ammonia was condensed into the flask. The mixture was warmed by hand until everything dissolved. The solution was refluxed and photolyzed (Hanovia lamp) for 3H; every 10-15 min the reaction was stopped and the vessel was washed with isopropanol to remove frost. The ammonia was blown off using nitrogen and the residue was partially dissolved in water and acidified to pH 4. Extracting quickly 3 x 30 ml ethyl acetate, drying over MgSO₄, and filtering gave 78.8 crude (69) which was subjected to

preparative TLC (silica, 15% MeOH/CHCl₃). This removed by-product (71) and left 37.6 mg crude (69) which was eluted from LH-20 with 50/50 acetone/methanol, leaving 23.2 mg of (69); ¹H NMR (CDCl₃) showed a mixture of about equal amounts of four rotamers; the major peaks only are given: δ 7.32 (~s, 5H), 7.30 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.12 (s), 6.96 (dd, J = 8.3, 1.8 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.3 (vbd, 1H), 5.12 (d, J = 12.6 Hz, 0.6H), 5.08 (d, J = 12.6 Hz, 0.6H), 5.00 (d, J = 13 Hz, 0.4 H), 4.94 (d, J = 13 Hz, 0.4H), 3.85 (s, 0.6 x 3H), 3.83 (s, 0.4 x 3H), 3.63 (s, 0.6 x 3H), 3.61 (s, 0.4 x 3H), 2.75 (s, 0.6 x 3H), 2.70 (s, 0.4 x 3H), 1.8 (bs, 9H). MS: FAB using glycerol with NaCl added gave M + Na 675 and M + 2Na 698.

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