Synthetic Studies on the Streptogramin Antibiotics. Enantioselective Synthesis of the Oxazole Dienyl Amine Moiety

A. I. Meyers,* J. P. Lawson, D. G. Walker, and R. J. Linderman[1]

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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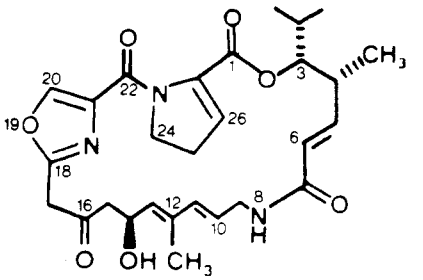
The syntheses of the oxazole dienyl amine portions of griseoviridin (2) and madumycin II (3) have been completed in optically active form. The novel preparation of a functionalized oxazole ring and the unique diastereomeric resolution of a 1,3-dihydroxy compound are described. The stereospecific synthesis of a dienylphthalimide by means of tributylvinylphosphonium bromide on a complex aldehyde has also been demonstrated.

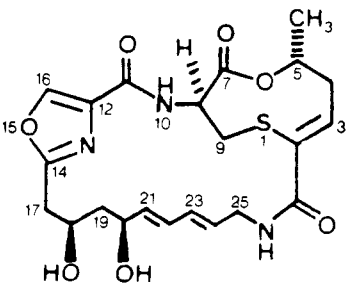
The broad spectrum antibiotic streptogramins are a family of compounds isolated from a number of different source microorganisms.[2] The name streptogramin was derived from the soil microorganism *streptomyces graminofaciens*, from which the antibiotic was first isolated in 1953.[3] Since that time the same group of compounds has been named as the mikamycins, pristinamycins, ostreogrycins, or virginiamycins. The nomenclature is thus somewhat confused, but the name virginiamycins has been adopted by Chemical Abstracts Service and an authoritative review.[4] Although an effort to clarify the nomenclature has been made, the numbering of the ring system in each compound is not consistent. The complete numbering of virginiamycin M_1 (1), griseoviridin (2), and madumycin II (3) as accepted by Chemical Abstracts Service[5] will be used in this paper.

The antibiotics of this family of mold metabolites consist of a number of compounds that belong to two distinct groups. The antibiotics of group A are polyunsaturated macrocyclic peptides, which can be considered as highly modified depsipeptides.[6] The first of these to have its structure elucidated was ostreogrycin A,[7] which is identical with virginiamycin M[1] (1). The structure has been confirmed by X-ray crystallography.[8] The structure of griseoviridin (2), the most structurally complex member of this class, was determined shortly thereafter and confirmed by single-crystal X-ray analysis.[9] The related antibiotic 3, designated A-2315A by a Lilly group,[10] was also isolated by a Polish group,[11] giving the compound the name madumycin II.

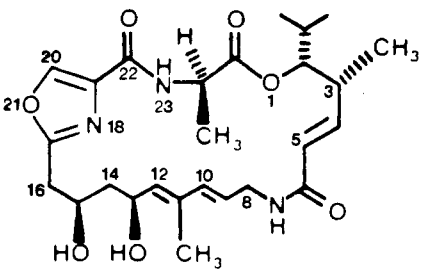
The antibiotics of group B are cyclic hexadipsipeptides of molecular weight about 800. Viridogrisein, also known as etamycin, has been synthesized by Sheehan.[12] While group A and B antibiotics are individually bacteriostatic, in combination they show a marked synergism and are bacteriocidal against gram-positive organisms.[13] The antibiotics act by inhibition of protein synthesis at the ribosomal level. In vitro studies have shown that type A compounds increase the affinity of ribosomes for type B compounds, an action that may account for the synergistic response in vivo.[14]



1, Virginiamycin M_1



2, Griseoviridin



3, Madumycin II
A-2315A

(1) National Research Service Award, National Cancer Institute Fellowship recipient; Grant CA-07389-01.
(2) Vazguez, D. "The Streptogramin Family of Antibiotics", In *Antibiotics III*; Corcoran, J. W., Hahn, F. H., Eds.; Springer-Verlag: New York, 1975.
(3) Charney, J.; Fisher, W. P.; Curran, C.; Machlowitz, R. A.; Tyteli, A. A. *Antibiot. Chemother. (Washington, D.C.)* **1953**, *3*, 1283.
(4) Cocito, C. *Microbial. Rev.* **1979**, 145-198.
(5) We would like to acknowledge the assistance of Dr. K. Loening of Chemical Abstracts Service for his assistance in this matter.
(6) Bycroft, B. W. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2464.
(7) Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, G. D. I.; Todd, A. R.; Williams, D. H. *J. Chem. Soc. C* **1966**, 1653.
(8) Durant, F.; Evard, G.; Declerq, J. P.; Germain, G. *Cryst. Struct.* **1974**, *3*, 503.
(9) Bycroft, B. W.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1996. Birnbaum, G. I.; Hall, S. R. *J. Am. Chem. Soc.* **1976**, *98*, 1926.
(10) Chamberlin, J. W.; Chem. S. *J. Antibiot. (Tokyo)* **1977**, *30*, 197.
(11) Brazhnikova, M. G.; Kudinova, M. K.; Potapova, N. P.; Filippova, T. M.; Borowski, E.; Zelinski, Y.; Golik, J. *Bioorgan. Khim.* **1976**, *2*, 149.
(12) Sheehan, J. C.; Ledis, S. L. *J. Am. Chem. Soc.* **1973**, *95*, 875.
(13) Ennis, H. L. *Bacteriol.* **1965**, *90*, 1102. Cocito, C. *J. Gen. Microbiol.* **1969**, *57*, 179.
(14) Parfait, R.; Cocito, C. *Proc. Natl. Acad. Sci. (U.S.A)* **1980**, *77*, 5496.

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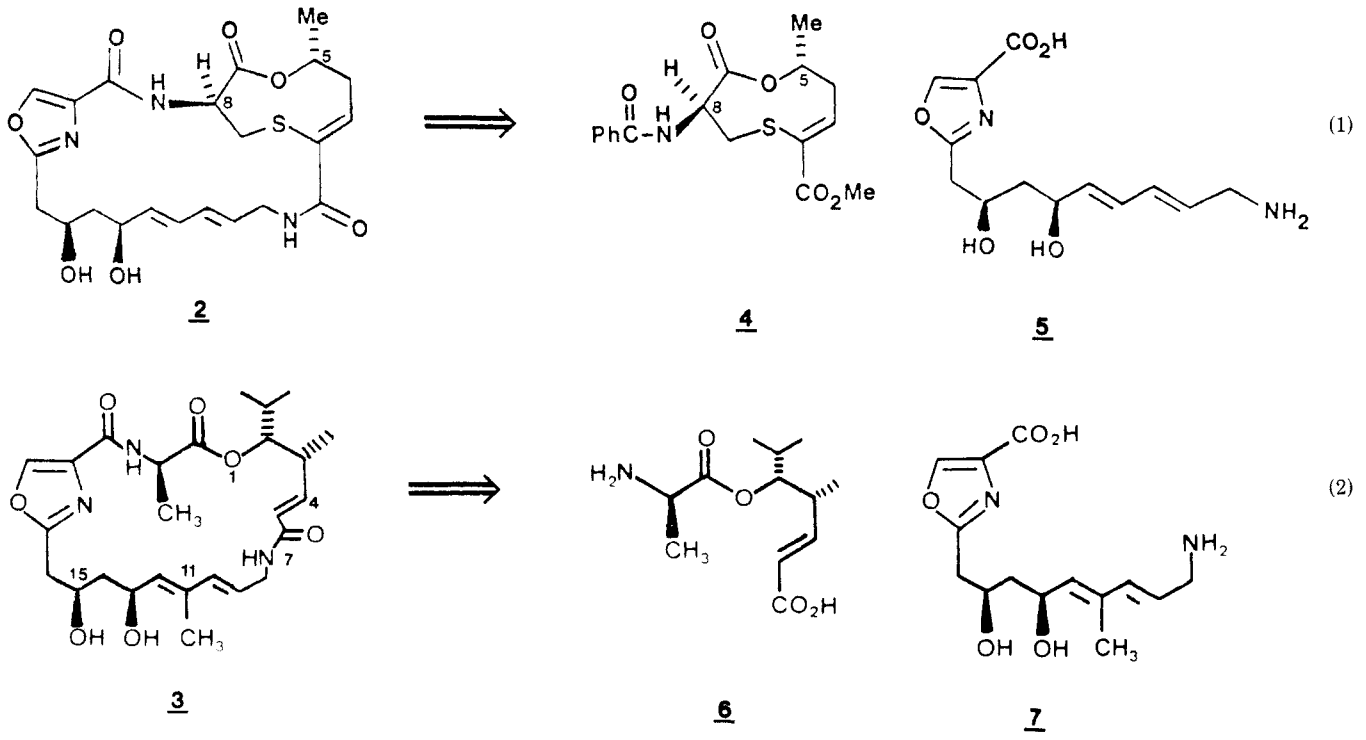
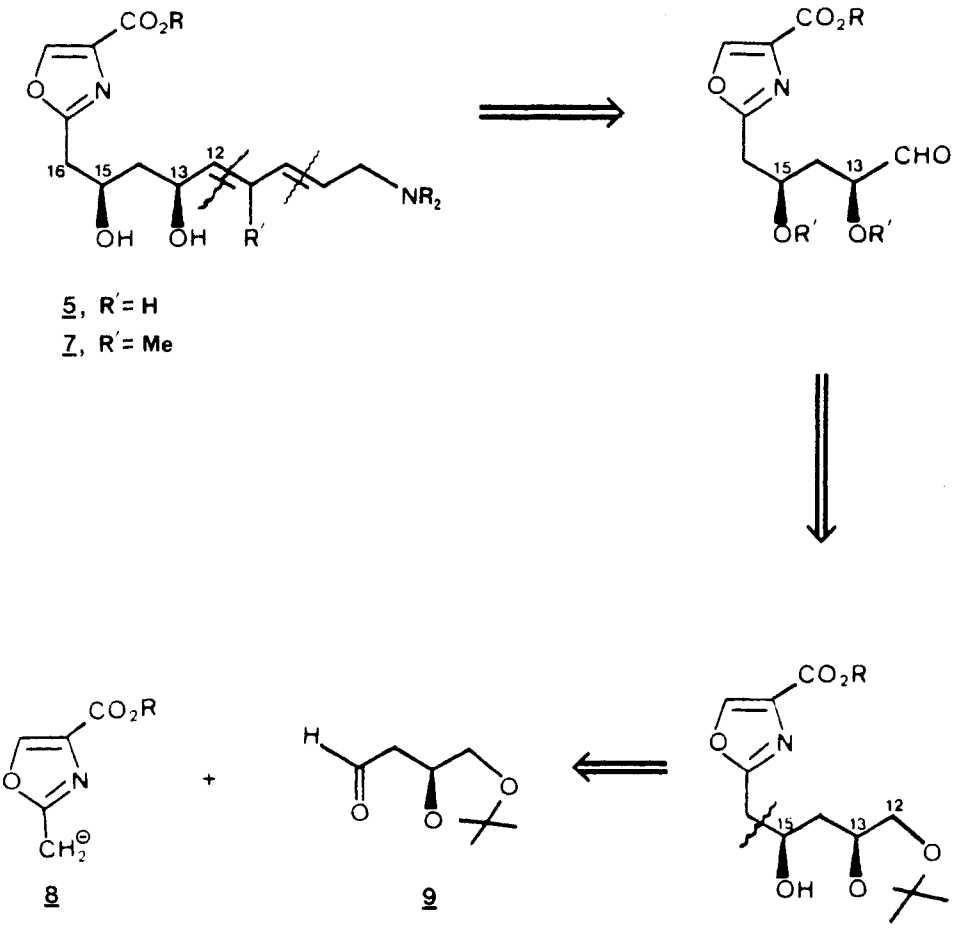


