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# Diastereofacial Selection in Nitrile Oxide Cycloaddition Reactions. The Anti-Directing Effect of an Allylic Oxygen and Some New Results on the Ring Metalation of Isoxazolines. A Synthesis of (±)-Blastmycinone

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## Abstract

The extent of diastereoselectivity associated with the reactions of nitrile oxides with alkenes bearing an allylic oxygen substituent has been studied. Reasonable levels of such diastereoselectivity have been found when the *tert*-butyldimethylsilyl ether derivative of 3-buten-2-ol (**5**) or (+)-(*S*)-isopropylidene-3-butene-1,2-diol (**1**) are employed as dipolarophiles. The stereochemical course of these cycloaddition reactions has been proven rigorously through the transformation of the adducts to known γ-lactones. The stereochemistry associated with the metalation/alkylation of 5-alkoxymethyl-substituted isoxazolines has also been probed in order to further expand the use of these heterocycles as aldol equivalents in natural products total synthesis. A synthesis of (±)-blastmycinone (**34**) is reported which combines the two foregoing aspects of stereocontrol. The levels of regio- and stereoselectivity found in the cycloaddition reactions of the cis- and trans-disubstituted alkenes **35** and **39** prepared from isopropylidene-D-glyceraldehyde are also discussed. A single example of the reaction of a chiral alkene with a chiral nitrile oxide is presented.

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During our efforts to synthesize the ergot alkaloid paliclavine, we had the occasion to examine the extent of diastereoselection which could be achieved in the addition of a nitrile oxide to a tethered olefin bearing an allylic asymmetric center.[1] Since the groups attached to this allylic site differed little in their steric or electronic makeup, it was not surprising to find that the extent of diastereoselection was small.

Prompted by this initial experiment, we have begun to explore such diastereoselective nitrile oxide cycloaddition reactions in a more thorough manner, for the successful execution of such chemistry would appear valuable to the stereoselective production of both γ-amino alcohol and β-hydroxy ketone fragments for use in natural products synthesis.[2]

We have already described in a brief communication that it is possible to achieve diastereoselection in intermolecular nitrile oxide cycloaddition reactions if a chiral olefin which bears an allylic oxygen substituent is employed as the dipolarophile.[3] Further examples of the “anti-directing effect” of an allylic oxygen substituent are presented and discussed in this article. A synthesis of (±)-blastmycinone, a degradation product of the antibiotic antimycin $A_3$ is described.[4] This synthesis features the anti-directing effect of an oxygen substituent in controlling both the course of the [3 + 2] cycloaddition reaction as

well as the stereochemistry of a subsequent isoxazoline ring metalation reaction. A single example of a cycloaddition reaction employing both an optically active olefin and an optically active nitrile oxide is also presented.

## Results

Our first indication that reasonable diastereoselectivity could be achieved in intermolecular nitrile oxide cycloaddition reactions was gleaned from the reactions of (+)-(*S*)-isopropylidene-3-butene-1,2-diol (**1**) (Scheme I). When carbethoxyformonitrile oxide (CEFNO)[5] was used as the dipole, an 80:20 mixture of diastereomers resulted, in which the major isomer after chromatographic separation could be converted through a few additional steps to 2-deoxy-D-ribose (**3**) (see Experimental Section for details).[3]

Acetonitrile oxide reacted with **1** to deliver after N–O bond hydrogenolysis the erythro *β*-hydroxy ketone **4** as the major product ($^1$H NMR ratio 88:12). The identity of the major isomer was established by hydrolyzing pure **2** to the corresponding *β*-hydroxy acid and then treating with excess methyllithium to afford a ketone whose $^1$H NMR spectrum matched that displayed by the major isomer **4** present in the hydrogenolysis mixture. With the nitrile oxide derived from the tetrahydropyranyl derivative of 2-nitroethanol, the extent of diastereoselection was even higher. Hydrogenolysis of the isoxazoline product under conditions which led to cleavage of the THP group yielded nearly a single dihydroxy ketone (>94% by HPLC analysis). Since this ketone could also be converted to **2**, the stereochemical sense of the addition of a nitrile oxide to the olefin **1** was shown to be independent of the nitrile oxide employed.

The reaction of olefin **1** with four other nitrile oxides can be found in the accompanying table. Benzonitrile oxide gave rise to a 83:17 mixture of diastereomeric isoxazolines. The 1-methoxycyclohexyl derivative of 2-nitroethanol was comparable in its diastereoselectivity to the tetrahydropyranyl ether of 2-nitroethanol.

The assignment of stereochemistry in these last four cases was made on the basis of $^1$H NMR comparisons (Table I). Proton $H_A$ in the anti isomer was found to consistently resonate at a higher field strength than $H_A$ in the syn isomer. Additionally, $J_{AX}$ for the anti isomer was found to be larger than $J_{AX}$ for the syn isomer. The major isoxazoline derived from the dioxolanyl bearing nitrile oxide (entry 7) has, moreover, been converted to a protected version of compactin lactone, a compound whose measured optical rotation was found to be identical with the reported literature value.[6]

### Diastereoselection in the Reactions of Derivatives of 3-Buten-2-ol.

Encouraged by the reasonable diastereoselection found for the olefin **1**, we decided to examine the same chemistry by using variously protected derivatives of 3-buten-2-ol. The diastereomeric ratios varied from a high of 81:19 to as little as 52:48 (Table II). Only the *tert*-butyldimethylsilyl ether derivative **5** of this alcohol led to a reasonable degree of diastereoselection with each of the nitrile oxides examined. The coupling patterns found for the major isoxazoline isomer in the majority of these cases were similar, thus suggesting that addition to a specific olefin face was preferred irregardless of the nitrile oxide employed.

Chemical evidence that these addition reactions proceed in a fashion analogous to that found for (+)-(*S*)-isopropylidene-3-butene-1,2-diol is presented below.

## Proof of the Stereochemical Course of the Nitrile Oxide Cycloaddition Reaction to the *tert*-Butyldimethylsilyl Ether Derivative of 3-Buten-2-ol.

As cited above, the ratio of isomers (disregarding those originating from the THP group) in the reaction of **5** with the tetrahydropyranyl ether derivative of 2-nitroethanol was 81:19. The assignment of stereochemistry to these isoxazolines was made by their conversion to the $\gamma$-lactones **11** and **12**. Accordingly, the hydroxyl group of **6** (Scheme II) was desilylated and then reprotected as its benzyl ether. Cleavage of isoxazoline **7** to $\beta$-hydroxy ketone **8**, followed by periodic acid oxidation led to a mixture of the $\beta$-hydroxy acids **9** and their corresponding methyl esters **10**.[5] Hydrogenolytic removal of the benzyl group in methanol/HCl gave rise to a 4:1 mixture of the lactones **11** and **12**. The upfield $^{1}$H NMR shift of the methyl resonance of lactone **11** as compared to that of lactone **12** as well as the downfield position of this same methyl group in its $^{13}$C NMR spectrum relative to that of **12** provided firm evidence for the assignment of structure in these cases. A configurationally related set of lactones has been prepared by Heathcock, and that lactone possessing a cis relationship between its C-3 hydroxyl and C-4 methyl groups was found to exhibit the higher field $^{13}$C NMR methyl resonance.[7] Additionally, the ABX coupling pattern found for the C-2 hydrogens of lactone **11** is identical with that exhibited by the C-2 hydrogens of 2-deoxyribonolactone.

## Metalation Reactions of the 5-Alkoxymethyl-Substituted Isoxazolines.

With the idea of further expanding the utility of these diastereofacial selective [3 + 2] cycloaddition reactions, we have also examined the metalation chemistry of isoxazolines bearing a protected hydroxymethyl group at C-5.[8]

The cycloadduct prepared from the reaction of the tetrahydropyranyl ether of allyl alcohol and propionitrile oxide (or acetonitrile oxide) was used for the preliminary investigations. We felt that it was necessary to first establish the stereochemical course of such metalation/alkylation reactions, for the neighboring oxygen substituent could either serve as a bulky shielding group thus directing the entry of the new alkyl group trans to itself, or it could lead via internal chelation to a configurationally stable sp$^3$ carbanion, thus suggesting the possibility of a cis-directed alkylation.[9] Isoxazoline **13** was deprotonated with LDA/HMPA and then alkylated with methyl iodide. A single C-4/C-5 stereoisomer **14** (from $^{1}$H NMR and HPLC analysis on **19**) was formed in high yield. A further deprotonation/alkylation reaction was carried out on **14** in order to establish the site selectivity of a second metalation process. When either methyl iodide or iodomethyl methyl ether was used as the electrophile, the new alkyl group was found to be appended to the C-3 ethyl group, thus indicating the higher kinetic acidity of the less substituted carbon atom $\alpha$ to the C=N bond.

In order to unambiguously assign stereochemistry to the product of the first metalation reaction, the minor regioisomer **17** (Scheme III) formed in the reaction of propionitrile oxide with methyl crotonate was reduced with lithium borohydride in diglyme to the corresponding 5-(hydroxymethyl) isoxazoline **19**. The $^{1}$H NMR of the

detetrahydropyranylated product of the methylation reaction (**14** → **19**) was found to be identical with that of the crotonate derived isoxazoline.

When the isoxazoline prepared from propionitrile oxide and the methoxymethyl derivative of methallyl alcohol was deprotonated and then methylated, a 3:1 mixture of products **21** and **22** resulted. In order to ascertain the stereochemistry of the major product in this instance, propionitrile oxide was first reacted with methyl tiglate, and then the carbomethoxy group of the isoxazoline **23** was reduced with sodium borohydride. Protection of the hydroxyl group of this new isoxazoline as its MOM ether provided the appropriate sample for spectral comparison. The major isomer from the metalation reaction did, in fact, match that prepared from methyl tiglate, thus signaling the greater syn-shielding capability of an alkoxymethyl group relative to a methyl group in directing the stereochemical course of the alkylation reaction.

Lastly, the isoxazoline prepared from (+)-(*S*)-isopropylidene-3-butene-1,2-diol and the nitrile oxide of the THP ether of 2-nitroethanol was also subjected to the metalation/ alkylation reaction. A single C-4/C-5 stereoisomer (within the limits of $^1$H NMR and HPLC detection) was generated on using methyl iodide as the electrophile. Presumably, the methyl group had been introduced into the isoxazoline ring anti to the C-5 substituent. To prove this point, the chiral isoxazoline **25** (Scheme IV) was converted to the known chiral lactone **28b** via a sequence of steps involving Raney nickel hydrogenolysis, oxidative cleavage of the *β*-hydroxy ketone to carboxylic acid, trifluoroacetic acid promoted acetonide cleavage with concomitant lactone formation, and finally *O*-acetylation. The chemical shift data and coupling constants exhibited by this lactone in its $^1$H NMR were identical with those reported by Heathcock[7] who prepared a mixture of **28b** and its C-2 epimer through chemistry utilizing the conventional aldol process. Additionally, the coupling constants observed for **28b** were similar to those reported by Novak for the related di-*p*-toluate derivative of this lactone.[10]

## A Synthesis of (±)-Blastmycinone.

To further illustrate the utility of the directing effect of an allylic oxygen atom in the dipolar cycloaddition process, as well as the directing effect of the alkoxymethyl group in the isoxazoline ring alkylation reaction, we undertook a synthesis of blastmycinone, a degradation product of the antibiotic antimycin $A_3$. The addition products formed in the reaction of the *tert*-butyldimethylsilyl ether of 3-buten-2-ol and the nitrile oxide prepared from the tetrahydropyranyl ether of 2-nitroethanol were disilylated and reprotected as their benzyl ethers. Subjection of the diastereomeric mixture of isoxazolines to LDA/HMPA treatment followed by reaction of their deep red anions with *n*-butyl iodide delivered the ring alkylated products **29** and **30**. Hydrogenolysis of these products with acetone-deactivated Raney nickel in the presence of boron trichloride, methanol, and water delivered a chromatographically separable 4:1 mixture of the *β*-hydroxy ketones **31** and **32**. The preference for N-O bond cleavage relative to O-debenzylation under these conditions is certainly noteworthy.

The major *β*-hydroxy ketone was stirred with periodic acid in methanol and water to afford a mixture of the corresponding carboxylic acid and its methyl ester. Removal of the benzyl

group by hydrogenation over palladium on carbon led solely to *epi*-blastmycinolactol (**33**) (Scheme V). That this compound was indeed the 2-epi isomer was easily verified through its conversion of (±)-blastmycinone. The lactone was first stirred with sodium methoxide to afford a 2.3:1 mixture of blastmycinolactol and starting lactone, respectively. The chromatographically purified major isomer was then reacted with isovaleric anhydride in pyridine for five days to afford a single new product whose 300-MHz $^1$H NMR spectrum matched precisely that reported for (±)-blastmycinone (**34**).[4d]

While the above reaction scheme does serve best in providing access to the 2,3-syn/3,4-anti-substituted lactone (i.e., 2-*epi*-blastmycinolactol), the overall conversion of **5** to (±)-blastmycinone does further verify both the stereochemistry of the initial [3 + 2] cycloaddition reaction as well as that of the metalation/alkylation process.

## Diastereoselection in the Reactions of 1,2-Disubstituted Alkenes Bearing an Allylic Oxygen Substituent.

The cis-disubstituted olefin **35** was prepared in a highly stereoselective fashion by reaction of isopropylidene-D-glyceraldehyde with ethylidenetriphenylphosphorane under salt free conditions (ratio 95:5). Some of the cis olefin was further isomerized to the trans olefin by treatment with thiophenol and AIBN in benzene.[11] These two alkenes were then reacted with propionitrile oxide in benzene. While the cis olefin gave rise to a single region- and stereoisomer (HPLC analysis), it was surprising to find that a 1:1 mixture of regioisomers resulted from the cycloaddition reaction of the trans product. As a consequence of the observed lack of regioselectivity in the trans case, no attempt was made to ascertain the level of diastereoselection associated with this cycloaddition reaction.

To determine the stereochemical course of the addition reaction to the cis olefin, the cycloaddition product was simply converted to its corresponding $\beta$-hydroxy ketone by hydrogenation using Raney nickel and acetic acid. Under these conditions, some epimerization was found to take place so as to yield **37** (major) and **38** (Scheme VI). Since the 300-MHz $^1$H NMR spectrum of the minor component **38** matched precisely the $^1$H NMR spectrum of the compound prepared through a sequence of steps involving: (a) addition of propionitrile oxide to **1**; (b) metalation/methylation of the major isoxazoline; and (c) hydrogenolysis to the corresponding $\beta$-hydroxy ketone, we conclude that the cycloaddition process has again occurred in the same sense as found for the monosubstituted olefin **1**.

It was also our intention to examine the level of diastereoselectivity associated with the dipolar cycloaddition reactions of *cis*-3-penten-2-ol. Surprisingly, however, the *tert*-butyldimethylsilyl ether derivative of this compound failed to give any cycloadduct with the various nitrile oxides examined. We have at present no good explanation for this peculiar result.

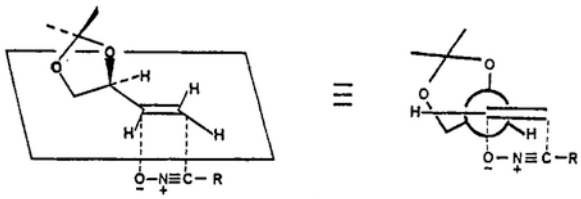
## An Example of the Reaction of a Chiral Alkene with a Chiral Nitrile Oxide.

The unique ability of an allylic oxygen substituent to control the diastereofacial course of a nitrile oxide cycloaddition reaction provides a mechanism for relating remote chiral centers. Thus, if the nitrile oxide component does itself bear an asymmetric center, the relationship

of this chiral center relative to the new center(s) formed in the cycloaddition reaction should be entirely predictable and in accord with the foregoing studies. The optically active nitro compound **44** was prepared from 3-hydroxy-2-methylpropionic acid by the sequence of steps displayed in Scheme VII. On exposure to phenylisocyanate/triethylamine in the presence of olefin **1**, an 80:20 mixture of isoxazolines was formed. Since the major isomer exhibited $^1$H NMR coupling constants and chemical shift data ($\delta_{H_A}$, $J_{AX}$ = 7.68 Hz, major isomer; $\delta_{H_A}$, $J_{AX}$ = 4.85 Hz, minor isomer) similar to those found for the “anti-addition” products listed in Table I, the course of the cycloaddition reaction is seen to be influenced little by the presence of $\alpha$-asymmetry in the nitrile oxide component.[12] This observation should prove valuable in the preparation of complex natural products systems through dipolar cycloaddition strategies.

## Discussion

To explain the stereoselectivity associated with the addition of a nitrile oxide to a chiral alkene bearing an allylic oxygen substituent, we suggest a transition state picture A which is similar to that proposed by Anh in support of

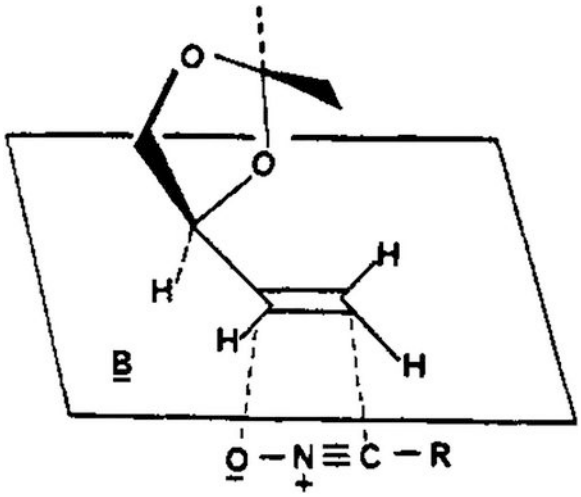


A

the Felkin type transition state.[13] Of the various transition state conformations available to the olefin **1**, cycloaddition may occur through that conformer in which the allylic oxygen is orthogonal to the plane of the carbon-carbon double bond and steric interactions are minimized (i.e., the “A$^{1,3}$-like” interaction involves two hydrogen atoms).[14] Addition of the nitrile oxide to this conformer now proceeds in accord with the anti-periplanar concept, in which the dipole adds anti to the C-O bond in order to minimize secondary antibonding orbital interactions.[15] It should be noted, however, that the directionality of addition to this particular conformer is also that which would be expected based on a simple electrostatic or steric argument.

A similar transition state picture can be used to explain the diastereofacial selectivity associated with the reactions of the *tert*-butyldimethylsilyl ether of 3-buten-2-ol. We do note, however, that since the acetate derivative of this same alcohol has the lower lying $\sigma^*_{c\text{-}o}$orbital,[16] higher diastereoselection should be observed with this derivative in comparison with the silyl ether. That this is not the case (Table II) does cast some doubt on the importance of secondary antibonding orbital interactions in these reactions. Such considerations do not require, however, that we change our transition state picture for these cycloaddition processes.

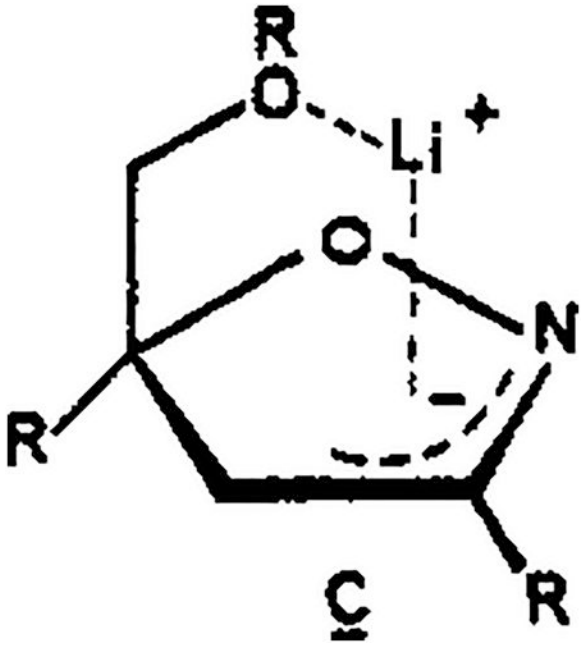
Furthermore, NMR work by Bothner-By et al. suggests that the minimum energy conformation of 3-methoxypropene is that in which the methoxy group eclipses the carbon-carbon double bond.[17] If we assume a similar transition-state conformation B for 1 (or for 5), then a




steric approach controlled addition reaction to this conformer leads to the same stereochemical result as predicted by the anti-periplanar argument. For olefin **35**, however, a transition state resembling A (see D) would seem preferable to one like B since the nonbonded interactions should be minimized in the former.