Scheme I

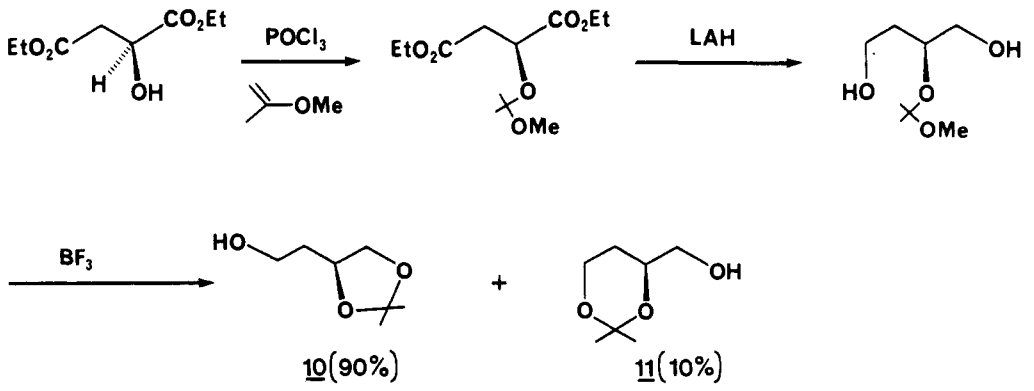


As a synthetic challenge, we have been interested in two members of this class, griseoviridin (**2**) and madumycin II (**3**). Since there are large structural similarities between these compounds and the remaining members of the class, we felt that a properly planned synthetic effort could be undertaken which would provide entry to all members of the class using **2** and **3** as our initial target molecules.[15]

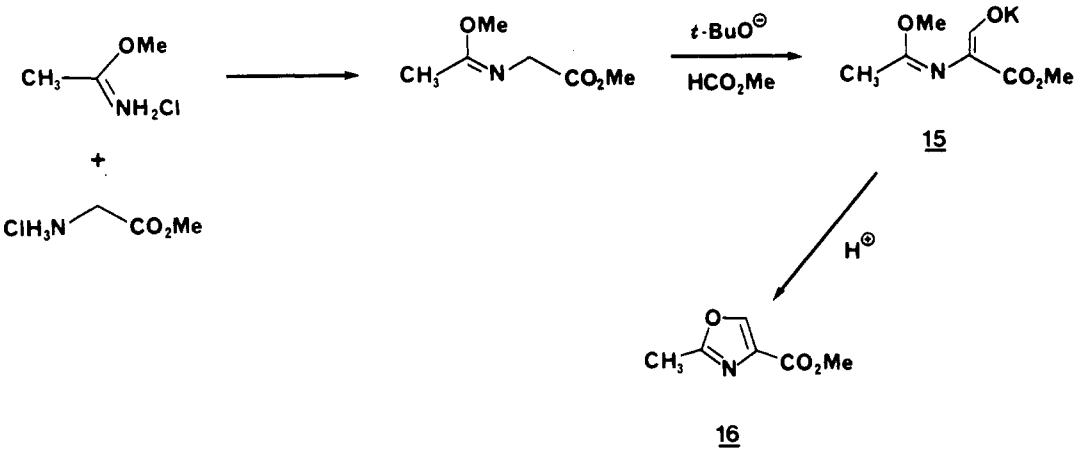
Retrosynthetic analysis of griseoviridin (**2**) revealed two fragments, **4** and **5**, by simple disconnection at the amide

(15) A partial account of our efforts has appeared: Meyers, A. I.; Lawson, J.; Amos, R. A.; Walker, D. G.; Spohn, R. F. *Pure Appl. Chem.* **1982**, *54*, 2537. Please note that the numbering used in this paper is incorrect.

Scheme II



Scheme III

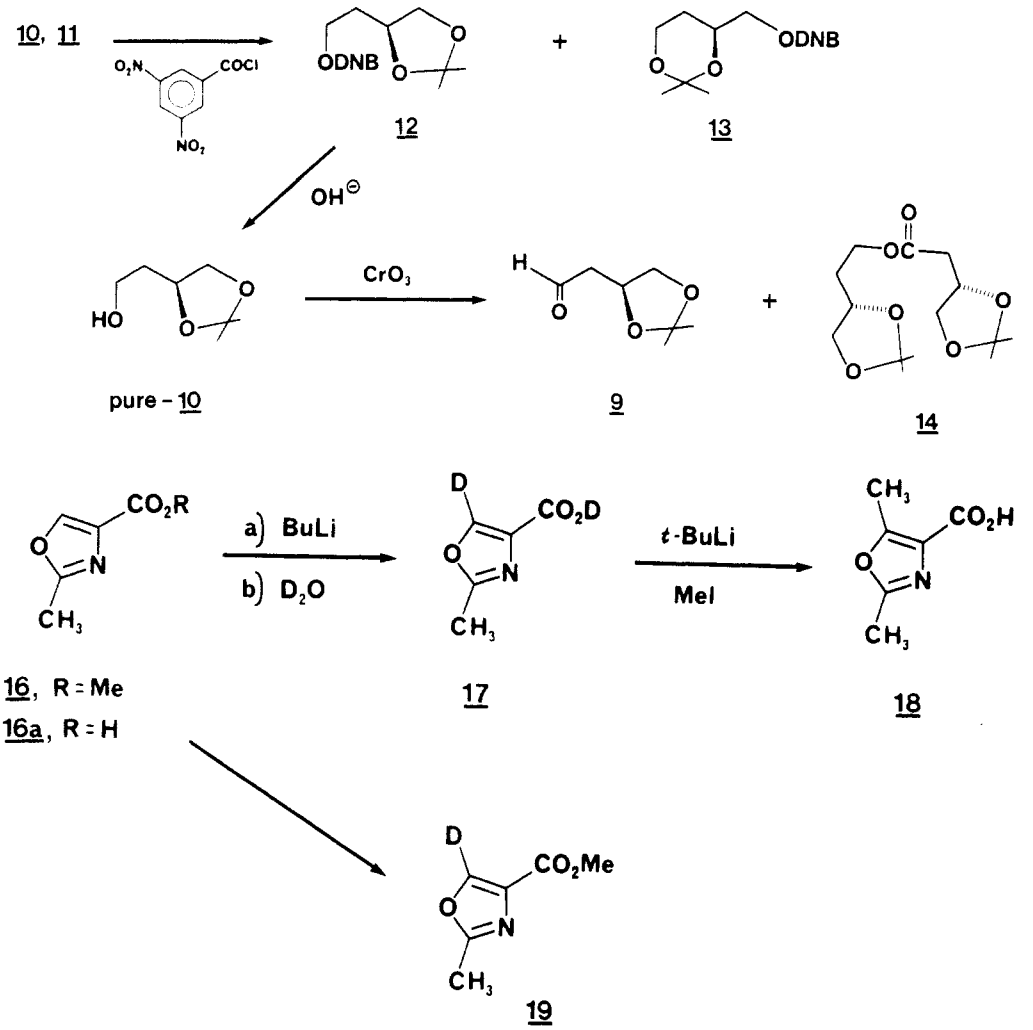


bonds (eq 1). For madumycin II (**3**), the molecule can be envisioned to arise from two fragments, **6** and **7**, by a similar disconnection (eq 2). It is noteworthy that the oxazole moieties **5** and **7** are identical with the exception of the methyl groups at the diene position (C-11, madumycin numbering). Therefore, a slight modification in synthesis should provide both the madumycin and griseoviridin oxazole fragments. We have successfully accomplished the synthesis of fragments **4**[16,17] and **6**[18] while the preparation of the oxazole dienyl amines, **5** and **7**, is described in this paper.

Further retrosynthetic analysis of the oxazole moieties **5** and **7** is shown in Scheme I. For the sake of clarity, we will use the madumycin II numbering system throughout the discussion. Several structural features may be pointed out at this stage; the relatively rare (in natural products) 4-carboxyoxazole ring; the syn-1,3-diol having the absolute configurations of C-13(*S*) and C-15(*R*); and the (*E*,*E*)-dienyl amine. The retrosynthetic sequence called for stepwise disconnection of the olefinic bonds. The stereocontrolled introduction of the allylamine would be accomplished by an application of the vinylphosphonium salt chemistry developed earlier in our group.[19] Control of the olefin geometry at C-10–C-12 would be achieved by a Wittig reaction on the hydroxy aldehyde. Modification of the reagent in this step would ultimately lead to oxazoles **5** and **7**. The two stereocenters at C-13 and C-15 would arise from the reaction of the oxazole methyl anion **8** and the known[20] chiral aldehyde **9**. Our first task, therefore, was to prepare optically active aldehyde **9** and then test the feasibility of the aldol reaction with oxazole anion **8**.

The chiral aldehyde **9** was prepared from L-malic acid as shown in Scheme II. Esterification of L-malic acid gave (*S*)-diethyl malate in 78% yield. The optical rotation of the ester varied from run to run ($[\alpha]^{20}_D$ −14.5 ± 6°); however, this variation had no effect on the rotation of the acetonide alcohol **10**. Protection of the secondary alcohol and reduction with lithium aluminum hydride smoothly produced the monoprotected butanetriol. Cyclization of the diol to the acetonide under the reported conditions (BF_3·Et_2O, 23 °C, 2 h)[20a] resulted in a 2:1 mixture of the five- and six-membered acetonides, **10** and **11**. The presence of the dioxane was revealed in the ^1H NMR spectrum by a singlet at δ 1.45 corresponding to one of the diastereotopic acetonide methyl groups. Further treatment of the mixture with boron trifluoride etherate for extended periods of time gave the equilibrium mixture of **10** and **11** as 9:1. The ratio was unaffected after a prolonged reaction time. The quantitative determination of the equilibrium mixture was ascertained by chiral shift reagent studies. Nakanishi[20c] had made an attempt to detect the dioxane regioisomer **11** by NMR shift studies using nonoptically active shift reagent but was unable to discern the presence of **11**, leading to the incorrect conclusion that only the

(16) Meyers, A. I; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.
(17) For a recent synthesis of **4**, see: Butera, J.; Rini, J.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 3676.
(18) Meyers, A. I.; Spohn, R. F.; Linderman, R. J. *J. Org. Chem.* **1985**, *50*, 3633.
(19) Meyers, A. I.; Lawson, J. P.; Carver, D. R. *J. Org. Chem.* **1981**, *46*, 3119.
(20) (a) Corey, E. J.; Shirahama, H.; Tamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schoaf, T. K. *J. Am. Chem. Soc.* **19718**, *93*, 1490. (b) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942. (c) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749. (d) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (f) Tang, K.-C.; Tropp, B. E.; Engel, R. E. *Tetrahedron* **1978**, *34*, 2873. (g) Isaac, K.; Kocienshi, P. *J. Chem. soc., Chem. Commun.* **1982**, 460.



dioxolane regioisomer **10** was present.

The regioisomeric mixture of acetonides could only be purified by preparing the 3,5-dinitrobenzoate derivatives, **12** and **13**. Repetitive recrystallization from absolute ethanol provided **12** in 99.9% regioisomeric purity as determined by HPLC analysis. The isomeric acetonide **13** was recovered from the mother liquor and purified by radial preparative chromatography. The specific rotation of the purified dinitrobenzoate **12** ($[\alpha]_D$ −13.7°) did not depend on the rotation of the (*S*)-diethyl malate from which it was derived. Two samples of the diester having different rotations were separately carried through the synthetic sequence to give dinitrobenzoates having equal rotations. Regeneration of isomerically pure **10** was accomplished by using potassium carbonate in methanol. The purity of the acetonide was then confirmed at this stage by NMR shift studies using $Eu(hfc)_3$. As proof that **10** and **11** were truly part of an equilibrium mixture formed in the cyclization of the acetonide, resubjecting the 99.9% isomerically pure **10** to BF_3-Et_2O in chloroform (25 °C) once again produced the 9:1 mixture.

Oxidation of pure **10** to the aldehyde **9** was accomplished by using the modified Collins procedure.[21] Also present after distillation of the product was a higher boiling fraction, suggested, but not characterized, by Mori[20d] to be the ester derived from oxidation of the hemiacetal formed by dimerization of **10** (eq 3). This structure (**14**) has been confirmed by isolation and characterization. The dimeric species **14** could be reduced back to the alcohol with lithium aluminum hydride for recycling.

Reduction of the pure aldehyde **9** to the alcohol **10** gave material that was completely free of the isomeric acetonide as determined by chiral LISR studies. Oxidation of the 9:1 equilibrium mixture of **10** and **11** with the modified Collins procedure produced an aldehyde that failed to reveal any regioisomeric mixture upon examination with several optically active or nonoptically active lanthanide shift reagents. The aldehydes are therefore insensitive to the LISR technique. To verify that the mixture of regioisomeric acetonides survived the oxidation conditions and were indeed present, reduction back to the alcohol and subsequent examination by ^1H NMR with $Eu(hfc)_3$ present clearly indicated the mixture.[22]

The synthesis of 2-methyl-4-carboxyoxazole ethyl ester was readily achieved by using the Cornforth synthesis,[23] which is illustrated in Scheme III. The imidate hydrochloride of acetonitrile and methanol was treated with methyl glycinate hydrochloride and triethylamine to afford the N-substituted imidate ester in good yield. Enolate generation in tetrahydrofuran with *tert*-butoxide and subsequent quench with methyl formate followed by precipitation of the salt with ether furnished the Cornforth intermediate **15**. Addition of the solid enolate to refluxing glacial acetic gave the oxazole **16**.

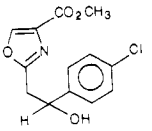
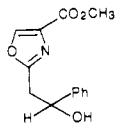
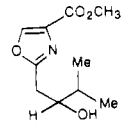
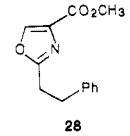
Attempted metalation of oxazole ester **16** with lithium diisopropylamide followed by quenching with deuterium

(21) Ratcliff, R.; Roderhorst, R. *J. Org. Chem.* **1975**, *35*, 4000.

(22) A preliminary account of this problem has been published: Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.

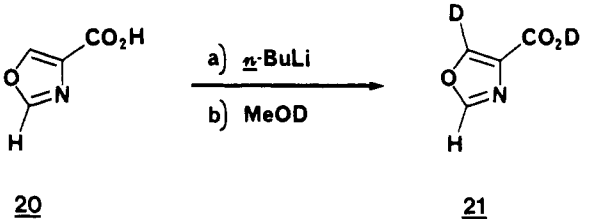
(23) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96.

Table I. Alkylation of Enolate 15 to Oxazoles

E^+		yield, %
p-ClC_6H_4CHO	 **25**	56
PhCHO	 **26**	51
Me_2CHCHO	 **27**	45
$PhCH_2Br$	 **28**	38

oxide did not result in any deuterium incorporation on the heterocycle (eq 4). Hydrolysis of the ester to the acid[23] **16a** and metalation with 2 equiv of n-butyllithium resulted in only 5-deuteriooxazole **17** after deuterium oxide quench (92% D incorporation as determined by ^1H NMR). The result was unaffected by using an excess of n-butyllithium. Treatment of **17** with n-butyllithium and a water quench of the reaction mixture provided only recovered **17**. Apparently the isotope effect inhibited D abstraction with this base. However, when **17** was metalated with 2 equiv of *tert*-butyllithium, only the deuterium was abstracted as evidenced by the products of methyl iodide quench and aqueous workup. Since the 5-methylated oxazole **18** comprised only 10% of the mixture, with the remaining 90% recovered as protonated material, the 5-lithio species acts as a very poor nucleophile. Furthermore, none of the 2-ethyloxazole derivative was detected in the reaction mixture.

In an effort to determine if deprotonation at the 5-position of **16** was kinetically favored while the 2-methyl group would form the thermodynamic anion, **16** was stirred for 96 h with MeOD/MeO^-. To our surprise, only **19** containing 99% D at the 5-position was obtained with no visible deuterium incorporation at the 2-methyl position. It is interesting to point out that oxazolecarboxylic esters have been reported as unstable to the conditions necessary for deuterium exchange.[24] The failure of 2-methyl-4-carboxyoxazoles to metalate at the methyl group is in contrast to the recent reports[25] that describe smooth deprotonation of 2,4,5-trisubstituted oxazoles with LDA and n-BuLi. In a related study, Schollkopf[26] showed that various 2-H oxazoles metalate at the 2-position. We therefore examined oxazole **20**,[27] which also provided the 5-deuterio derivative **21** as the sole product after metalation with 2 equiv of n-BuLi and quenching the reaction mixture with MeOD (eq 5). Therefore, the acidity of the



20 **21** (5)

5-H is not only a result of the inductive effect of the neighboring oxygen atom[28] but also due to the strong activation of the 4-carboxy group. In the absence of the carboxyl substituent, metalation at the 2-H or 2-methyl group proceeded with ease. The kinetic preference for proton abstraction to occur at a carbon having a β-carboxylate substituent has been observed. For example, metalation of 3-thiophenecarboxylic acid leads to the 2-lithio species exclusively.[29] We have demonstrated that deprotonation of 4-carboxyoxazoles occurs exclusively at the 5-position under thermodynamic and kinetic conditions. Furthermore, we described a further example wherein the 2-methyl group of oxazoles was resistant to deprotonation.[30]

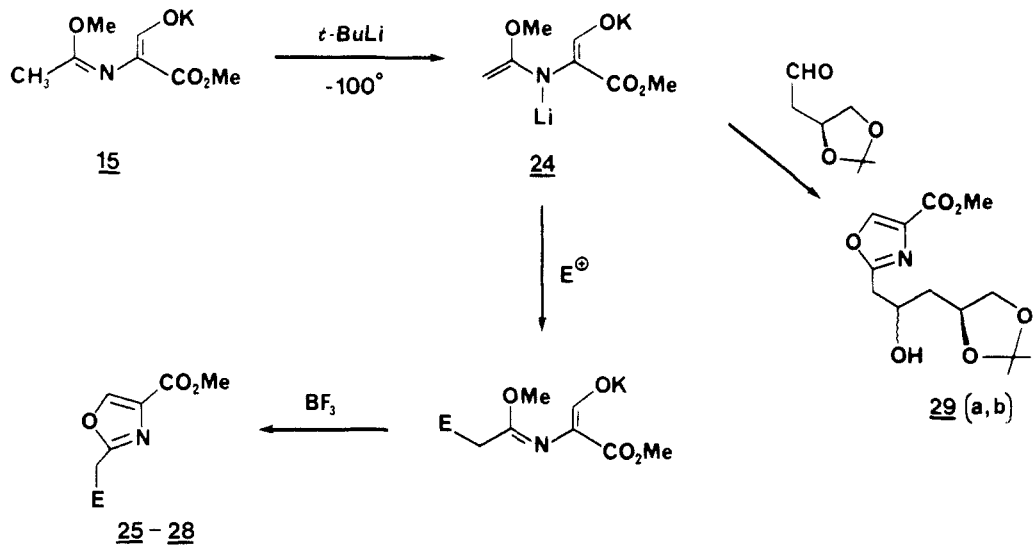
The solution to the 2-methyl deprotonation problem lay in the Cornforth synthesis. Examination of this synthesis of oxazoles revealed the useful acyclic intermediate **15**. It was reasoned that metalation of **15** to the amide enolate **24** followed by the addition of an electrophile would result in a novel approach to the introduction of various 2-substituents in 4-carboxyoxazoles (**25**–**28**) (eq 6). Therefore, metalation–alkylation of **15** followed by acid-catalyzed ring closure to the oxazole is tantamount to direct metalation of the 2-methyl group. Indeed, we found that this was a viable sequence leading to elaborated oxazoles in fair yields. Some representative examples are given in Table I. In addition to the alkylation of anion **24**, we sought to further modify the original Cornforth procedure by affecting ring closure under milder conditions. Toward this goal, the Lewis acid catalyzed cyclizations of the alkylated oxazole precursor was found to be effective using either boron trifluoride or zinc chloride.

Since our initial report,[31] two other approaches to the oxazole problem have been reported. Ganem[32] was able to metalate the 2-methyl position after first blocking the C-5 proton as a trimethylsilyl group on the 4-carboxyoxazolic acid. Fujita[33] overcame the problem by resorting to stabilization of the anion by a sulfonyl substituent on the 2-methyl group. Both of these methods require extra steps to incorporate the activating or protecting groups as well as the need for removal of the same in the presence of other functionality.

The reaction of **24** with the chiral aldehyde **9** was then carried out by using the optimized conditions. Treatment of the imidate **15** with t-BuLi at −100 °C and then aldehyde **9** and finally adding 2 equiv of boron trifluoride etherate produced the elaborated oxazole **29** as a mixture of diastereomers in 25% yield after aqueous workup and chromatography. The unelaborated oxazole **16** was also present in the crude product mixture.

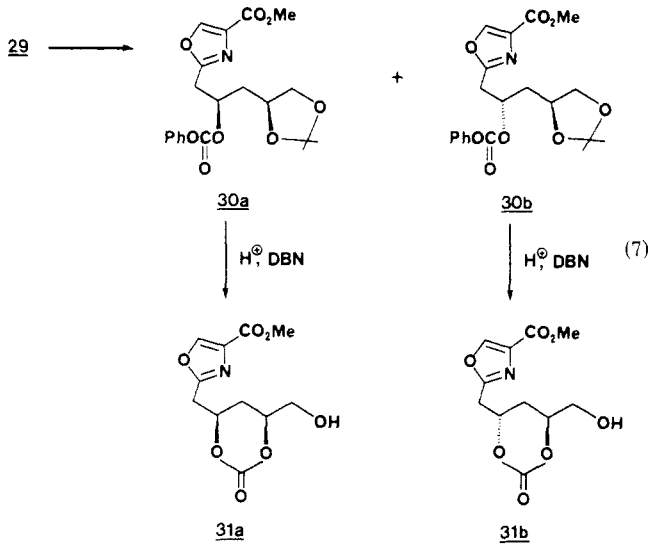
With the diastereomeric alcohols **29** in hand, two problems had to be addressed: the redistribution of the triol

(24) Brown, D. J.; Josh, B. P. *J. Chem. Soc. B* **1969**, 270.
(25) Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410. Wasserman, H. H.; Gambale, R. J.; M. J. Pulver *Tetrahedron Lett.* **1981**, *22*, 1737.
(26) Schroeder, R.; Schollkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533.
(27) See ref 23; for a convenient preparation of isopropylformimidate hydrochloride that avoids the use of hydrogen cyanide, see: Ohme, R.; Schmitz, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 556.
(28) For a review on heteroatom-facilitated lithiations, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1978**, *26*.
(29) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507.
(30) Meyers, A. I.; Walker, D. G. *J. Org. Chem.* **1982**, *47*, 2999.
(31) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163.
(32) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1983**, *24*, 4391.
(33) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2291.



(6)

protecting group to provide a free primary alcohol (at C-12) and the resolution of the stereocenter at C-15. Acylation of the secondary hydroxyl group with phenyl chloroformate and pyridine afforded the phenyl carbonate derivatives **30a** and **30b** in 74% yield as a 1:1 mixture of diastereomers (eq 7). Separation of the diastereomers was achieved by



(7)

preparation liquid chromatography, and each diastereomer was then carried on to the cyclic carbonate **31a** or **31b** under acid catalysis. Neither ^1H nor ^{13}C NMR analysis could conclusively establish the stereochemical identity of the cyclic carbonate; however, assignment of the stereochemistry became inconsequential when a variety of oxidation reagents to reach the corresponding aldehyde were ineffective. For example, pyridinium chlorochromate,[34] oxalyl chloride–Me_2SO,[35] or NCS–dimethyl sulfide[36] all failed to produce the aldehyde. Conversion of the alcohol to the primary iodide followed by reaction with dimethyl sulfoxide and sodium bicarbonate (Kornblum oxidation)[37] was also unsuccessful. Therefore, despite the efficient process of redistribution and the resolution of the C-15 stereocenter, the carbonate was not a suitable 1,3-diol protecting group.

Perhaps the most common protecting group for 1,2- or 1,3-diols is an acetal. Ketones, such as acetone, preferentially form five-membered dioxolanes when reacted with polyols, as we have already demonstrated in the synthesis of **9**, while aldehydes generally form six-membered dioxanes preferentially.[38] The geminal substituents of a ketal cause severe 1,3-diaxial interactions in six-membered rings while these interactions are much less severe in a five-membered ring.[39] In addition, most 1,3-dioxane acetals have been shown to exist in the chair conformation with the acetal proton disposed in an axial position.[40] We then felt it reasonable to assume that the dioxane regioisomer would form predominantly when an aldehyde was reacted with 1,2,4-butanetriol. In practice the acid-catalyzed formation of the benzylidene acetal gave a crude product that contained three compounds as revealed by ^1H NMR. The lower field signals at δ 5.90 and 5.77 were of approximately equal area and comprised 10% of the total mixture, with the remaining 90% identified by a singlet at δ 5.50. The ring size of a benzylidene acetal can be assigned on the basis of the chemical shift of either the acetal proton[41] or the acetal carbon.[42] The chemical shift of the upfield acetal proton was consistent with that expected for a 1,3-dioxane, while both of the downfield signals fell into the range expected for a dioxolane acetal. It is interesting to note that the dioxane/dioxolane ratio of 9:1 for the benzylidene acetals was exactly the reverse of the acetonide equilibrium mixture of **10** and **11**. The two five-membered acetals are presumably a diastereomeric mixture. The formation of a single dioxane isomer reflects the conformational preference for 1,3-substituents being equatorial in six-membered rings.