While it would thus appear difficult to develop a general (predictive) transition-state picture which can precisely accommodate all of these cycloaddition processes,[18] the high stereoselectivity found in several of these reactions can nonetheless be put to important synthetic use.

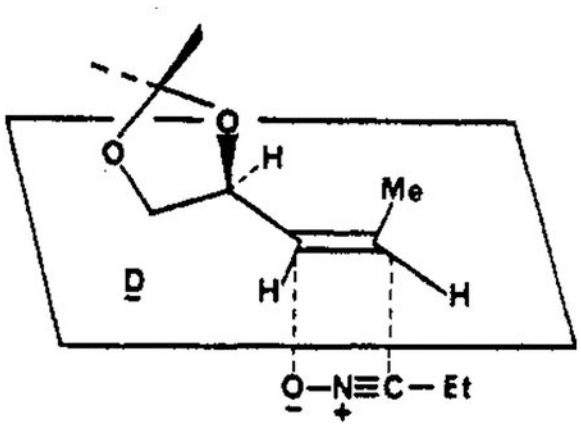
As regards the trans stereospecificity observed in the metalation reaction, we suggest that this is solely a consequence of steric effects. Internal chelation of the oxygen bearing C-5 substituent to the lithiated “imine” anion sterically shields the syn face of the isoxazoline as depicted below.[19] An intermediate such as C would also explain



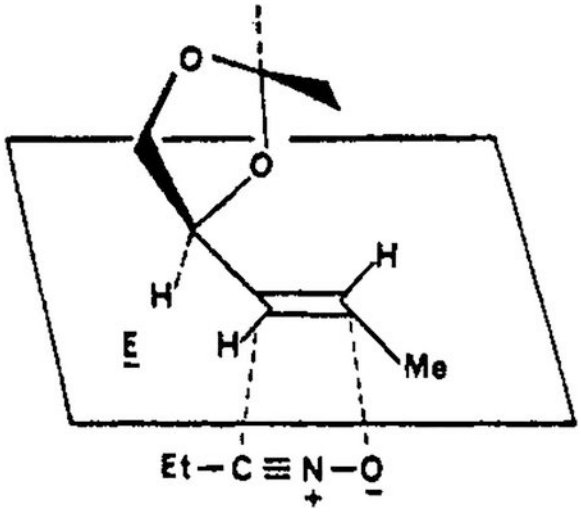

the preference for introduction of the new alkyl group opposite to this alkoxymethyl substituent when the 5-position of the isoxazoline bears both an alkyl and an alkoxymethyl group.

Furthermore, we call attention to the fact that these 3-(straight chain)-alkyl-substituted isoxazolines undergo exclusive deprotonation at the 4-endo position rather than at the 3'-exo position. Previous metalation studies of isoxazolines were carried out on the 3-phenyl derivatives in order to "exclude competing 3'-exo anion formation shown to occur with 3-alkyl substituents present."[8] We have thus shown that such competition is not the case, and that therefore the isoxazoline ring oxygen must play a decisive role in raising the kinetic acidity of the C-4 methylene group through its electron-withdrawing character.[20]

The difference in the degree of regioselection associated with the cis and trans alkenes **35** and **37** also deserves comment. For the cis olefin, cycloaddition probably occurs through a transition state D resembling that shown below.




If the nitrile oxide were to add to this olefin such that the oxygen end of the dipole becomes attached to the methyl-bearing carbon, then nonbonded interactions between the dioxolane ring methylene and the alkyl group of the nitrile oxide would develop. In the trans case, however, cycloaddition could well occur through that conformation in which the acetonide oxygen eclipses the carbon-carbon double bond. In this conformation, it appears to make no difference sterically whether the oxygen end of the nitrile oxide adds to the C-3 or C-4 carbon atom.[21] The lack of regiochemistry in the trans case is offset by the fact that one can carry out a metalation/methylation reaction on an isoxazoline like **24** so as to obtain exclusively the C-4/C-5 trans-disubstituted product **25** (also see Scheme VI).




## Summary

The studies discussed herein provide the basic ground-work necessary for the rational utilization of nitrile oxide cycloaddition chemistry as a tool for handling problems associated with acyclic stereocontrol. The reaction of a nitrile oxide bearing an $\alpha$-asymmetric center with an alkene bearing an allylic oxygen substituent provides an isoxazoline which can be subjected to metalation/alkylation and hydrogenolysis to generate a $\beta$-hydroxy ketone of defined stereochemistry at its $\alpha'$, $\alpha$, $\beta$, and $\gamma$ centers. The utilization

of this chemistry in the context of natural products total synthesis is being explored (Figure 1).

## Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 247 spectrophotometer or a Beckman Model Acculab **4** spectrophotometer and are calibrated to a polystyrene absorption at 1602 $cm^{-1}$. Spectra were obtained as approximately 3% w/v solutions in the solvent noted in 0.2-mm path NaCl microcavity cells (Barnes Analytical Inc.) vs. pure solvent as reference, as neat thin films between 25 × 4 mm NaCl disks (Wilkes) vs. air as reference, or as approximately 1% w/w KBr disks (air reference). $^1$H NMR were obtained on a Varian Model T-60A (60 MHz), Varian Model EM-360 (60 MHz), Varian Model EM-390 (90 MHz), or on a Brüker Model WH-300 (300 MHz) spectrometer. Spectra were obtained in the solvents noted and chemical shifts are reported in ppm downfield from $Me_4Si$ as an internal reference (1% or 0.05% for FT) at $\delta$ 0.000. Low-resolution mass spectra were obtained on a LKB-9000 instrument operating at 15 or 70 eV ionization potential unless otherwise noted. High-resolution spectra were obtained on a Varian-MAT CH-5DF instrument by peak matching. Optical rotations were determined on a Per-kin-Elmer 241 polarimeter. Specific rotations are reported as $[\alpha]_D$ in units of degrees. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. All reported values are uncorrected. Elemental analyses were carried out at Galbraith Laboratory, Knoxville, TN. Silica column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM), or with SilicAR CC-7 (Mallinckrodt). Thin-layer chromatography was performed on Merck silica gel 60 F-254 (0.25 mm, precoated on glass or 0.2 mm precoated on aluminum). Experimental procedures have not been provided for the preparation of lactones **11** and **12**, or for the initial metalation-alkylation studies, since these procedures are closely related to those reported for the blastmycinone synthesis.

### Reaction of (+)-(*S*)-Isopropylidene-3-butene-1,2-diol with Propionitrile Oxide.

To a solution of 200 mg (1.56 mmol) of 1,347 mg (3.9 mmol) of nitropropane, and 0.1 mL of triethylamine in 5 mL of dry benzene at room temperature was added by means of a motor driven syringe over a 5-h period a solution of 780 mg (6.55 mmol) of phenyl isocyanate in 3 mL of benzene. The reaction mixture was stirred for an additional 2 h, diluted with 10 mL of water, stirred for 4 h, and filtered. The layers were separated, and the aqueous phase was extracted with benzene. The combined organics were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel with 25% ethyl acetate-hexanes as eluent to furnish 258 mg (83.1%) of a 90:10 mixture of diastereomers which can be separated by careful chromatography: IR (thin film) 2980, 2910, 1420, 1350, 1250, 1125, 1050, 940 $cm^{-1}$;$^1$H NMR ($CDCl_3$) $\delta$ 1.17 (t, 3 H, $J$ = 7.48 Hz), 1.34 (s, 3 H), 1.42 (s, 3 H), 2.37 (q, 2 H, $J$ = 7.48 Hz), 2.82–3.12 (m, 2 H), 3.70–4.30 (m, 3 H), 4.47 (ddd, 1 H, $J$ = 10.30, 7.68, 6.26 Hz, major), 4.62 (ddd, 1 H, $J$ = 10.81, 7.88, 4.85 Hz, minor); mass spectrum (15 eV), *m/z* 199 ($M^+$), 184 ($M^+$ - $CH_3$), 169, 147, 142, 101. Anal. Calcd for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.03; H, 8.55; N, 7.12.

### Reaction of (+)-(*S*)-Isopropylidene-3-butene-1,2-diol with Carbethoxyformonitrile Oxide.

Ethyl chlorooximinoacetate[5] (1.419 g, 9.37 mmol) was added to a solution of (+)-(*S*)-isopropylidene-3-butene-1,2-diol (1.00 g, 7.81 mmol) in 25 mL of diethyl ether. The resulting mixture was stirred for 10 min at room temperature, and a solution of sodium carbonate (993 mg, 9.37 mmol) in water (15 mL) was added dropwise from a motor driven syringe over a period of 5 h. When the addition was completed the solution was allowed to stir for an additional 30 min. The layers were separated, and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic fractions were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (25% ethyl acetate-hexanes) to yield 1.336 g (70.8%) of a 4:1 diastereomeric mixture of isoxazolines which were separated by a second chromatography.