We then applied the acetal/acetonide exchange concept to the oxazole acetonide **29**. As with the simple triol, the crude product contained three compounds exhibiting benzylidene acetal proton resonances at δ 5.55, 5.77, and 5.90. In an attempt to control the regiochemistry of the acetal/acetonide exchange reaction, acetaldehyde and pivaldehyde were also examined; however, these aldehydes also led to isomeric mixtures. Using sterically congested

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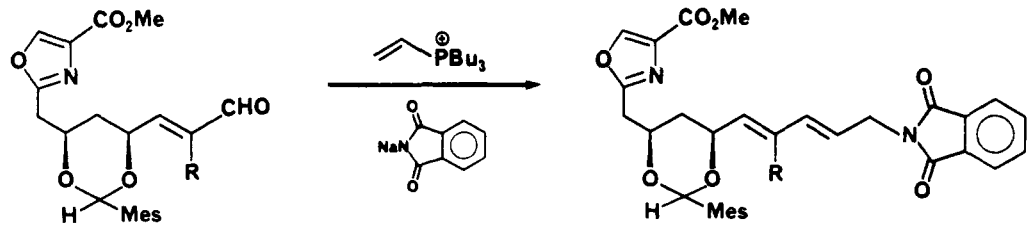
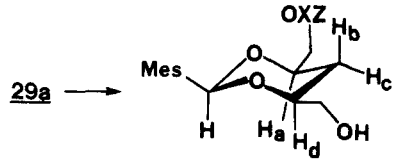


(8)

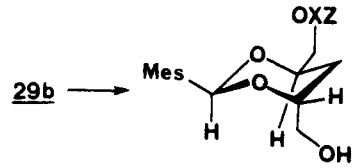
35, R = H
38, R = Me

41, R = H
42, R = Me

mesitaldehyde led to the formation of the 1,3-dioxane acetal in greater than 95% regioselectivity, albeit in only 25% yield. Analysis of the mesitylidene acetal product by HPLC and ^1H and ^{13}C NMR revealed that only a *single diastereomer* was present. The diastereomer most likely to selectively form the 1,3-dioxane was the 13*S*,15*R* isomer, giving the all-equatorial acetal **32**. The 13*S*,15*S* isomer



32



33

33 would require an axial ring substituent that in this case is apparently very unfavorable. To verify that the acetal produced was in fact the 13*S*,15*R* isomer, a conformational analysis by ^1H NMR was carried out. Homonuclear decoupling of the C-16 protons disclosed a 10.7-Hz coupling constant beteen H_a and an adjacent dioxane ring proton, which is indicative of an axial–axial relationship[43] in **32a**. This evidence established the equatorial nature of the oxazole substituent but did nothing to determine the configuration at C-15. An accurate measurement of the coupling constant of H_d was not possible on the alcohol due to the oxazole methyl ester resonance. Swern oxidation[35] to the aldehyde isolated the signal for H_d, simplifying the analysis. In this case, an axial–axial coupling constant of 11.1 Hz and an axial–equatorial coupling constant of 3.3 Hz of H_d with H_b and H_c, respectively, was observed. The axial nature of both H_a and H_d established the syn relationship of the oxygen atoms. Since the absolute configuration at C-13 was known to be *S*, the acetal can be assigned the 13*S*,15*R* absolute configuration: the same absolute configuration found in the streptogramins. The resolution of C-15 has been accomplished, but the low yield of the acetal had to be addressed.

Mesitaldehyde dimethyl acetal prepared from trimethyl orthoformate and the aldehyde has been used to form mesitylidene acetals under mild conditions.[44] Reaction with oxazole acetonide **29** was accomplished using camphorsulfonic acid as the catalyst rather than *p*-toluenesulfonic acid (Scheme IV). The progress of the reaction was monitored by analytical HPLC using conditions that separated the diastereomeric acetonides. The 13*S*,15*R* mesitylidene acetal **32** formed from acetonide **29a**; however, the 13*S*,15*S* diastereomer **29b** remained inert under the mild reaction conditions. Even in the presence of a large excess of mesitaldehyde dimethyl acetal and prolonged reaction times, the *S*,*S* diastereomer of **29b** remained unreactive. Chromatographic separation of **32** and **29b** resulted in a 90% yield of enantiomerically pure **32** and a 70% recovery of the *optically active S*,*S*-acetonide **29b**.

The acetal/acetonide exchange reaction had successfully accomplished a diastereomeric resolution of the acetonides **29**, as well as provide the correct distribution of protection for the triol system.

The requisite alcohol **32** was subjected to Swern oxidation and provided the aldehyde **34** in 82% yield. For the griseoviridin synthesis, aldehyde **34** was treated with the Wadsworth–Emmons reagent prepared in situ from the *tert*-butylimine of acetaldehyde.[45] Hydrolysis of the imine intermediate using pH 5 acetate buffered solution minimized the cleavage of the mesitylidene acetal. The unsaturated aldehyde **35** was only the desired (*E*)-olefin as indicated by a 15.9-Hz olefinic coupling constant in the ^1H NMR spectrum; however, **35** was obtained in only 16% yield.

For incorporation of the vinylogous methyl at C-11 of madumycin, aldehyde **34** was reacted with the phosphonate reagent derived from the *tert*-butylimine of propionaldehyde.[45,46] After pH 7 aqueous quench and workup, none of the expected unsaturated imine was detected by ^1H NMR or IR analysis of the crude reaction product. The spectra were consistant with the adduct being the condensation product **36**. In an attempt to accelerate the elimination process, the sodium salt of **36** was prepared (NaH in THF) and the suspension stirred overnight at room temperature; however, none of the elimination product was observed. This result was in contrast to the reaction of **34** and the acetaldehyde imine phosphonate reagent. Presumably, the excessive steric crowding present in **36** inhibited the syn relationship of the hydroxyl and phosphonate group necessary for elimination (molecular models). Attempts to effect elimination by transforming **36** into its sodium salt did not alter the outcome.

Silyl imine anions have been used to synthesize unsaturated olefins by means of the Peterson olefination reaction.[47] We have thoroughly investigated the reaction of the 2-(trimethylsilyl)propional *tert*-butylimine[48] **37** and the oxazole aldehyde **34**. Using this reagent, the methyl-substituted unsaturated aldehyde **38** was obtained, but in a low yield (20–30%) (eq 8). Since the reaction was carried

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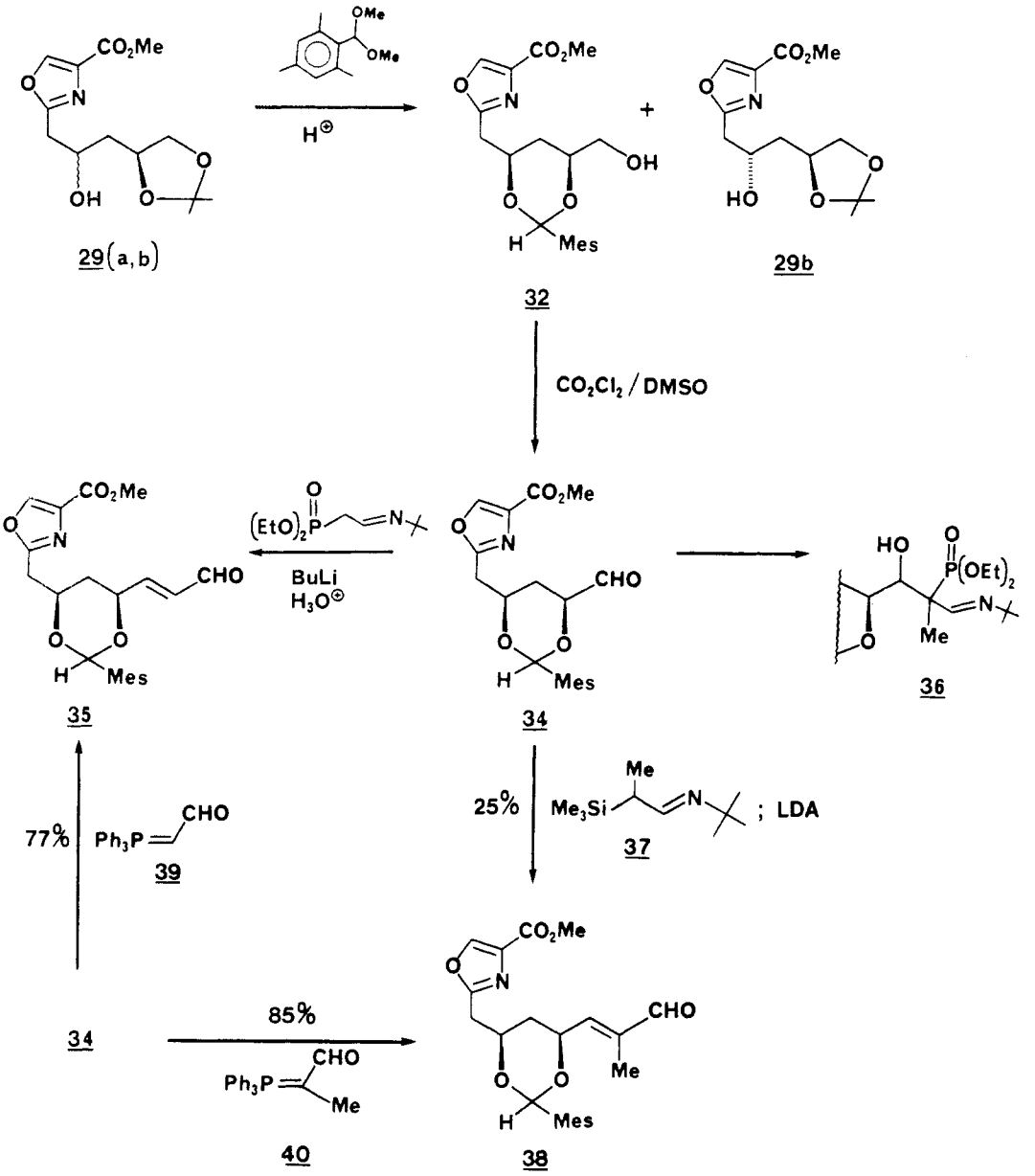
Scheme IV



out under basic conditions, the syn elimination process required for formation of the unsaturated imine should encounter the same problems as the phosphonate adduct. To possibly alleviate this problem, conditions under which an anti elimination pathway would be operating were chosen.[49] By quenching the condensation reaction with acetic anhydride and then treating the mixture with tetrabutylammonium fluoride,[50] the yield of the aldehyde **38** (after imine hydrolysis) was increased to the 40–45% range as a 15:1 *E*/*Z* ratio.

Considerable improvement in yield and simplification of the experimental procedure was achieved by using the stabilized phosphorane reagents **39** and **40**.[51] For the griseoviridin fragment, the aldehyde **35** was obtained with greater than 90% stereoselectivity for the *E* isomer. After flash chromatography only the *E* isomer was isolated in 67–77% yield. The homogeneity of the pure compound by TLC and HPLC indicated that no racemization of the chiral center at C-13 had occurred in the homologation step. In the case of the madumycin fragment **38**, only the *E* isomer was obtained if slightly greater than 1 equiv of **40** was used and the reaction mixture refluxed (in benzene) for a minimum of 24 h. The pure *E* aldehyde **38** was then isolated in 79–85% yields.

Application of the vinylphosphonium salt chemistry[19,52] then completed the synthesis of the oxazole fragments. Treating aldehyde **35** with sodium phthalimide, in the presence of vinyltributylphosphonium bromide, led to the isolation of the oxazole dienyl phthalimide **41** in 26% yield. ^{1}H NMR spectral analysis of the product indicated that the *E*/*Z* selectivity of this reaction was not as favorable as with simple aldehydes.[19] An *E*:*Z* ratio of 65:35 was determined by integration of the two C-20 oxazole proton resonances. Using a somewhat modified procedure, the homologation of aldehyde **38** to the madumycin oxazole amine **42** was accomplished with greater success. The *E*,*E*

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isomer was obtained exclusively in 51% yield after chromatography. Interestingly, the same reaction conditions using triphenylvinylphosphonium bromide (Schweizer's reagent[53]), which should give the *E*, *Z* isomer, did not provide any homologated material.

In summary, we have succeeded in the stereospecific preparation of the oxazole dienyl amine moiety of griseoviridine (**41**) and madumycin II (**42**) in optically active form. The problems of regiochemical control in the protection of a 1,3,4-triol as an acetonide or an acetal have been demonstrated, and methods for the regiospecific preparation of the dioxane or dioxolane protected form have been disclosed. In particular, the unique diastereomeric resolution of the mesitylidene acetal may prove valuable in the synthesis of other natural products.

Experimental Section

General. The infrared data were obtained from one of the following instruments: a Beckman 4240, Perkin-Elmer 267, or Beckman Acculab 3 spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Varian T60 (60 MHz), Varian EM360A (60 MHz), JEOL JNMFX100 (100 MHz), or a Nicolet NT360 (360 MHz) spectrophotometer for proton spectra. Carbon spectra were recorded on the JEOL JNMFX100 instrument. Mass spectra were obtained on a VG Micromass MM16F mass spectrometer and the data are reported as mass to charge ratio (*m/e*). High resolution mass spectra were recorded at the NSF Regional Instrumentation Facility, University of Nebraska, Lincoln, NE. Optical rotations were recorded on a Perkin-Elmer 241 or a Rudolph Research Autopol III polarimeter in a 1-dm cell.

Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, IN, or MicAnal, Tucson, AZ. The active organometallic content of the organolithium reagents was checked periodically by titration with diphenylacetic acid or 1,10-phenathroline and *sec*-propanol.[54]

(*S*)-Diethyl Malate. To 130 g (970 mmol) of L-malic acid in 800 mL of absolute ethanol was added 3 mL of concentrated HCl. The mixture was heated to reflux for 11 h and the ethanol was removed by distillation. The residue was diluted with ether and was washed with 3 × 20 mL of saturated $NaHCO_3$ and 30 mL of brine. Drying (Na_2SO_4), concentration, and distillation gave 144 g (78.3%) of a colorless oil, bp 80–85 °C (0.05 mm): $[\alpha]^{25}_D$ −15.12° (*c* 5.65, acetone) [lit.[55] −14.16° (*c* 6.43, acetone)]; NMR ($CDCl_3$) δ 4.42 (t, *J* = 6 Hz, 1), 4.20 (q, *J* = 7 Hz, 2), 4.13 (q, *J* = 7 Hz, 2), 3.05 (br s, 1), 2.80 (d, *J* = 6 Hz, 2), 1.30 (t, *J* = 7 Hz, 3), 1.26 (t, *J* = 7 Hz, 3).

(*S*)-Diethyl Malate 2-(1-Methyl-1-methoxyethyl ether).[20b] To 148 g (780 mmol) of (*S*)-diethyl malate in 75 mL of dry ether was added 235 mL (2.5 mol) of 2-methoxypropene. The solution was cooled to 0 °C and 20 drops of $POCl_3$ were added. The mixture was stirred at 0 °C for 3 h at which time TLC (silica gel, acetone–hexane (1:9), Ce^{IV} visualization) showed that no starting material was present. To the solution was added 1 mL of triethylamine, and the mixture was concentrated. The cloudy residue was diluted with 300 mL of ether and was filtered through a 2-cm pad of alumina with suction. Concentration gave 202 g (99.1%) of a clear light yellow oil: NMR ($CDCl_3$) δ 4.65 (t, *J* = 6 Hz, 1), 4.25 (q, *J* = 7 Hz, 2), 4.18 (q, *J* = 7 Hz, 2), 3.2 (s, 3), 2.72 (d, *J* = 6 Hz, 2), 1.43 (s, 6), 1.25 (t, *J* = 7 Hz, 3), 1.23 (t, *J* = 7 Hz, 3).

(*S*)-1,2,4-Butanetriol 2-(1-Methyl-1-methoxyethyl ether).[20b] To 1 L of dry THF at 0 °C was slowly added 37.5 g (988 mmol) of lithium aluminum hydride. To the mechanically stirred suspension at 0 °C was slowly added 199 g (760 mmol) of (*S*)-diethyl malate 2-(1-methyl-1-methoxyethyl ether) in 300 mL of dry THF. The temperature was maintained below 15 °C during the 4-h addition. The mixture was allowed to warm to ambient temperature and after 5 h TLC showed no starting material was present (acetone/hexane (1:9), Ce^{IV} visualization). The suspension was stirred overnight and was cooled to 0 °C. To the grey mixture was slowly added 37.5 mL of H_2O in 90 mL of THF followed by 37.5 mL of 15% NaOH and 112.5 mL of H_2O. The mixture was stirred until the suspension became white and was then vacuum filtered. The residue was washed with 500 mL of THF and the combined filtrates were concentrated to give a cloudy oil. Toluene was added (200 mL) and the mixture was again concentrated to constant weight to give 104 g (77%) of a clear colorless syrup: NMR ($CDCl_3$) δ 4.05 (m, 1), 3.69 (t, *J* = 6 Hz, 2), 3.58 (t, *J* = 5 Hz, 2), 3.38 (s, exchanges with D_2O, 2), 3.35 (s, 3), 1.74 (q, *J* = 6 Hz, 2), 1.42 (br s, 6).

Cyclization of (*S*)-1,2,4-Butanetriol 2-(1-Methyl-1-methoxyethyl ether).[20b] To 104 g (584 mmol) of diol in 500 mL of dry ether at 0 °C was added 150 μL of $BF_3{\cdot}Et_2O$. Within seconds the mixture became cloudy and the mixture was allowed to slowly warm to ambient temperature. After 3 h the insoluble triol had completely disappeared and TLC (acetone/hexane, 1:2) indicated that no starting material was present. An aliquot was removed, quenched with triethylamine, filtered through a short plug of Florisil, and concentrated. NMR ($CDCl_3$, 60 MHz) revealed the presence of about a 3:2 ratio of 1,2- and 1,3-acetonides, **10** and **11**, respectively. The reaction mixture was stirred at 23 °C for an additional 48 h and 1 mL of triethylamine was added. The mixture was filtered through a 3-cm pad of alumina and was concentrated and distilled to give 74.7 g (90.3%) of a colorless oil, bp 59.5–62 °C (0.15 mm). The NMR spectrum ($CDCl_3$) in the presence of 0.2 equiv of $Eu(hfc)_3$ indicated that the two acetonides (**10**, **11**) were present in a ratio of 9:1.

Reaction of (±)-1,2,4-Butanetriol with Acetone. To 100 g (943 mmol) of racemic 1,2,4-butanetriol was added 175 mL (2.4 mmol) of acetone and 500 mL of benzene. A few crystals of *p*-toluenesulfonic acid monohydrate were added and the mixture was heated to reflux. The water was removed with a Dean–Stark trap and the reaction was continued until production of water ceased (48–96 h). The homogeneous mixture was concentrated and the residue was distilled to give 123 g (94.2%) of colorless material, bp 107 °C (20 mm), 93–94 °C (4 mm). The spectra data were identical with those of the optically active acetonides **10** and **11**. Addition of 51.5 mg of $Eu(hfc)_3$ (0.20 equiv) to 31 mg of the mixture in about 0.4 mL of $CDCl_3$ resulted in the separation of an otherwise obscured pair of acetonide methyl signals from beneath the acetonide methyls belonging to the major isomer. Integration indicated a ratio of approximately 9:1.

(*S*)-1,2,4-Butanetriol 1,2-Acetonide 1-(3,5-Dinitrobenzoate) (12). To 83.4 g (362 mmol) of 3,5-dinitrobenzoyl chloride in 600 mL of CH_2Cl_2 (distilled from P_2O_5) at 23 °C was added 52 mL (373 mmol) of triethylamine (distilled from CaH_2). The deep red solution was cooled to 0 °C and 2.15 g (0.05 equiv) of 4-(dimethylamino)pyridine was added. A precipitate quickly formed and 51.3 g (351 mmol) of the isomeric mixture of acetonides in CH_2Cl_2 was added dropwise over 15 min. The suspension was allowed to warm to ambient temperature and was stirred for 15 h at which time TLC (acetone/hexane, 1:9) indicated that no starting alcohol was present. The dark red suspension was diluted with 300 mL of H_2O and the mixture was stirred for 10 min. The layers were separated and the organic layer was washed with 2.5% HCl, saturated $NaHCO_3$, and brine. After drying (Na_2SO_4), the solution was passed down a 3 × 15 cm column of silica gel and was concentrated to give 105 g (88%) of a dark solid. The material was recrystallized three times from absolute ethanol at 50 °C (5 mL of EtOH/g of solid) to give 48.8 g (41%) of an off-white solid, mp 62.1–63.0 °C. HPLC (μ-Porosil, 8% THF in hexane, 2 mL/min) indicated that the material was 99.9% regiochemically pure. The retention time for **12** was 10.8 min and 12.7 min for **13**. Pure **12**: $[\alpha]^{24}_{589}$ −13.7°, $[\alpha]^{24}_{546}$ −16.0°, $[\alpha]^{24}_{436}$ −26.8°; NMR ($CDCl_3$) δ 9.15 (m, 3), 4.70–3.50 (m, 5), 2.10 (q, *J* = 6 Hz, 2), 1.42 (s, 3), 1.33 (s, 3). Anal. Calcd for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.57; H, 4.78; N, 8.31.

A sample enriched in the minor isomer **13** was obtained by radial preparative TLC (Chromatotron, 2-mm plate, acetone/hexane, 1:2) and was recrystallized from absolute ethanol to give a colorless solid, mp 92.5–93.0 °C: $[\alpha]^{24}_{589}$ +14.4°, $[\alpha]^{24}_{546}$ +16.9°, $[\alpha]^{24}_{436}$ +28.5° (*c* 1.3, $CHCl_3$) [HPLC indicated that **13** was 96.5% regiochemically pure]; NMR (360 MHz, $CDCl_3$) δ 9.24 (m, 1), 9.135 (m, 2), 4.47–4.25 (m, 3), 4.30–3.87 (m, 2), 1.82–1.50 (m, 2), 1.52

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(s, 3), 1.43 (s, 3). MS (70 eV), m/e 325 (relative intensity) (49.6, molecular ion minus acetonide methyl), 195 (80.3), 149 (20.6), 115 (25.8), 43 (base peak). Anal. Calcd for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.33; H, 4.74; N, 8.33.

(*S*)-1,2,4-Butanetriol 1,2-Acetonide (10).[20] To 36 g (350 mmol) of a pulverized anhydrous K_2CO_3 suspended in 1200 mL of anhydrous methanol (used without further drying) was added 59.5 g (175 mmol) of dinitrobenzoate **12** (99.9% regiochemically pure). The mixture became pink and was stirred at 23 °C for 18 h. The suspension was vacuum filtered, the filtrate was concentrated, and the residue was diluted with ether to precipitate the remaining inorganic salts. The suspension was vacuum filtered through a 10 × 10 cm column of silica gel topped with 2 cm of Celite. The column was rinsed with ether and the combined filtrates were concentrated and distilled to give 21.3 g (83.3%) of a colorless oil, bp 55–61 °C (0.05 mm): $[\alpha]^{24}_{589}$ −2.23° (*c* 9.8, MeOH); NMR (100 MHz, $CDCl_3$) δ 4.26–3.95 (m, 2), 3.73–3.44 (m, 3), 2.65 (br s, 1), 1.74 (dt, J = 5.5 Hz, J = 6 Hz), 1.35 (s, 3), 1.29 (s, 3).

(*S*)-3,4-Dihydroxybutanal Acetonide[20] **(9).** To 146 mL of dry pyridine (distilled from CaH_2) in 1600 mL of CH_2Cl_2 (distilled from P_2O_5) at 5 °C was added 90.4 g (904 mmol) of chromium trioxide (dried over P_2O_5 at 0.01 mm). The temperature rose to 12 °C and was allowed to slowly warm to 23 °C over 2 h. The dark solution was transferred via a Teflon cannula to a 3-L three-necked Morton flask that was fitted with a mechanical stirrer. The solution was cooled to 0 °C and 14.6 g (100 mmol) of the alcohol **10** in 30 mL of CH_2Cl_2 was added. The mixture was stirred at 0 °C for 20 min and was warmed to 23 °C. After 20 min, TLC (acetone/hexane, 1:2, Ce^{IV} visualization) indicated that no alcohol was present. The mixture was poured into 1.5 L of 1:1 ether/hexane. The flask was rinsed with 300 mL of CH_2Cl_2 and the rinsing was added to the ether/hexane mixture. The combined organics were stirred for 10 min and then vacuum filtered through a 2 × 20 cm column of Florisil topped with 5 cm of Celite. The column was rinsed with ether and the combined filtrates were concentrated. The residue was diluted with 200 mL of toluene and was concentrated to remove excess pyridine. The residue was fractionally distilled and gave two fractions. The low boiling fraction was colorless aldehyde **9** (6.95 g, 48.3%), bp 57 °C (3 mm): $[\alpha]^{24}_{589}$ +16.5°, $[\alpha]^{24}_{546}$ +19.3°, $[\alpha]^{24}_{436}$ +31.4°, $[\alpha]^{24}_{365}$ +39.4° (*c* 5.32, $CHCl_3$); NMR (100 MHz, $CDCl_3$) δ 9.80 (t, J = 1.5 Hz, 1), 4.53 (m, 1), 4.18 (dd, J = 8 Hz, J = 6 Hz, 1), 3.58 (dd, J = 8 Hz, J = 6 Hz, 1), 2.74 (m, 2), 1.41 (s, 3), 1.37 (s, 3) [The higher boiling fraction, bp 131–135 °C (1 mm), was the dimeric ester[20d] **14**.]; IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.8–4.0 (m, 6), 3.7 (m, 2), 2.62 (m, 2), 2.0 (m, 2), 1.45 (s, 3), 1.37 (s, 3); MS (70 EV), m/e (relative intensity) 273 (molecular ion minus acetonide methyl, 50.6), 129 (54.2), 101 (58.5), 85 (36.9), 72 (60.3), 71 (base), 59 (32.3), 43 (99.3).