Major isomer: $R_f$ 0.31 (silica gel, 25% ethyl acetate-hexanes); IR (thin film) 2950, 2910, 1740, 1610, 1475, 1370, 1330, 1250, 1200, 1060, 920 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (s, 3 H), 1.35 (t, 3 H, $J$ = 7.07 Hz), 1.41 (s, 3 H), 3.23 (dd, 1 H, $J$ = 17.98, 7.60 Hz), 3.30 (dd, 1 H, $J$ = 17.98,10.30 Hz), 3.87 (m, 1 H), 4.12 (m, 2 H), 4.34 (q, 2 H, $J$ = 7.07 Hz), 4.73 (ddd, 1 H, $J$ = 10.3, 7.60, 6.46 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.1, 25.1, 26.7, 36.1, 62.1, 66.9, 75.7, 83.6, 110.0, 151.8, 160.4; mass spectrum (15 eV), *m/z* 228 ($M^+ - CH_3$), 198, 156, 140, 115; $[\alpha]^{24}_D$ +95.1° (*c* 1.88, CHC1$_3$); exact mass calcd for $C_{10}H_{14}O_5N$ 228.2267, found 228.2254.

Minor isomer: $R_f$ 0.16; IR (thin film) 2975, 2910, 1720, 1600, 1350, 1260, 1120, 1020, 940 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.36 (s, 3 H), 1.37 (t, 3 H, $J$ = 7.07 Hz), 1.43 (s, 3 H), 3.13 (dd, 1 H, $J$ = 17.78, 8.50 Hz), 3.27 (dd, 1 H, $J$ = 17.78, 11.52 Hz), 3.87 (dd, 1 H, $J$ = 8.69, 6.23 Hz), 4.08 (dd, 1 H, $J$ = 8.69,6.87 Hz), 4.28 (m, 1 H), 4.35 (q, 2 H, $J$ = 7.07 Hz), 4.85 (ddd, 1 H, $J$ = 11.5, 8.49, 4.24 Hz); mass spectrum, (15 eV) *m/z* 228 ($M^+ - CH_3$), 200,198, 156, 140, 115; $[\alpha]^{24}_D$ −93.6° (*c* 0.692, CHC1$_3$).

### (3*S*,4*R*)-Methyl 4,5-*O*-Isopropylidene-3,4,5-trihydroxy-pentanoate (2).

To a 50-mL, round-bottomed flask equipped with a high efficiency reflux condenser was added the above (major) isoxazoline (260 mg, 1.07 mmol), 10% sodium hydroxide (15 mL), and a few drops of ethanol (enough to produce a homogeneous solution). The resulting mixture was stirred at room temperature for 1 h, and then water (3 mL) was added. The reaction mixture was refluxed for 8 h, at which time the evolution of ammonia had ceased (detected by holding a piece of pH paper at the top of reflux condenser). The reaction mixture was cooled to 0 °C, acidified carefully to a pH of 3 with 10% HC1, saturated with sodium chloride, and extracted with ethyl acetate. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting acid was converted to its methyl ester by treatment with diazomethane in ether. The crude $\beta$-hydroxy ester was further purified by column chromatography on silica gel (25% ethyl acetate-hexanes) to give 161 mg (73.7%) of $\beta$-hydroxy methyl ester **2:** $R_f$ 0.18 (silica gel, 25% ethyl acetate-hexanes); IR (thin film); 3450, 2980, 2925, 1725, 1445, 1360, 1260, 1215, 1050, 865 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30 (s, 3 H), 1.38 (s, 3 H), 2.45 (dd, 1 H, $J$ = 16.58, 8.49 Hz), 2.69 (dd, 1 H, $J$ = 16.58, 2.52 Hz), 3.25 (br s, 1 H), 3.80 (s, 3 H), 3.95 (m, 3 H), 4.05 (m, 1 H); mass

spectrum (15 eV), *m/z* 205 ($M^+ + 1$), 189 ($M^+ - CH_3$), 173, 157, 147, 129, 115; $[\alpha]^{24}_D$ −11.2° (*c* 0.602, $CH_2Cl_2$); exact mass calcd for $C_9H_{16}O_3 - CH_3$ 189.1885, found 189.1884.

### (3*S*,4*R*)-Methyl 4,5-*O*-Isopropy lidene-3-acetoxy-4,5-dihydroxypentanoate.

To a solution of the *β*-hydroxy ester **2** (134 mg, 0.66 mmol) in 1 mL of triethylamine was added acetic anhydride (149 mg, 1.45 mmol) and 0.1 mg of 4-(dimethylamino) pyridine. The resulting mixture was stirred under an argon atmosphere for 4 h at room temperature, and then extracted (2 × 10 mL) with ethyl acetate. The combined extracts were washed with 5% HC1, 5% $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated in vacuo. The crude product (yellow syrup) was purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to give 138 mg (85.4%) of the title compound as a colorless oil: $R_f$ 0.25 (silica gel, 25% ethyl acetate-hexanes); IR (thin film) 2990, 2915, 1740, 1440, 1360, 1230, 1150, 1060, 940, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 1.33 (s, 3 H), 1.40 (s, 3 H), 2.06 (s, 3 H), 2.63 (dd, 1 H, *J* = 15.96, 7.88 Hz), 2.71 (dd,1 H, *J* = 15.96, 4.45 Hz), 3.68 (s, 3 H), 3.78 (dd, 1 H, *J* = 8.69, 5.46 Hz), 4.05 (dd, 1 H, *J* = 8.69, 6.67 Hz), 4.25 (m, 1 H), 5.25 (m, 1 H); mass spectrum (15 eV), *m/z* 231, 157, 111, 101, 43; $[\alpha]^{24}_D$ −10.25° (*c* 0.6, $CH_2C1_2$); exact mass calcd for $C_nH_{18}O_6 - CH_3$ 231.2274, found 231.2274.

### (4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-4,5-dihydrofuran-2(3*H*)-one.

To 101 mg (0.49 mmol) of **2** in a 10-mL round-bottomed flask was added 2.5 mL of trifluoroacetic acid and 0.25 mL of water. The resulting solution was stirred at room temperature for 2 h, and the solvent was removed in vacuo to give a yellow syrup. The crude material was purified by column chromatography on silica gel (10% MeOH-$CHCl_3$) to yield 54.3 mg (83.1%) of the title compound as a colorless oil: IR (thin film) 3500, 2990, 2910, 2850, 1740, 1405, 1260, 1150, 850 $cm^{-1}$; $^1H$ NMR ($D_2O$) *δ* 2.24 (dd, 1 H, *J* = 18.70, 2.72 Hz), 2.71 (dd, 1 H ,*J* = 18.70, 6.77 Hz), 3.43 (dd, 1 H, *J* = 12.83, 4.34 Hz), 3.53 (dd, 1 H, *J* = 12.83, 3.03 Hz), 4.05–4.28 (m, 2 H); mass spectrum (15 eV), *m/z* 114 ($M^+ - H_2O$), 101, 95, 79, 50; $[\alpha]^{24}_D$–7.8° (*c* 0.506, $H_2O$). Anal. Calcd for $C_5H_gO_4$: C, 45.40; H, 6.10. Found: C, 45.38; H, 6.25.

### (4S,5*R*)-4-Acetoxy-5-(hydroxymethyl)-4,5-dihydrofuran-2(3*H*)-one.

A mixture of the acetate of **2** (110 mg, 0.44 mmol), 2 mL of trifluoroacetic acid, and four drops of water were stirred for 2 h at room temperature. The solvent was removed by rotary evaporation to give a yellow syrup. The crude product was purified by column chromatography on silica gel with 80% ethyl acetate-hexanes as eluent to afford 55 mg (70.6%) of the ribonolactone derivative as a colorless syrup: IR (thin film) 3450, 2960, 2920, 1785, 1740, 1380, 1240, 1160, 1090, 1040, 940 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 2.07 (s, 3 H), 2.55 (dd, 1 H, *J* = 18, 2.50 Hz), 2.95 (dd, 1 H, *J* = 18, 7 Hz), 3.40–3.60 (m, 1 H), 3.85 (d, 2 H, *J* = 2.50 Hz),4.40–4.60 (m, 1 H), 5.20–5.50 (m, 1 H); mass spectrum (15 eV), *m/z* 175 ($M^+ + 1$), 143 ($M^+ - CH_2OH$), 84, 83, 53; $[\alpha]^{24}_D$ −12° (*c* 0.75, $CH_2CI_2$); exact mass calcd for $C_7H_{10}O_5 - CH_2OH$ 143.0344, found 143.0345.

**(4*S*,5*R*)-4-[[(l,l-Dimethylethyl)dimethylsUyl]oxy]-5-[[[(l,l-Dimethylethyl)dimethylsilyl]oxy]methyl]-4,5-dihydrofuran-2(3*H*)-one.**

To a solution of 30 mg (0.227 mmol) of 2-deoxy-D-ribonolactone in 3 mL of dry methylene chloride was added imidazole (47.8 mg, 0.703 mmol) and *tert*-butyldimethylsilyl chloride (106 mg, 0.703 mmol). The resulting mixture was stirred under a nitrogen atmosphere at room temperature overnight and then poured into water (3 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (2 × 5 mL). The combined organic extracts were washed with 5% HG1 and brine, dried over $MgSO_4$, and concentrated. The crude product was further purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to yield 80 mg (97.8%) of the silyl ether as white crystals: mp 76 °C; IR ($CC1_4$) 2980, 2850, 1770, 1450, 1350, 1250, 1155, 1100, 1000, 960, 870 $cm^{-1}$; $^1H$ NMR ($CDCI_3$) $\delta$ 0.10 (s, 12 H), 0.88 (s, 18 H), 2.38 (dd, 1 H, $J$ = 17.68, 2.52 Hz), 2.82 (dd, 1 H, $J$ = 17.68, 6.67 Hz), 3.75 (dd, 1 H, $J$ = 11.42, 2.52 Hz), 3.81 (dd, 1 H, $J$ = 11.42, 3.23 Hz), 4.34 (m, 1 H), 4.52 (ddd, 1 H, $J$ = 6.87, 2.52, 2.22 Hz); mass spectrum (15 eV), *m/z* 345 ($M^+ - CH_3$), 303, 273, 261, 231, 147, 125; $[\alpha]^{24}_D$ +3.8° (*c* 0.106, $CHCI_3$); exact mass calcd for $C_{17}H_{36}O_4Si_2 - CH_3$ 345.1917, found 345.1912.