Oxazoles from the Cornforth Synthesis (Scheme III). Methyl Acetimidate Hydrochloride. A 500-mL Erlenmeyer flask was charged with 82.1 g (2.0 mol) of acetonitrile and 64.1 g (2.0 mol, 1.0 equiv) of absolute methanol. The resulting solution was cooled to 0 °C with good stirring. Anhydrous hydrogen chloride gas was bubbled into the solution with continued good stirring at such a rate so as to maintain a reaction temperature of 15–20 °C. Introduction of the gas was monitired by periodic weighing of the tared reaction vessel (note: weighing of the reaction flask was done as quickly as possible, as the reaction exothermed significantly on removal from the cooling bath). A total of 96 g (2.6 mol, 1.3 equiv) of gas was introduced over ca. 135 min. Following the addition of gas, viscous reaction was stirred at 0 °C for 45 min, during which time the reaction solidified. After this time, 50 mL of dry ether (from benzophenone ketyl) was added, and the flask was refrigerated overnight. Filtration of the solid under argon followed by drying under reduced pressure afforded 209.0 g (95%) of **9** as a hygroscopic, colorless solid. This material was used immediately for the subsequent transamination reaction with methyl glycinate hydrochloride.

Methyl α-[(Methoxyethylidene)amino]acetate A flame-dried flask under a blanket of dry argon was charged with 179.60 g (1.64 mol) of methyl acetimidate hydrochloride and 2.5 L of dry dichloromethane (from phosphorus pentoxide). The resulting suspension was cooled to 0 °C, and 210 g (1.64 mol, 1.0 equiv) of methyl glycinate hydrochloride was added in one portion with good stirring. The heterogeneous reaction mixture was stirred at 0 °C for an additional 45 min. After this time, a solution of 165.90 g (1.64 mol, 1.0 equiv) of dry triethylamine (from calcium hydride) in 200 mL of dry dichloromethane was added dropwise over 150 min with continued good stirring at 0 °C. Following the addition, the reaction mixture was stirred for 5 h while slowly being warmed to ambient temperature. A total of 500 mL of pH 7 buffered water was added, and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 250 mL), and the combined organic phases were washed with pH 7 buffered water (1 × 300 mL) and brine (1 × 300 mL). Drying over anhydrous magnesium sulfate, filtration, and concentration under reduced pressure gave 227.1 g (95%) of crude reaction product. Distillation under reduced pressure afforded 179.0 g (75%) as a colorless liquid, which solidified on standing: bp 98 °C (33 mm); NMR ($CDCl_3$) δ 1.87 (s, 3 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 4.00 (s, 2 H); IR (film) 2955 (m), 1750 (s), 1684 (s), 1439 (m), 1328 (m), 1272 (s), 1200 (s), 1179 (s), 1058 (m), 803 (w) cm^{-1}.

Potassium Methyl α-[(Methoxyethylidene)amino]-β-hydroxyacrylate (15). A flame-dried flask under a blanket or dry argon was charged with 7.73 g (69 mmol, 1.0 equiv) of potassium *tert*-butoxide and 200 mL of dry tetrahydrofuran. The resulting mixture was cooled to −10 °C. After ca. 15 min, a solution of 10 g (69 mmol) of freshly distilled methyl α-[(methoxyethylidene)amino]acetate and 5.0 mL (83 mmol, 1.2 equiv) of dry methyl formate (from phosphorus pentoxide) in 50 mL of dry tetrahydrofuran was added dropwise with good stirring over a period of 20 min. Following the addition, the resulting yellow solution was stirred at −10 °C for 5 min, after which time 750 mL of dry ether (from benzophenone ketyl) was added via a cannula. The heterogeneous mixture thus obtained wa stirred at 0 °C for 2 h. The precipitate was collected by filtration of the reaction through a Schlenk tube under argon. The collected solid was washed with dry ether (3 × 45 mL) and was dried under a stream of dry argon. Further drying under reduced pressure yielded 11.0 g (76%) of a hygroscopic, light yellow powder. This material was used immediately. ^1H NMR δ (Me_2SO-d_6), 1.61 (s, 3 H), 3.35 (s, 3 H), 3.53 (s, 3 H), 8.62 (s, 1 H).

General Procedure for 2-Substituted-4-carbomethoxyoxazoles 25–28. The freshly prepared potassium enolate **15** was transferred under argon to a three-necked flask fitted with serum caps. The flask was cooled to −78 °C and to n g of the enolate was added 30n mL of dry THF at 0 °C. To the suspension was added 10n mL of dry purified diglyme, and the mixture was allowed to warm to −20 °C. The temperature was maintained at −20 °C until all of the enolate had dissolved to give a clear light yellow solution. The mixture was cooled to −100 °C and 1.0 equiv of *tert*-butyllithium (pentane) was added over a 5-min period (2–4-mmol scale). The solution became amber and remained clear. The mixture was stirred at −100 °C for 1 h and 1.0 equiv of an aldehyde or halide in THF was added over a 5-min period. The color of the dianion faded during the addition. The mixture was stirred at −100 °C for 20 min and 2.05 equiv of boron trifluoride etherate (distilled from CaH_2) was added at once. The mixture was stirred at −100 °C for 5 min and the colling bath was removed and stirring continued at 23 °C for 16 h when 1 mL of saturated aqueous $NaHCO_3$ was added. The solvents were removed at reduced pressure and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with three portions of ether and the combined organic layer was washed with 4 × 10 mL of saturated aqueous $NaHCO_3$ and brine and was dried over K_2CO_3. Concentration gave a yellow syrup that was chromatographed on silica gel (PLC) using acetone/hexane (1:2) to give the desired oxazoles (Table I).

4-Carbomethoxy-2-(2-(4-chlorophenyl)-2-hydroxyethyl)-oxazole (25). The oxazole was isolated in 56% yield following PLC. Recrystallization from THF/hexane gave an off white powder, mp 100.5–101.5 °C: ^1H NMR ($CDCl_3$) δ 8.1 (s, 1), 7.26 (s, 4), 5.25 (t, J = 6 Hz, 1), 4.18 (br s, 1, OH), 3.85 (s, 3), 3.2 (d, J = 3 Hz, 2). Anal. Calcd for $C_{13}H_{12}NO_4Cl$: C, 55.43; H, 4.29; N, 4.97. Found: C, 55.53; H, 4.24; N, 4.77.

4-Carbomethoxy-2-(2-phenyl-2-hydroxyethyl)oxazole (26). The oxazole was isolated in 51% yield following PLC. Recrystallization from ethanol/ether gave colorless crystals, mp 91.5–92 °C: IR (melt) cm^{-1} 3360 (m), 1730 (s), 1586 (s), 1438 (s), 1322 (s), 1200 (s), 1113 (s), 701 (s); ^1H NMR ($CDCl_3$) δ 8.10 (s, 1), 7.38

(s, 5), 5.22 (t, J = 6 Hz, 1), 3.82 (br s, 1, OH), 3.80 (s, 3), 3.15 (d, J = 6 Hz, 2). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.17; H, 5.11; N, 5.90.

4-Carbomethoxy-2-(2-hydroxy-3-methyl-1-butyl)oxazole (27). The oxazole was isolated in 45% yield following PLC: ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1), 3.9 (m, 1), 3.9 (s, 3), 3.92 (m, 2), 1.04 (s, 3), 0.96 (s, 3); IR (cap film) cm^{-1} 3440 (m), 2978 (s), 1736 (s), 1587 (s), 1440 (m), 1325 (s), 1196 (s), 1141 (s), 1112 (s), 1005 (s), 732 (s). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.05, H, 6.95.

4-Carbomethoxy-2-(2-phenethyl)oxazole (28). The above procedure was followed for the metalation, and benzyl bromide in THF was added at −100 °C. The color of the anion faded within minutes. The mixture was stirred at −100 °C for 1 h and at −78 °C for 20 h. Precipitation occurred on warming to −78 °C. The THF was removed at reduced pressure (10 mm) and the residue was slowly added to refluxing glacial acetic acid (3 mL of HOAc/mmol). The mixture was heated at reflux for 10 min and the solution was cooled. The mixture was neutralized with solid K_2CO_3 followed by saturated $NaHCO_3$ and was extracted with three portions of ether. The combined organic layer was dried over K_2CO_3 and was concentrated to give a dark red oil. Chromatography gave the β-phenethyloxazole **28** in 38% yield, mp 64–66 °C: ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1), 7.20 (s, 5), 3.85 (s, 3), 3.08 (s, 4). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.23; H, 5.63; N, 5.86.

Oxazole Acetonides 29. To 3.94 g (18.7 mmol) of freshly prepared potassium enolate **15** at −78 °C under argon was added 118 mL of dry THF at 0 °C. The suspension was stirred at −78 °C and 39 mL of dry diglyme was added, and the mixture was allowed to slowly warm to −20 °C. The enolate dissolved to give a clear yellow solution and the homogeneous mixture was cooled to −100 °C. To the clear solution was added 9.33 mL (18.7 mmol) of 2.0 M t-BuLi (pentane) dropwise over 10 min. The solution became amber and was stirred at −100 °C for 40 min. To the solution of the dianion was added 2.69 g (18.7 mmol) of aldehyde **9** in 20 mL of THF. The color of the dianion faded during the addition to give a clear yellow solution. The mixture was stirred at −100 °C for 20 min and 4.7 mL (38.3 mmol) of BF_3·Et_2O (distilled from CaH_2) was added. The mixture was warmed to 0 °C and was allowed to slowly warm to ambient over a 12-h period by transferring the reaction flask to a small Dewar containing water at 0 °C. The cloudy yellow suspension was stirred at 23 °C for 26 h and 2 mL of saturated $NaHCO_3$ was added. The material was transferred to a single-necked flask and the THF was removed at reduced pressure. The diglyme was removed by warming the flask to 35 °C at 0.05 mm and was collected at −78 °C. The residue was dissolved in saturated $NaHCO_3$ and ether. The layers were separated and the aqueous layer was washed with 2 × 100 mL of ether. The combined organic layers were washed with 2 × 30 mL of saturated $NaHCO_3$ and 30 mL of brine. Drying (K_2CO_3) and concentration gave 2.12 g (40%) of a yellow syrup. The NMR spectrum indicated a mixture of the desired oxazole and the unelaborated heterocycle **16** was present. The molar ratio of **29** to **16** was 57:43.

The material from several reactions was combined and chromatographed (Waters Prep 500) using 1:4 acetone/hexane at 500 mL/min. The retention time of the unelaborated oxazole **16** was 2–3 min and the desired oxazole acetonide was eluted in 5–8 min. HPLC (μ-Porosil, EtOAc/$CHCl_3$, 35:65) indicated the ratio of the *RS* to *SS* diastereomer was 54:46. The retention time of the *RS* diastereomer **29a** was 6.4 min and that of **29b** was 7.9 min. Spectral data for the mixture: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.10 (s, 1), 4.65–3.45 (m, 5, 4 after exchange with D_2O), 3.90 (s, 3), 3.00 (d, J = 6 Hz, 2, 1.82 (t, J = 6 Hz, 2), 1.45 (s, 3), 1.38 (s, 3). The 25-MHz ^{13}C NMR spectrum exhibited 20 resonances for the 1:1 mixture of the 13 carbon diastereomers: ($CDCl_3$) δ 163.2, 163.1, 161.3, 143.7, 132.9, 109.2, 108.6, 77.0, 74.7, 73.1, 69.4, 68.1, 66.4, 52.0, 39.8, 39.6, 36.1, 35.8, 26.8, 25.6. IR (cap film) cm^{-1} 3438 (m), 3145 (w), 2975 (s, 2925 (s), 2863 (m), 1735 (s), 1583 (s), 1436 (s), 1378 (s), 1368 (s), 1321 (s), 1199 (s), 1139 (s), 1108 (s), 1063 (s), 1002 (s), 856 (m), 826 (m), 804 (m), 762 (m). MS (70 eV), m/e (relative intensity) 270 (molecular ion minus acetonide methyl, base), 228 (29.0), 210 (54.8), 178 (52.9), 141 (77.6), 87 (83.2), 43 (56.2). Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71. Found: C, 54.40; H, 6.46.