**3,5-Bis[[(1,1-dimethylethyl)dı́methylsilyl]oxy]-2-deoxy-D-ribose.**

A solution of the above ribonolactone derivative (25 mg, 0.069 mmol) in 3 mL of dry toluene was cooled to −78 °C and treated dropwise with 0.14 mL (0.112 mmol) of a 0.8 M solution of diisobutylaluminum hydride in hexanes. After 1 h at −78 °C, the reaction mixture was quenched by the slow addition of 1.5 mL of 10% citric acid and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. The product was purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to yield 23 mg (91.6%) of the title compound: IR (thin film) 3450, 2990, 2850, 1420, 1305, 1215, 1090, 990 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.10 (s, 12 H), 0.89 (s, 18 H), 1.85–2.18 (m, 2 H), 3.32 (dd, 1 H, $J$ = 10.71, 7.07 Hz), 3.63 (dd, 1 H, $J$ = 10.71, 4.04 Hz), 3.57–3.90 (m, 3 H), 4.05 (m, 1 H), 4.22 (dd, 1 H, $J$ = 7.47, 4.04 Hz), 4.40 (d, 0.8 H, $J$ = 4.65 Hz), 4.52 (m, 0.2 H), 5.40 (dd, 0.8 H, $J$ = 10.6, 4.35 Hz), 5.48 (m, 0.2 H); mass spectrum (15 eV), *m/z* 305 ($M^+ - C_4H_9$), 303, 286, 261, 231, 215, 213, 189, 175; $[\alpha]^{24}_D$ +23.6° (*c* 0.096, MeOH, after 8 h); exact mass calcd for $C_{17}H_{38}O_4Si_2 - C_4H_9$ 305.5456, found 305.5451.

**2-Deoxy-*N*-phenyl-3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-D-*erythro*-pentosylamine.**

An aniline solution was prepared by mixing aniline (1.0 mL), ethanol (1.2 mL), and water (3.5 mL) at room temperature. To 0.5 mL of this solution was added 18 mg (0.0497 mmol) of the above deoxyribose derivative, and the resulting mixture was kept in the refrigerator at 4 °C overnight. The solvent was removed in vacuo, and the residue was extracted with ethyl acetate. The combined extracts were washed with 5% hydrochloric acid, saturated sodium bicarbonate, and brine, dried over $MgSO_4$, and concentrated to give a yellow syrup. The product was purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to yield 17.2 mg (79.2%) of the anilide as a yellow oil: $R_f$ 0.71; IR (thin film) 3300, 3010, 2990, 2850, 1600, 1590, 1460, 1350, 1325, 1250, 1050, 1000, 940 $cm^{-1}$;

$^1$H NMR ($CDC1_3$) $\delta$ 0.06 (s, 12 H), 0.89 (s, 18 H), 1.85–2.35 (m, 2 H), 3.25–4.55 (m, 4 H), 5.30–5.75 (m, 2 H), 6.80–7.25 (m, 5 H); mass spectrum (15 eV), *m/z* 437 ($M^+$), 411, 380, 337, 305, 287, 261; $[\alpha]^{24}_D$ +19.9° (*c* 0.406, MeOH, after 8 h); exact mass calcd for $C_{23}H_{43}O_3NSi_2$ 437.7760, found 437.7758.

### (3*R*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-3-methyl-4,5-dihydrofuran-2(3*H*)-one (28a).

The experimental procedures required to transform **24** into **27** are essentially identical with those reported for blastmycinone. To a solution of 15.3 mg (0.075 mmol) of the $\beta$-hydroxy acid **27** in 0.25 mL of water was added 1.0 mL of trifluoroacetic acid. After 2 h at room temperature the solvent was removed by rotary evaporation to leave a yellow syrup. The crude material was chromatographed on silica gel with 10% methanol-chloroform as eluent to yield 8.6 mg (87%) of 28a as a colorless oil: IR (thin film) 3500, 2980, 2920, 1735, 1425, 1300, 1280, 1160, 910 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.16 (d, 3 H, *J* = 7.3 Hz), 2.98 (dq, 1 H, *J* = 9.70, 7.40 Hz), 3.60–4.10 (m, 3 H), 4.20 (m, 1 H), 4.52 (m, 2 H); $[\alpha]^{24}_D$ +8.8° (*c* 0.103, $H_2O$) [lit.[10] $[\alpha]^{20}$ D +10.1° (*c* 0.54, $H_2O$)]. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31, H, 6.92. Found: C, 49.48; H, 6.89.

### 5-[l-[[(l,l-Dimethylethyl)dimethylsilyl]oxy]ethyl]-3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-4,5-dihydro-isoxazole (6).

To a stirred solution of 1.00 g (5.37 mmol) of the *tert*-butyldimethylsilyl ether of 3-buten-2-ol, 1.141 g (6.52 mmol) of the tetrahydropyranyl ether of 2-nitroethanol, and 0.2 mL of triethylamine in 15 mL of dry benzene at room temperature was added dropwise a solution of 1.596 g (13.4 mmol) of phenyl isocyanate in 2 mL of benzene over a period of 5 h. The reaction mixture was stirred for an additional 2 h, diluted with 15 mL of water, stirred for 4 h, and filtered. The layers were separated and the aqueous layer was extracted with benzene (2 × 15 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel with 20% ethyl acetate-hexanes as eluent to yield 1.543 g (83.7%) of a 81:19 mixture of diastereomers: IR (thin film) 2990, 1460, 1370, 1325, 1250, 1200, 910, 880 $cm^{-1}$; $^1$H NMR ($CDC1_3$) $\delta$ 0.001 (s, 6 H), 0.88 (s, 9 H), 1.10 (d, 3 H, *J* = 6.25 Hz), 1.40–1.90 (m, 6 H), 2.80–3.20 (m, 2 H), 3.52 (m, 1 H), 3.92 (m, 2 H), 4.20–4.60 (m, 3 H), 4.65 (m, 1 H); mass spectrum (15 eV), *m/z* 286 ($M^+ - C_4H_9$), 260, 258, 243, 192, 160; exact mass calcd for $C_{17}H_{33}NO_4Si - C_4H_9$ 286.1475, found 286.1476.

### 5-[l-(Benzyloxy)ethyl]-3-[[(tetrahydro-2*H*-pyran-2-yl)-oxy]methyl]-4,5-dihydroisoxazole (7).

To a solution of 600 mg (1.75 mmol) of **6** in 10 mL of THF was added 2.1 mL (2.1 mmol) of tetra-*n*-butylammonium fluoride in THF. The mixture was stirred 2 h at room temperature and concentrated by rotary evaporation. The residue was extracted with ethyl acetate and washed with a saturated sodium chloride solution. The organic extract was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel with 50% ethyl acetate-hexanes as eluent to yield 385 mg (96.3%) of an inseparable mixture (81:19) of diastereomers: IR (thin film) 3450, 2990, 1460, 1370, 1325, 1250, 960 $cm^{-1}$; $^1$H NMR ($CDC1_3$) $\delta$ 1.15 (d, 3 H, *J* = 6.26 Hz, major), 1.22 (d, 3 H, *J* = 6.20 Hz, minor), 1.45–1.92 (m, 6 H), 2.10–2.90 (br s, 1 H), 3.10 (m, 2 H), 3.52 (m, 1 H), 3.85 (m, 1

H), 4.05 (m, 1 H), 4.29 (dd, 1 H, $J$ = 12.75, 5.30 Hz), 4.43 (dd, 1 H, $J$ = 12.75, 6.37 Hz, major), 4.52 (m, 2 H, minor), 4.68 (m, 1 H).

To 350 mg (1.53 mmol) of the above alcohol in 12.5 mL of dry THF was added 55 mg (2.29 mmol) of NaH (washed with dry benzene three times) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then benzyl bromide (0.5 mL, 4.2 mmol) and tetra-*n*-butylammonium iodide (10 mg) were added. After 3 h, the solvent was removed by rotary evaporation, brine was added, and the mixture was extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to furnish 478 mg (91%) of a 4:1 mixture of **29** and **30**: $R_f$ 0.31; IR (thin film) 3010, 2990, 2880, 1610, 1490, 1360, 1310, 1025, 960 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) $\delta$ 1.18 (d, 3 H, $J$ = 6.26 Hz, major), 1.21 (d, 3 H, $J$ = 6.20 Hz, minor), 1.40–1.91 (m, 6 H), 2.85–3.20 (m, 2 H), 3.50–3.90 (m, 3 H), 4.25–4.80 (multiplets, 6 H), 7.31 (m, 5 H); mass spectrum (15 eV), *m/z* 275, 234 ($M^+ - C_5H_9O$), 218, 201, 200, 191, 147, 135; exact mass calcd for $C_{18}H_{25}O_4N - C_5H_9O$ 234.1130, found 234.1130.

### *trans*-4-*n*-Butyl-5-[l-(benzyloxy)ethyl]-3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-4,5-dihydroisoxazole (29 and 30).

To a solution of 0.2 mL (1.43 mmol) of diisopropylamine in 10 mL of dry THF at 0 °C was added 1.1 mL (1.39 mmol) of a 1.27 M solution of *n*-butyllithium in hexane. The solution was cooled to −65 °C after 15 min and 0.45 mL (3.66 mmol) of HMPA was added. After 30 min 301 mg (0.943 mmol) of isoxazoline **7** (+ isomer) in 4 mL of THF was added over 15 min. The mixture was stirred for 30 min at −65 °C, and then it was cooled to −78 °C. After 2 h 0.4 mL (3.51 mmol) of *n*-butyl iodide was added. The reaction mixture was stirred at −78 °C for 30 min, then warmed to room temperature, and extracted with ethyl acetate (2 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel with 25% ethyl acetate-hexanes as eluent to yield 253 mg (71.5%) of a mixture of diastereomers: IR (thin film) 3010, 2920, 1500, 1460, 1350, 1245, 1160, 1100, 1040, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.91 (m, 3 H), 1.22 (d, 3 H, $J$ = 6.2 Hz, major), 1.24 (d, 3 H, $J$ = 6.3 Hz), 1.26–1.92 (m, 12 H), 3.32 (m, 1 H), 3.65 (m,2 H), 3.82 (m, 1 H), 4.20–4.80 (m, 6 H), 7.32 (m, 5 H); mass spectrum (15 eV), *m/z* 376 ($M^+ + 1$), 330,302,290 ($M^+ - C_5H_9O$), 260, 246, 240, 217; exact mass calcd for $C2_2H_{33}O_4N - C_4H_9O$ 290.1756, found 290.1756.

### Preparation of the β-Hydroxy Ketones 31 and 32.

To a solution of the isoxazolines **29** and **30** (253 mg, 0.67 mmol) in 10 mL of a 5:1 methanol-water mixture was added 1.0 mL (1.00 mmol) of a 1.0 M solution of boron trichloride in methylene chloride and 5 mg of W-2 Raney nickel (deactivated by refluxing with acetone for 1 h).[22] The reaction mixture was stirred under a balloon filled hydrogen atmosphere for 2 h and then filtered through Celite. The filtrate was diluted with 10 mL of a saturated $NaHCO_3$ solution, concentrated to a small volume, and extracted with ethyl acetate (3 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel with

25% ethyl acetate-hexanes as eluent to yield 243 mg (95.3%) of a 4:1 mixture of β-hydroxy ketones which were separated by a second column chromatography.

**31** (major isomer): $R_f$ 0.32 (silica gel, 25% ethyl acetate-hexanes); IR (thin film) 3450, 3010, 2980, 1725, 1500, 1450, 1360, 1260, 1190, 910, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.88 (m, 3 H), 1.32 (d, 3 H, *J* = 6.52 Hz), 1.25–1.93 (m, 12 H), 2.95 (m, 1 H), 3.31–3.82 (m, 5 H), 4.10 (d, 1 H, *J* = 17.92, major), 4.22 (d, 2 H, *J* = 1.61 Hz, minor), 4.32 (d, 1 H, *J* = 17.92 Hz, major), 4.43 (d, 1 H, *J* = 11.52 Hz, major), 4.51 (m, 1 H, minor), 4.61 (d, 1 H, *J* = 11.6 Hz, major), 4.62 (m, 1 H, major), 7.32 (s, 5 H); mass spectrum (15 eV), *m/z* 378 ($M^+$), 348,294, 293 ($M^+ - C_5H_9O$), 277, 263, 243, 187; exact mass calcd for $C_{22}H_{34}O_5 - C_5H_9O$ 293.1753, found 293.1753.

**32** (minor isomer): $R_f$ 0.23 (silica gel, 25% ethyl acetate-hexanes); IR (thin film) 3450, 3105, 2980, 2880, 1725, 1520, 1460, 1300,1250, 1140, 940, 880 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) δ 0.85 (m, 3 H), 1.29 (d, 3 H, *J* = 6.47 Hz), 1.15–1.92 (m, 12 H), 2.90 (m, 2 H), 3.41–3.88 (m, 4 H), 4.05–4.32 (m, 2 H), 4.39 (d, 1 H, *J* = 12.09 Hz), 4.58 (m, 1 H), 4.68 (d, 1 H, *J* = 12.09 Hz), 7.35 (s, 5 H); mass spectrum (15 eV), *m/z* 348,294,293 ($M^+ - C_6H^9O$), 277, 263, 242, 217, 187; exact mass calcd for $C_{22}H_{34}O_5 - C_6H_9O$ 293.1753, found 293.1751.

### (2*SR*, 3*RS*,4*SR*)-4-(Benzyloxy)-2-butyl-3-hydroxy-pentanoic Acid and *(2SR,3RS* 4*SR*)-Methyl 4-(Benzyl-oxy)-2-butyl-3-hydroxypentanoate.

To a solution of the major hydroxy ketone (189 mg, 0.502 mmol) in 3 mL of methanol was added a solution of $H_5IO_6$ (57.3 mg, 2.5 mmol) in 0.5 mL of water. The resulting mixture was stirred overnight, concentrated by rotary evaporation, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography on silica gel with 35% ethyl acetate-hexanes as eluent to yield 87.9 mg (59.5%) of the methyl ester and 52.3 mg (37.2%) of the β-hydroxy acid.

β-Hydroxy acid: IR (thin film) 3500–2900 (br), 1705,1450,1300, 1220,1010, 960 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) δ 0.89 (m, 3 H), 1.09–1.89 (m, 6 H), 1.23 (d, 3 H, *J* = 6.21 Hz), 2.55 (m, 1 H), 3.42 (dq, 1 H, *J* = 6.1, 5.2 Hz), 3.85 (dd, 1 H, *J* = 6.1, 5.2 Hz), 4.33 (d, 1 H, *J* = 11.06 Hz), 4.52 1 H, *J* = 11.06 Hz), 7.26 (s, 5 H).

β-Hydroxy ester: IR (thin film) 3500, 3010, 2980, 1740, 1500, 1450 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) δ 0.88 (m, 3 H), 1.10–1.92 (m, 6 H),1.25 (d, 3 H, *J* = 6.47 Hz), 2.55 (m, 1 H), 3.44 (m, 1 H), 3.71 (s,3 H), 3.85 (dd, 1 H, *J* = 6.27, 5.40 Hz), 4.28 (d, 1 H, *J* = 12.01 Hz), 4.48 (d, 1 H, *J* = 12.06 Hz), 7.30 (s, 5 H).

### (2*SR*,3*RS*,4*SR*)-2-Butyl-3,4-dihydroxypentanoic Acid 1.4-Lactone [(±)-*epi*-Blastmycinolactol (33)].

To a solution of the above β-hydroxy ester (80 mg, 0.272 mmol) in 3.0 mL of methanol was added 35 mg of 10% Pd on carbon and 3 drops of concentrated HCl. The reaction mixture was stirred under a balloon filled hydrogen atmosphere for 2 h at room temperature. The mixture was filtered through a pad of Celite and concentrated to a small volume. The residue was diluted with 5 mL of brine and extracted with ethyl acetate. The combined extracts were

dried ($MgSO_4$) and concentrated, and the crude product was purified by column chromatography on silica gel with 50% ethyl acetate-hexanes as eluent to yield 40.8 mg (87.2%) of *epi*- blastmycinolactol as a colorless oil: IR (thin film) 3500, 2980, 1760, 1450,1160,1025 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) $\delta$ 0.93 (m, 3 H), 1.35 (d, 3 H ,$J$ = 6.87 Hz), 1.35–1.92 (m, 6 H), 2.60 (m, 1 H), 4.22 (m, 1 H), 4.52 (dd, 1 H, $J$ = 13.34, 6.67 Hz); mass spectrum (15 eV), *m/z* 172 ($M^+$), 155, 148, 129, 117, 116, 100, 99; exact mass calcd for $C_9H_{16}O_3$ 172.1099, found 172.1104.

### (2*RS*,3*RS*,4*SR*)-2-Butyl-3,4-dihydroxypentanoic Acid 1.4-Lactone [(±)-Blastmycinolactol].

To a solution of 21 mg (0.12 mmol) of *epi*-blastmycinolactol in 2 mL of methanol was added 2 drops of a freshly prepared sodium methoxide solution (obtained by dissolving 1 mg of sodium in 1.2 mL of methanol). The mixture was stirred overnight at room temperature, acidified to a pH of 3 by the addition of dilute HC1, and extracted with ethyl acetate. The extracts were washed successively with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to give a 2.3:1 mixture of blastmycinolactol and the starting lactone. The mixture was separated by HPLC with 25% ethyl acetate-hexanes as eluent to yield 7.0 mg of 33 and 12.8 mg (91.4% based on recovered starting material) of blastmycinolactol: mp 49.5–51 °C; IR ($CC1_4$) 3450, 2925, 1740, 1450, 1220, 1160, 1025, 960 $cm^{-1}$; $^1H$ NMR ($CDC1_3$) $\delta$ 0.90 (m, 3 H), 1.13–1.97 (m, 6 H), 1.45 (d, 3 H, $J$ = 6.2 Hz), 2.58 (m, 1 H), 3.84 (dd, 1 H, $J$ = 8.5 Hz) 4.25 (dq, 1 H, $J$ = 7.0 Hz); mass spectrum (15 eV), *m/z* 172 ($M^+$), 155, 141, 129, 117, 100; exact mass calcd for $C_9H_{26}O_3$ 172.1099, found 172.1100.

### (2*RS*,3*RS*,4*SR*)-2-Butyl-4-hydroxy-3-(isovaleryloxy)pentanoic Acid 1,4-Lactone [(±)-Blastmycinone (34)].

To a solution of 12.8 mg (0.074 mmol) of blastmycinolactol in 0.5 mL of dry pyridine was added a solution of 29.1 mg (0.156 mmol) of isovaleric anhydride in 0.2 mL of pyridine. The mixture was stirred at room temperature for 24 h, and additional isovaleric anhydride (29.1 mg in 0.2 mL of pyridine) was added. After a further 3 days at room temperature 5 mL of water was added, and the reaction mixture was extracted with ether. The ether extracts were washed successively with 5% hydrochloric acid, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on SilicAR CC-7 with 25% ethyl acetate-hexanes as eluent to give 17.9 mg (93.9%) of (±)-blastmycinone as a colorless oil. An analytical sample was prepared by HPLC purification: IR (thin film) 2910, 1785, 1745, 1470, 1260, 1180, 1120, 1040, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (m, 3 H), 0.98 (d, 6 H, $J$ = 6.47 Hz), 1.25–2.30 (m, 9 H),1.45 (d, 3 H, $J$ = 6.50 Hz), 2.70 (m, 1 H), 4.37 (dq, 1 H, $J$ = 6.67, 4.60 Hz), 4.95 (dd, 1 H, $J$ = 5.70, 4.60 Hz); mass spectrum (15 eV), *m/z* 256 ($M^+$), 241 ($M^+ - CH_3$), 200, 184, 155, 154; exact mass calcd for $C_{14}H_{24}O_4 - CH_3$ 241.1440, found 241.1432.