(+)-Acetonide Oxazole Phenyl Carbonates 30a,b. To 373 μL (4.62 mmol) of dry pyridine in 10 mL of dry ether was added 723 mg (4.62 mmo6) of phenyl chloroformate in 5 mL of ether. The thick white suspension was stirred for 10 min and 1.25 g (4.4 mmol) of diastereomeric oxazole acetonide **29** in 20 mL of ether was added. Stirring was continued for 48 h at which time TLC (acetone/hexane, 1:2) showed incomplete conversion. An additional 344 μL (2.2 mmol) of phenyl chloroformate and 178 μL of pyridine (2.2 mmol) were added. After stirring for 4 h TLC indicated that no starting alcohol was present. The mixture was filtered through Celite and was concentrated to give 1.86 g (104%) of a syrup. A 312-mg portion of the material was subjected to PLC (20 × 40 cm plate, acetone/hexane, 1:2) and gave 291 mg (97%) of purified material. Material from several reactions was combined and chromatographed (Waters Prep 500, acetone/hexane, 12:88, 300 mL/min) to give (after peak shaving and recycling) **30a** and **30b**. Physical properties of **30a**: t_R (HPLC, μ-Porosil, $CHCl_3$/hexane, 4:1) was 8.5 min at 2.0 mL/min; ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.22 (s, 1), 7.6–7.0 (m, 5), 5.39 (q, J = 6 Hz, 1), 4.5–3.4 (m, 3), 3.91 (s, 3), 3.30 (d, J = 6 Hz, 2), 2.05 (m, 2), 1.40 (s, 3), 1.35 (s, 3); 25-MHz ^{13}C NMR ($CDCl_3$) δ 161.1, 152.5, 150.6, 144.1, 133.1, 129.2, 125.8, 120.7, 109.1, 73.5, 72.1, 69.0, 52.0, 37.1, 36.5, 32.7, 26.8, 25.5; IR (cap film) 3400 (w), 2980 (m), 1759 (s), 1589 (s), 1490 (m), 1440 (m), 1370 (s), 1320 (s), 1250 (s), 110 (m), 1060 (m), 760 (m), 730 (m), 690 (m). Physical properties of **30b**: t_R (HPLC, μ-Porosil, $CHCl_3$/hexane, 4:1) was 7 min at 2.0 mL/min; ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.20 (s, 1), 7.5–7.0 (m, 5), 5.30 (q, J = 6 Hz, 1), 4.50–3.42 (m, 3), 3.88 (s, 3), 3.27 (m, 2), 2.00 (m, 2), 1.39 (s, 3), 1.31 (s, 3); ^{13}C NMR (25 MHz, $CDCl_3$) δ 160.6, 152.1, 150.3, 144.2, 143.6, 132.6, 129.2, 128.7, 125.4, 125.3, 120.34, 120.29, 108.5, 73.4, 71.8, 68.7, 51.5, 37.6, 32.8, 26.7, 26.6, 26.4, 25.4, 25.3, 25.1, 24.9.

(+)-Oxazole Carbonate 31a. To 360 mg (0.89 mmol) of phenyl carbonate **30a** in about 10 mL of THF was added 3.5 mL of 1 N HCl. The mixture was stirred at 23 °C for 23 h and was poured into ether. The mixture was washed with brine, saturated $NaHCO_3$, and brine and was dried over $MgSO_4$. Concentration gave 231 mg (71%) of the diol as a colorless syrup. The diol was dissolved in 7 mL of dry THF and 2 drops of DBN were added. The solution was stirred for 21 h and was concentrated. The mixture was chromatographed (PLC, acetone/hexane, 1:1) to give 92 mg (54%) of the cyclic carbonate **31a** as a colorless solid, mp 86–91.5 °C: R_f 0.2; ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.22 (s, 1), 5.25–4.15 (m, 4), 3.90 (s, 3), 2.80 (br s, 1), 3.10 (d, J = 6 Hz, 2), 2.15 (m, 2); ^{13}C NMR (25 MHz, $CDCl_3$) δ (off resonance multiplicity) 162.7 (s), 161.0 (s), 154.8 (s), 143.8 (d), 132.4 (d), 74.4 (d), 69.3 (t), 64.8 (d), 51.9 (q), 39.1 (t), 35.5 (t); IR (cap film) cm^{-1} 3330 (s), 1790 (s, carbonate), 1736 (s, methyl ester), 1590 (s, oxazole), 1175 (s), 1112 (s), 1072 (s), 768 (s). Anal. Calcd for $C_{11}H_{13}NO_7$: C, 48.71; H, 4.83. Found: C, 48.98; H, 5.10.

(+)-Oxazole Carbonate 31b. The cyclic carbonate was prepared from **30b** exactly as for carbonate **31a**. The diol was obtained in 80% yield and gave **31b** in 52% yield upon treatment with DBN. The compound crystallized from $CDCl_3$ to give colorless needles, mp 128–129 °C: ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1), 5.2–3.7 (m, 4), 3.90 (s, 3), 3.0 (m, 2), 2.0 (m, 2).

Oxazole Mesitylidene Acetal 32. To 2.22 g (7.80 mmol) of the mixture of diastereomeric acetonides **29** in 65 mL of CH_2Cl_2 (distilled from P_2O_5) at 0 °C was added 3.03 g (15.6 mmol) of mesitaldehyde dimethyl acetal[56] and 362 mg (1.56 mmol) of camphorsulfonic acid (dried by azeotropic removal of water with toluene at reduced pressure).

The solution was stirred at 0 °C and the progress of the reaction was monitored by HPLC (μ-Porosil, EtOAc/$CHCl_3$, 35:65, 254 nm, 2.0 mL/min). After 48 h, the (*R,S*)-acetonide **29a** (t_R 6.8 min) was absent and the (*S,S*)-acetonide **29b** (t_R 7.9 min) remained. The mesitylidene acetal **32** had t_R 5.4 min. The solution was diluted with EtOAc and was wshed with 30 mL of saturated $NaHCO_3$ and brine. After drying (K_2CO_3), the yellow solution was concentrated onto 35 mL of Florisil. The free flowing solid was placed on top of a 4 × 2 cm column of Florisil and was eluted with 1:4 ether/hexane until the eluent did not absorb UV (TLC plate, 254 nm). Concentration of the eluent permitted recovery

(56) Davis, T. S.; Feil, P. D.; Kuber, D. G.; Wells, J. *J. Org. Chem.* **1975**, *40*, 1478.

of excess mesitaldehyde. The column was then eluted with about 400 mL of EtOAc. Concentration gave 2.69 g of a yellow syrup. The mixture of acetals was chromatographed (Waters Prep 500, 1 column, acetone/hexane, 22:78, 400 mL/min) and gave 780 mg (70%) of acetonide **29b** (t_R 5.5–9.5 min) and 1.31 g (90%) of acetal **32** (t_R 10.0–17.0 min) as a colorless solid, mp 68–71 °C: $[\alpha]^{24}_{589}$ −6.91°, $[\alpha]^{24}_{436}$ −17.0°8 (*c* 1.49, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.15 (s, 1), 6.80 (br s, 2), 5.90 (s, 1), 4.35 (m, 1), 3.9 (m, 1), 3.90 (s, 3), 3.62 (m, 2), 3.17 (dd, *J* = 6.8 Hz, *J* = 14.8 Hz, 1), 3.07 (dd, *J* = 6.8 Hz, *J* = 14.8 Hz, 1), 2.40 (s, 6), 2.24 (s, 3), 1.63 (m, 2); ^{13}C NMR (25 MHz, $CDCl_3$) δ 161.8, 161.2, 143.7, 138.1, 136.4, 133.0, 130.5, 129.6, 99.7, 77.1, 73.8, 65.3, 52.0, 34.6, 31.8, 20.8, 20.4. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.69; H, 6.91.

Oxazole Aldehyde 34. A three-necked, 100-mL round-bottomed flask, fitted with two addition funnels, was flame-dried and purged with argon. The flask was charged with 30 mL of dry methylene chloride (distilled from P_2O_5) and freshly distilled oxalyl chloride (96 μL, 1.1 mmol). A solution of dry dimethyl sulfoxide (156 μl, 22 mmol) (distilled from BaO, stored under argon) in 4 mL of dry methylene chloride was then placed in an addition funnel and a solution of the oxazole alcohol **32** (375 mg, 1 mmol) in 4 mL of methylene chloride was added to the second addition funnel. The flask was then cooled to −70 °C (CO_2/acetone, bath temperature) and the dimethyl sulfoxide solution added dropwise. The mixture was stirred for 10 min (at −70 °C) and the alcohol solution was then added dropwise. The mixture was allowed to warm to −55 °C (bath temperature) and maintained at that temerature for 20 min. After recooling to −70 °C, triethylamine (697 μL, 5 mmol) (distilled from CaH_2) was added via syringe. The mixture was then allowed to warm to room temperature over a 1-h period. A warm water bath (approximately 35 °C) was then placed under the flask until the solution began to boil. The reaction mixture was then diluted with an additional 75 mL of methylene chloride, washed with water (1 × 20 mL) and 5% aqueous potassium carbonation solution (1 × 25 mL), and then dried over anhydrous potassium carbonate. The solution was filtered and evaporated, and the residue was chromatographed (silica gel, 230–400 mesh, 35% acetone/hexane eluent), obtaining 305 mg of a colorless solid (82%): mp 56–58 °C; $[\alpha]^{20}_{589}$ −26.2°, $[\alpha]^{20}_{546}$ −31.9°, $[\alpha]^{20}_{436}$ −62.3° (*c* 1.80, $CHCl_3$); IR (film) cm^{-1} 2950 (m), 1732 (s), 1610 (m), 1580 (s), 1432 (s), 1320 (s), 1108 (s), 1062 (s), 982 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 9.67 (s, 1), 8.15 (s, 1), 6.83 (br s, 2), 5.96 (s, 1), 4.40 (m, 1), 4.30 (dd, *J* = 11.1 Hz, *J* = 3.3 Hz, 1), 3.90 (s, 3), 3.15 (m, 2), 2.41 (s, 6), 2.24 (s, 3), 1.90 (m, 2); ^{13}C NMR (25 MHz, $CDCl_3$) δ (off resonance multiplicity) 199.7 (d, aldehyde), 161.5 (s), 161.3 (s), 143.9 (d), 138.7 (s), 136.7 (s), 133.3 (d), 129.8 (s), 129.8 (d), 100.0 (d, acetal), 80.2 (d), 74.0 (d), 52.1 (q), 34.6 (s), 30.8 (t), 21.0 (q), 20.5 (q). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.32; H, 6.22. Found: C, 64.08; H, 6.05.

Oxazole Aldehyde 35 via Phosphorane 39. A 50-mL round-bottomed flask was flame-dried and purged with argon. The flash was charged with 25 mL of dry benzene (distilled from Na/benzophenon), the oxazole aldehyde **34** (150 mg, 0.4 mmol), and formyltriphenylphosphorane[51] (134 mg, 0.44 mmol). The solution was then heated to reflux under an inert atmosphere for 24 h. After cooling to room temperature, the solvent was evaporated and the residue chromatographed (silica gel, 230–400 mesh, 100% ether eluent), obtaining 123.6 mg of a colorless foam (77% yield): R_f 0.17; $[\alpha]^{24}_{589}$ +17.7°, $[\alpha]^{24}_{436}$ +34.2° (*c* 0.78, $CHCl_3$); MS (CI, NH_3), *m/e* (relative intensity) 416 (molecular ion plus NH_3, 25), 399 (M^+, 91.6), 251 (base); IR (film) cm^{-1} 2905 (m), 1732 (s), 1685 (s), 1610 (m), 1580 (m), 1432 (m), 1318 (m), 1210 (m), 1138 (m), 1108 (s), 1030 (m), 990 (s); ^1H NMR (100 MHz, $CDCl_3$) δ 9.55 (d, *J* = 7.6 Hz, 1), 8.15 (s, 1), 6.8 (br s, 2), 6.70 (dd, *J* = 15.9 Hz, *J* = 3.7 Hz, 1), 6.30 (ddd, *J* = 15.9 Hz, *J* = 7.6 Hz, *J* = 1.5 Hz, 1), 5.97 (s, 1), 4.52 (m, 1), 4.45 (m, 1), 3.91 (s, 3), 3.15 (m, 2), 2.40 (s, 6), 2.23 (s, 3), 2.15–1.70 (m, 2); ^{13}C NMR ($CDCl_3$) δ 192.7, 161.6, 161.3, 153.4, 143.8, 138.4, 136.5, 130.9, 130.1, 129.7, 100.0, 75.0, 74.0, 52.1, 35.3, 34.5, 20.9, 20.4. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31. Found: C, 66.02; H, 6.18.