### (2*SR*,3*RS*,4*SR*)-2-Butyl-4-hydroxy-3-(isovaleryloxy)pentanoic Acid 1,4-Lactone [(±)-*epi*-Blastmycinone].

A procedure identical with that described above was employed for the preparation of (±)-*epi*-blastmycinone. The crude product was purified on silica gel with 25% ethyl acetate-hexanes as eluent to give 10.2 mg (81.3%) of a 2:1 mixture of *epi*-blastmycinone and

blastmycinone. An analytical sample was prepared by HPLC separation on a silica gel column with 20% ethyl acetate-hexanes as eluent: IR (thin film) 2910, 1880, 1760, 1465, 1245, 1200, 1180, 1110, 1050, 980 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) ($\delta$ 0.95 (m, 9 H), 1.21−2.45 (m, 9 H), 1.40 (d, 3 H, $J$ = 6.87 Hz, major), 1.46 (d, 3 H, $J$ = 6.55 Hz, minor), 3.72 (m, 1 H), 4.37 (dq, 1 H, $J$ = 6.67,4.60 Hz, minor), 4.49 (m, 1 H, major), 4.95 (dd, 1 H, $J$ = 5.70,4.62 Hz, minor), 5.14 (d, 1 H, $J$ = 6.26 Hz); mass spectrum (15 eV), $m/z$ 256 ($M^+$), 241 ($M^+ - CH_3$), 200, 184, 183, 155, 154, 141; exact mass calcd for $C_{14}H_{24}O_4 - CH_3$ 241.1440, found 241.1435.

### Reaction of Cis Olefin 35 with Propionitrile Oxide.

The reaction was run on a 0.86-mmol scale in toluene as solvent at 90 °C (for other reaction variables, see the first experiment) to obtain a 57% yield of 36 after chromatography on silica gel with 20% ethyl acetate-hexanes as eluent. This compound was found to be >95% pure by HPLC analysis: IR (thin film) 2980, 2880, 1600, 1525, 1480, 1425, 1350, 1210, 1050, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19 (t, 3 H, $J$ = 7.48 Hz), 1.21 (d, 3 H, $J$ = 7.47 Hz), 1.36 (s, 3 H), 1.42 (s, 3 H), 2.24 (dq, 1 H, $J$ = 15.76, 7.48 Hz), 2.43 (dq, 1 H, $J$ = 15.76, 7.48 Hz), 3.28 (dq, 1 H, $J$ = 9.09, 7.47 Hz), 3.98 (m, 1 H), 4.15–4.26 (m, 3 H), 4.31 (t, 1 H, $J$ = 9.09 Hz); $^{l3}C$ NMR ($CDCl_3$) $\delta$ 10.8, 11.3, 19.8, 25.8, 26.9, 45.9, 68.1, 73.1,83.4, 109.5,165.2; mass spectrum (15 eV), $m/z$ 213 ($M^+$), 198 ($M^+ - CH_3$), 175, 138, 127; $[\alpha]^{24}_D$ −5.2° ($c$ 0.321, $CHC1_3$); exact mass calcd for $C_{11}H_{19}NO_3 - CH_3$ 198.1130, found 198.1131.

### (2*R*)-2-Methyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propan-l-ol (43).

A solution of (*S*)-(+)-$\beta$-hydroxyisobutyric acid (42) (1.0 g, 9.61 mmol), dihydropyran (2.19, 25 mmol), and pyridinium *p*-toluenesulfonate (753 mg, 3 mmol) in 15 mL of dry methylene chloride was stirred at room temperature overnight. The reaction mixture was diluted with 30 mL of ethyl ether and washed with sodium bicarbonate and brine. The organic extracts were dried ($Na_2SO_4$) and concentrated. The crude product was chromatographed on silica gel with 15% ethyl acetate-hexanes as eluent to afford 2.25 g (86%) of pure product: IR (thin film) 2925, 2880, 1750, 1350, 1220, 1050, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) $\delta$ 1.20 (d, 3 H, $J$ = 7.0 Hz), 1.30–2.30 (m, 12 H), 2.60 (m, 1 H), 3.10–3.95 (m, 6 H), 4.52 (m, 1 H), 5.85 (m, 1 H).

To a refluxing solution of the above ester (1.20 g, 4.41 mmol) and sodium borohydride (359 mg, 9.5 mmol) in *t*-BuOH (10 mL) was added 3.5 mL of methanol over a period of 1.5 h. After stirring for an additional hour, the reaction mixture was quenched with a brine solution, concentrated to a small volume, and extracted with ethyl acetate (3 ×). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel with 35% ethyl acetate-hexanes as eluent to yield 607 mg (79.1%) of alcohol: IR (thin film) 3500, 2910, 2880, 1450, 1325, 1160, 960, 890 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.91 (d, 3 H, $J$ = 6.80 Hz), 1.40–1.90 (m, 6 H), 2.05 (m, 1 H), 2.75 (br 1 H), 3.30–3.90 (m, 6 H), 4.61 (m, 1 H); mass spectrum (15 eV), $m/z$ 174 ($M^+$), 173, 156.

**(*S*)-l-(Benzyloxy)-2-methyl-3-nitropropane (44).**

To 500 mg (2.87 mmol) of alcohol 43 in 15 mL of dry THF was added 108 mg (4.5 mmol) of sodium hydride (washed with dry benzene three times) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then benzyl bromide (0.5 mL, 4.2 mmol) and tetra-*n*-butylammonium iodide (20 mg) were added. After 3 h, the solvent was removed by rotary evaporation, brine was added, and the mixture was extracted with ethyl acetate. The combined extracts were dried and concentrated. The crude mixture was purified by flash chromatography on silica gel with 15% ethyl acetate-hexanes as eluent to furnish 727 mg (96%) of the benzyloxy ether derivative as a colorless oil: IR (thin film) 3010, 2990, 1440, 1320, 1025, 980 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.02 (d, 3 H, $J$ = 6.67 Hz), 1.45–1.90 (m, 6 H), 2.15 (m, 1 H), 3.30–3.93 (m, 6 H), 4.52 (br s, 2 H), 4.58 (m, 1 H), 7.38 (m, 5 H).

A solution of the above ether (600 mg, 2.27 mmol) and 75 mg of pyridinium *p*-toluenesulfonate in 10 mL of ethanol was heated at 55°C for 3 h. When all the starting material was consumed, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3 ×). The combined extracts were dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash chromatography over silica gel with 25% ethyl acetate-hexanes as eluent to yield 374 mg (91.6%) of the alcohol as a colorless oil: IR (thin film) 3500, 3015, 2900, 1450, 1325, 1200, 1100, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$,) $\delta$ 0.90 (d, 3 H, $J$ = 7.03 Hz), 2.10 (m, 1 H), 3.42–3.71 (m, 5 H), 4.53 (s, 2 H), 7.39 (m, 5 H).

To a solution of 300 mg (1.66 mmol) of the preceding alcohol in 3 mL of pyridine at 0 °C was added 477 mg (2.5 mmol) of *p*-toluenesulfonyl chloride. After stirring at 0 °C for 1 h, the mixture was chilled in the freezer for 24 h, then poured into ice, and extracted with ether (3 ×). The etheral extracts were washed successively with 5% HC1, saturated $NaHCO_3$, and brine, dried over anhydrous $Na_2SO_4$, and concentrated to afford 517 mg (96.5%) of the tosylate.

To a solution of 517 mg (1.59 mmol) of this tosylate in 10 mL of acetone was added 1.5 g (100 mmol) of sodium iodide. The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, diluted with 10 mL of water, and extracted with ether (3 ×). The combined extracts were washed successively with saturated sodium thiosulfate and brine, dried ($Na_2SO_4$, and concentrated. The crude product was purified by flash chromatography on silica gel with 20% ethyl acetate-hexanes as eluent to give 429 mg (93.1%) of the iodide as a colorless oil: IR (thin film) 3010, 2910, 2880, 1480, 1425, 1350, 1180, 1080, 1010 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.97 (d, 3 H, $J$ = 6.67 Hz), 1.75 (m, 1 H), 3.22–3.45 (m, 4 H), 4.51 (s, 2 H), 7.35 (m, 5 H).

To 429 mg (1.48 mmol) of the above iodide in 5 mL of dry ether was added 456 mg (2.96 mmol) of silver nitrite. The resulting mixture was stirred in the dark at room temperature for 2 days. The silver salts were filtered, the filter cake was washed with ether, and the filtrate was concentrated. The crude product was purified by chromatography on silica gel with 15% ethyl acetate-hexanes as eluent to afford 245 mg (79.3%) of the nitro compound 44 as a colorless oil: IR (thin film) 3010, 2920, 1540, 1500, 1450, 1360, 1200, 1180, 1025 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05 (3 H, d, $J$ = 6.87 Hz), 2.65 (m, 1 H), 3.35 (dd, 1 H, $J$ = 9.50, 7.27 Hz),

3.50 (dd, 1 H, $J$ = 9.50, 4.65 Hz), 4.28 (dd, 1 H, $J$ = 12.13, 7.88 Hz), 4.52 (m, 2 H), 4.58 (dd, 1 H, $J$ = 12.13, 6.06 Hz), 7.35 (m, 5 H); $[\alpha]^{24}_{D}$ −14.2° ($c$ 0.425, $CH_2C1_2$)

### Reaction of (+)-(*S*)-Isopropylidene-3-butene-1,2-diol with the Chiral Nitrile Oxide from 44.

The reaction was run on a 0.24-mmol scale under the standard conditions (see the first experiment) to give a 78.3% yield of an 80:20 mixture ($^1$H NMR analysis) of diastereomers after chromatography on silica gel with 25% ethyl acetate-hexanes as eluent: IR (thin film) 3010, 2990, 2850, 1620, 1520, 1400, 1350, 1200, 1090, 1025 $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (d, 3 H, $J$ = 6.67 Hz), 1.32 (s, 3 H), 1.42 (s, 3 H), 2.82–3.15 (m, 3 H), 3.52 (m, 2 H), 3.80 (m, 3 H), 4.46 (ddd, 1 H, $J$ = 10.10, 7.68, 6.26 Hz, major), 4.52 (m, 2 H), 4.62 (ddd, 1 H, $J$ = 11.11, 7.88, 4.85 Hz, minor), 7.38 (m, 5 H); mass spectrum (15 eV), $m/z$ 319 ($M^+$), 304 ($M^+ - CH_3$), 289, 218, 213, 119, 117; exact mass calcd for $C_{18}H_{25}NO_4$ 319.1784, found 319.1786.