Oxazole Aldehyde 38 from Phosphorane 40. A 50-mL round-bottomed flask was flame-dried and purged with argon. The flask was charged with 35 mL of dry benzene (distilled from Na/benzophenone), the oxazole aldehyde **34** (563 mg, 0.15 mmol), and α-methylformyltriphenylphosphorane[51] (528 mg, 1.65 mmol). The solution was heated to reflux under an inert atmosphere for 24 h. After cooling to room temperature, the solvent was evaporated and the residue chromatographed (silica gel, 230–400 mesh, 30% acetone–hexane eluent), obtaining 494 mg of a colorless foam (80% yield): ^1H NMR ($CDCl_3$) δ 9.20 (s, 1 H), 7.97 (s, 1 H), 6.65 (s, 2 H), 6.27 (br d, *J* = 7 Hz, 1 H), 5.85 (s, 1 H), 4.83–4.53 (m, 1 H), 4.47–4.20 (m, 1 H), 3.80 (s, 3 H), 3.08 (br d, *J* = 7 Hz, 2 H), 2.37 (s, 6 H), 2.17 (s, 3 H), 1.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 194.2, 161.7, 161.3, 149.8, 143.9, 139.0, 138.4, 136.5, 133.3, 130.2, 129.7, 100.0, 73.9, 52.1, 34.8, 34.6, 21.0, 20.4; IR ($CDCl_3$) cm^{-1} 1735, 1715, 1690, 1612, 1582. Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.59. Found: C, 66.98; H, 6.55.

Oxazole Phthalimide 41. To 13.5 mg (0.034 mmol) of unsaturated aldehyde **35** in 750 mL of dry THF containing 2.1 mg (0.051 mmol) of NaH (60% oil dispersion, oil removed by washing with THF) at 23 °C was added 13.6 mg (0.044 mmol) of freshly recrystallized vinyltributylphosphonium bromide and 6.5 mg (0.044 mmol) of phthalimide. The mixture quickly became light brown and was stirred at 23 °C for 46 h. To the mixture was added 3 mL of 5% citric acid and the color faded to light yellow. The solution was poured into ether and was washed with 5% citric acid, saturated $NaHCO_3$, and brine. Drying (K_2CO_3) and concentration gave 18.3 mg of material. The mixture was chromatographed (acetone/hexane, 2:3) to give 5 mg (26.6%) of a white solid. TLC showed that the material contained some phthalimide. No further purification was attempted. MS (CI, NH_3), *m/e* (relative intensity) 573 (molecular ion plus NH_3, 0.6), 556 (M^+, 1.8), 425 (5.2), 408 (47.6), 390 (base); ^1H NMR (100 MHz, $CDCl_3$) δ 8.17 and 8.14 (pair of singlets, 1 total), 7.8 (m, 8, contains phthalimide), 6.78 (br s, 2), 6.4–5.2 (m, 4), 5.89 (s, 1), 4.36 (m, 2), 4.30 (d, *J* = 5.9 Hz, 2), 3.1 and 3.90 (pair of singlet, 3 total), 3.13 (m, 2), 2.44 and 2.38 (pair of singlets, 6 total), 2.21 and 2.18 (pair of singlets, 3 total), 1.60 (m, 2); high resolution MS (CI, isobutane, *m/e*). Anal. Calcd for $C_{32}H_{32}N_2O_7$: 557.228778. Found: 557.22713 (−3.1 ppm).

Oxazole Phthalimide 42. A 50-mL round-bottomed flask was flame-dried and purged with argon. The flask was charged with 25 mL of dry tetrahydrofuran (distilled from Na/benzophenone), aldehyde **38** (50 mg, 0.12 mmol), vinyltri-*n*-butylphosphonium bromide (83.4 mg, 0.27 mmol), and potassium phthalimide (51.9 mg, 0.28 mmol). The heterogeneous mixture was then heated to reflux for 50 h (under argon). The dark tan slurry was cooled to room temperature, diluted with 75 mL dry ether, and filtered. The filtrate was washed with water (1 × 20 mL) and brine (1 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue chromatographed (silica gel, 230–400 mesh, 100% ether eluent), obtaining 34 mg of a colorless foam (51% yield): $[\alpha]_D$ +13.2° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.137 (s, 1 H), 7.85–7.83 (m, 2 H), 7.72–7.69 (m, 2 H), 6.769 (s, 2 H), 6.255 (d, *J* = 16.1 Hz, 1 H), 5.916 (s, 2 H), 5.75–5.65 (m, 1 H), 5.482 (m, 1 H), 4.65–4.60 (m, 2 H), 4.40–4.30 (m, 2 H), 4.28 (d, *J* = 7 Hz, 2 H), 3.90 (s, 3 H), 3.20–3.00 (m, 2 H), 2.39 (s, 6 H), 2.20 (s, 3 H), 1.75 (s, 3 H), 1.65–1.60 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 162.4, 161.9, 143.7, 141.5, 137.8, 137.1, 136.4, 133.6, 131.9, 130.7, 129.5, 123.0, 99.7, 73.7, 60.1, 52.0, 34.6, 34.4, 20.8, 20.4; IR ($CDCl_3$) cm^{-1} 1735, 1720, 1615, 1585, 990, 925. Anal. Calcd for $C_{33}H_{34}N_2O_7$: C, 69.46; H, 6.02. Found: C, 69.75; H, 6.13.

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Registry No. **9**, 32233-44-6; **10**, 32233-43-5; **11**, 85287-64-5; **12**, 85287-65-6; **13**, 85287-66-7; **14**, 105183-43-5; **15**, 105205-36-5; **16**, 85806-67-3; **16a**, 23012-17-1; **17**, 85806-68-4; **18**, 23000-14-8; **19**, 85806-69-5; **20**, 23012-13-7; **21**, 105183-44-6; **24**, 105183-45-7; **25**, 80314-36-9; **26**, 105183-52-6; **27**, 80314-38-1; **28**, 80314-39-2; **29a**, 85806-70-8; **29b**, 85806-72-0; **30a**, 105183-53-7; **30a** (diol deriv.), 105183-54-8; **30b**, 105228-50-0; **30b** (diol deriv.), 105228-51-1; **31a**, 105183-55-9; **3ua** (aldehyde), 105183-56-0; **31b**, 105228-52-2; **32**, 105228-53-3; **34**, 105228-54-4; **35**, 105307-17-3; **36**, 105183-58-2; **37**, 58707-01-0; **38**, 105228-55-5; **39**, 2136-75-6; **40**, 24720-64-7; **41**, 105228-56-6; **42**, 105183-57-1; 4-$ClC_6H_4CH(OH)CH_2C(OMe)=NC^-(CHO)CO_2Me\cdot Li\cdot K^+$, 105183-46-8; $PhCH(OH)CH_2C(OMe)=NC^-(CHO)CO_2Me\cdot Li\cdot K^+$, 105183-47-9; $Me_2CHCH(OH)CH_2C(OMe)=NC^-(CHO)CO_2Me\cdot Li\cdot K^+$, 105183-48-0; $PhCH_2CH_2C(OMe)=NC^-(CHO)CO_2Me\cdot K^+$, 105183-49-1; (*R,S*)-$CH_2OC(Me)_2OCHCH_2CH(OH)CH_2C(OMe)=NC^-(CHO)$-

$CO_2Me{\cdot}Li{\cdot}K^+$, 105183-50-4; (*S,S*)-$\overline{CH_2OC(Me)_2OCHCH_2CH(OH)CH_2C(OMe)}$=$NC^-(CHO)CO_2Me{\cdot}Li{\cdot}K^+$, 105183-51-5; 4-$ClC_1H_4CHO$, 104-88-1; PhCHO, 100-52-7; Me_2CHCHO, 78-84-2; $PhCH_2Br$, 100-39-0; $(EtO)_2P(O)CH_2CH$=NBu-*t*, 29940-81-6; mesitaldehyde dimethyl acetal, 64761-29-1; (*S*)-diethyl malate, 691-84-9; (L)-malic acid, 97-67-6; (*S*)-diethyl malate 2-(1-methyl-1-methoxyethyl) ether, 66348-32-1; 2-methoxypropene, 116-11-0; (*S*)-1,2,4-butanetriol 2-(1-methyl-1-methoxyethyl) ether, 66348-33-2; (±)-1,2,4-butanetriol, 6810-31-7; methyl α-[(methoxyethylidene)amino]acetate, 64991-38-4; vinyltributylphosphonium bromide, 1883-19-8; methyl acetimidate hydrochloride, 14777-27-6; methyl glycinate hydrochloride, 5680-79-5.

$(\eta^5\text{-}C_5H_5)Fe(CO)_2(\eta^1\text{-}C_5H_5)$. A Useful Synthetic Equivalent of 5-Amino-1,3-cyclopentadiene in Cycloaddition Reactions[1]

Richard S. Glass,* Wesley W. McConnell, and Stephen W. Andruski

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

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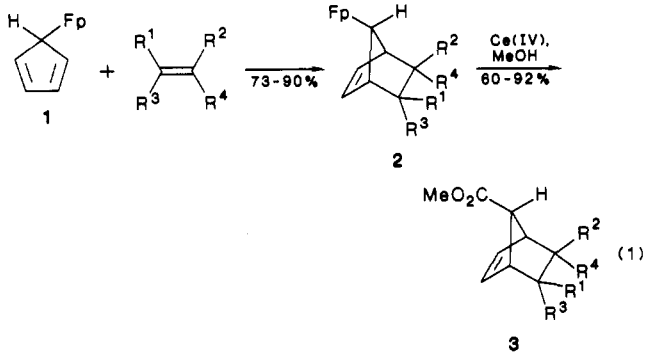
Diels–Alder reactions of 5-amino-1,3-cyclopentadiene have not been reported, and other stereoselective, high-yield routes to substituted bicyclo[2.2.1]hept-2-en-7-*syn*-amines are limited. This paper reports use of $(\eta^5\text{-}C_5H_5)Fe(CO)_2(\eta^1\text{-}C_5H_5)$ (**1**) as a synthetic equivalent of 5-amino-1,3-cyclopentadiene in cycloaddition reactions. The previously reported cycloadducts of **1** and alkenes were treated with ammonium cerium(IV) nitrate, bromine, or chlorine in acetonitrile containing sodium azide to give the corresponding acyl azides in which the CON_3 group replaced the $(\eta^5\text{-}C_5H_5)Fe(CO)_2$ group with retention of stereochemistry in good yield. Thermal Curtius rearrangement of these acyl azides proceeded stereospecifically in excellent yield. This regioselective and stereoselective sequence provides a useful route to substituted 7-*syn*-amino-2-norbornenes.

Recently, the reaction of $Fp(\eta^1\text{-}C_5H_5)$ (**1**), where Fp = $(\eta^5\text{-}C_5H_5)Fe(CO)_2$, with a variety of unsaturated compounds to give cycloadducts in good yield was reported.[2,3] These reactions all occur regio- and stereoselectively to afford 7-*syn*-Fp cycloadducts **2**, as shown in eq 1. Furthermore, stereospecific replacement of the Fp moiety in these cycloadducts by a CO_2Me group with retention of configuration to give **3** was found to occur in good yield by oxidation with ammonium cerium(IV) nitrate in methanol saturated with carbon monoxide.[2,3] This two-step sequence, cycloaddition followed by oxidation, renders $Fp(\eta^1\text{-}C_5H_5)$ a synthetic equivalent of methyl 1,3-cyclopentadiene-5-carboxylate in cycloaddition reactions.



The utility of this synthetic methodology would be enhanced if the Fp moiety in cycloadducts **2** could be stereospecifically converted to other functional groups. One approach to achieve this goal is based on the suggested mechanism for the cerium(IV) oxidation. The mechanism for this oxidation is believed to be that shown in eq 2, that is, one-electron oxidation of the formally iron(II) complex to an iron(III) complex, which rapidly undergoes rearrangement to acyl iron(III) complex **4**. Nucleophilic attack on the carbonyl group by methanol followed by loss of the iron moiety leads to the observed esters.[4,5] In support of such a mechanism, migratory insertion of a CO group of methyl iron(II) complexes to give acetyl complexes has been shown[6] to be greatly accelerated on one-electron oxidation. In principle, nucleophiles other than alcohols could be used to attack acyl iron(III) complex **4**. Indeed, chlorine in chloroform converts FpR into acid chlorides, RCOCl,[5] presumably via chloride ion attack on acyl iron(III) complex **4**, and β-amino groups have been reported[7] to intramolecularly attack presumed acyl iron(III) complexes to form β-lactams.[8]

This paper reports the intermolecular trapping of presumed acyl iron(III) complexes by azide ion resulting in the formation of acyl azides. Curtius rearrangement[9] of these compounds provides substituted 7-*syn*-amino-2-norbornenes.[10] Overall this represents a new, selective, stereospecific transformation of the Fp moiety in cycloadducts **2** into an amino group, as shown in eq 3. Such

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