### Registry No.

**1**,62214-38-4; 2, 83159-90-4; **2** (acid), 90344-33-5; **2** (acetate), 84044-91-7; **3** (bis-*t*-$BuMe_2Si$ ether), 90344-34-6; **3** (anilide), 90344-35-7; **3** (lactone), 34371-14-7; **3** (lactone, 4-acetate), 81366-68-9; **3** (lactone, bis-*t*-$BuMe_2Si$ ether), 83159-91-5; *anti*-**4**, 64482-42-4; *syn*-**4**, 64482-63-9; (±)-**5**, 90344-37-9; (±)-*anti*-**6**, 90344-38-0; (±)-*syn*-**6**, 90410-16-5; (±)-*anti*-**6** (desilyl), 90344-39-1; (±)-*syn*-**6** (desilyl), 90410-17-6; (±)-*anti*-**7**, 90344-40-4; (±)-*syn*-**7**, 90410-18-7; *(±)-anti*-**8**, 90344-67-5; (±)-*syn*-**8**, 90344-68-6; (±)-*anti*-**9**,90344-69-7; (±)-*syn*-**9**, 90344-70-0; (±)-*anti*-**10**, 74262-64-9; (±)-*syn*-**10**, 74262-67-2; (±)-**11**, 90344-66-4; (±)-**12**, 38996-22-4; **20**, 90344-71-1; **21**, 90344-73-3; **22**, 90344-74-4; **23**, 90344-75-5; **23** (alcohol), 90344-76-6; **27**, 90344-36-8; **28a**, 35786-19-7; (±)-**29**, 90344-41-5; (±)-**30**, 90344-42-6; (±)-**31**, 90344-43-7; (±)-**31** (acid), 90344-45-9; (±)-**31** (methyl ester), 90344-46-0; (±)-**32**, 90344-44-8; (±)-**33**, 90410-19-8; (±)-**33** (isovalerate), 53494-50-1; (±)-**34**, 31203-09-5; (±)-**34** (alcohol), 53402-76-9; **35**, 90344-47-1; **36**, 90344-48-2; **42**, 26543-05-5; **42** (bis-THP deriv), 88671-01-6; **43**, 88728-99-8; **43** (*O*-benzyl, THP deriv), 88671-02-7; **43** (*O*-benzyl, alcohol), 63930-46-1; **43** (*O*-benzyl, tosylate), 90367-65-0; **43** (*O*-benzyl, iodide), 90344-49-3; **44**, 90344-50-6; **44** (nitrile oxide), 90344-51-7; **45**, 90344-52-8; *epi*-**45**, 90410-20-1; CEFNO, 51983-62-1; $CH_3C{\equiv}N^+{-}O^-$, 7063-95-8; $THPOCH_2C{\equiv}N^+{-}O^-$, 77790 67-1; $PhC{\equiv}N^+{-}O^-$, 873-67-6; $CH_3CH_2C{\equiv}N^+{-}O^-$, 71494-92-3; $PhNH_2$, 62-53-3; $CH_3(CH_2)_3I$, 542-69-8; $(Me_2CHCH_2CO)_2O$, 1468-39-9; $CH_2{=}CHCH(CH_3)OSiPh_2Bu$-*t*, 90344-53-9; $CH_2{=}CHCH(CH_3)OCH_2Ph$, 53329-00-3; $CH_2{=}CHCH(CH_3)OAc$, 6737-11-7; $CH_2{=}CHCH(CH_3)OH$, 598-32-3; $CH_2{=}C(CH_3)$-$CH_2OMOM$, 90344-72-2; (*E*)-$CH_3CH{=}C(CH_3)CO_2Me$, 6622-76-0; (1-methoxy-l-cyclohexyl)oxyacetonitrile oxide, 90344-23-3; 1,3-dioxolane-2-acetonitrile oxide, 82045-43-0; ethyl 5(*S*)-*anti*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline-3-carboxylate, 83159-89-1; ethyl 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-isoxazoline-3-carboxylate, 90344-24-4; 5(*S*)-*anti*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-isoxazoline, 90344-25-5; 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyl-2-isoxazoline, 90344-26-6; 5(*S*)-*anti*-5-(2,2-dimethyl-l,3-dioxolan-4-yl)-3-[(tetrahydropyranyloxy)methyl]-2-isoxazoline, 90344-27-7; 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-[(tetrahydropyranyloxy)-methyl]-2-isoxazoline, 90410-13-2; 5(*S*)-*anti*-5-

(2,2-dimethyl-l,3-dioxolan-4-yl)-3-phenyl-2-isoxazoline, 90410-14-3; 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenyl-2-isoxazoline, 90410-15-4; 5(*S*)-*anti*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-[(1-methoxy-1-cyclohexyloxy)methyl]-2-isoxazoline, 90344-28-8; 5(*S*)-*anti*-5-(2,2-dimethyl·1,3-dioxolan-4-yl)-3-ethyl-2-isoxazoline, 90344-29-9; 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-ethyl-2-isoxazolme, 90344-30-2; 5(*S*)-*anti*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-[(1,3-dioxolan-2-yl)methyl]-2-isoxazoline, 90344-31-3; 5(*R*)-*syn*-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-[(1,3-dioxolan-2-yl)methyl]-2-isoxazoline, 90344-32-4; *anti*-3-methyl-5-[1 (*tert*-butyldiphenylsilyloxy)ethyl]-2-isoxazoline, 90344-54-0; *syn*-3-methyl-5-[1-(*tert*-butyldiphenylsilyloxy)ethyl]-2-isoxazoline, 90344-55-1; ethyl *anti*-5-(1-benzyloxyethyl)-2-isoxazoline-3-carboxylate, 90344-56-2; ethyl *syn*-5-(1-benzyloxyethyl)-2-isoxazoline-3-carboxylate, 90344-57-3;*anti*-3-ethyl-5[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline 90344-58-4; *syn*-3-ethyl-5-[1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-isoxazoline, 90344-59-5; *anti*-3-methyl-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline, 90344-60-8; *syn*-3-methyl-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline 90344-61-9; ethyl *anti*-5-[1-(*tert*-butyldimethylsiyloxy)ethyl]-2-isoxazoline-3-carboxylate, 90344-62-0; ethyl *syn*-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline-3-carboxylate, 90344-63-1 *anti*-3-phenyl-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-isoxazoline 90270-62-5; *syn*-3-phenyl-5-[1-*tert*-butyldimethylsilyloxy)-ethyl]-2-isoxazoline, 90270-63-6; *anti*-3,α-dimethyl-2-isoxazoline-5-methanol acetate, 90344-64-2; *syn*-3,α-dimethyl-2-isoxazoline-5-methanol acetate, 90344-65-3; *anti*-3-phenyl-2-isoxazoline-5-methanol, 90270-51-2; *syn*-3-phenyl-2-isoxazoline-5-methanol, 90270-52-3.

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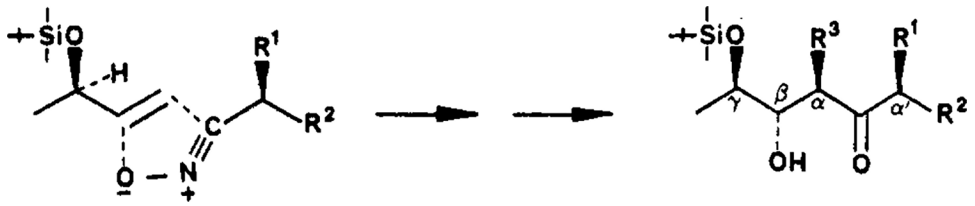
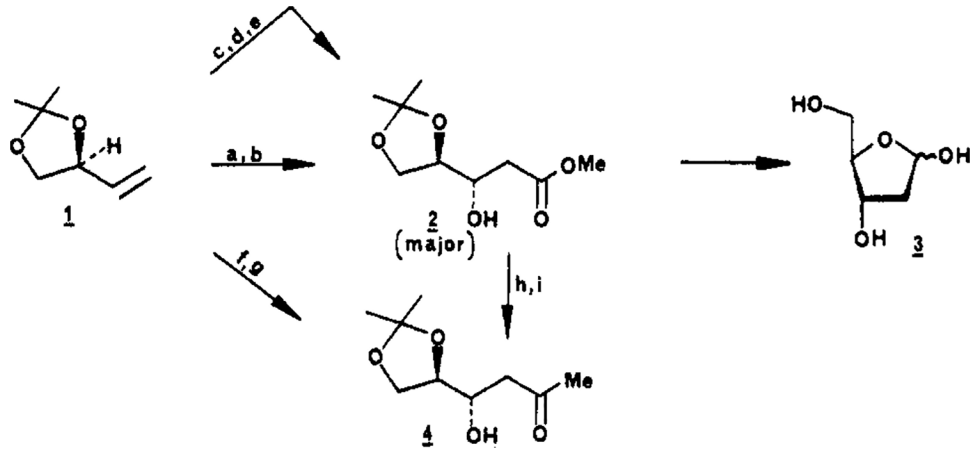
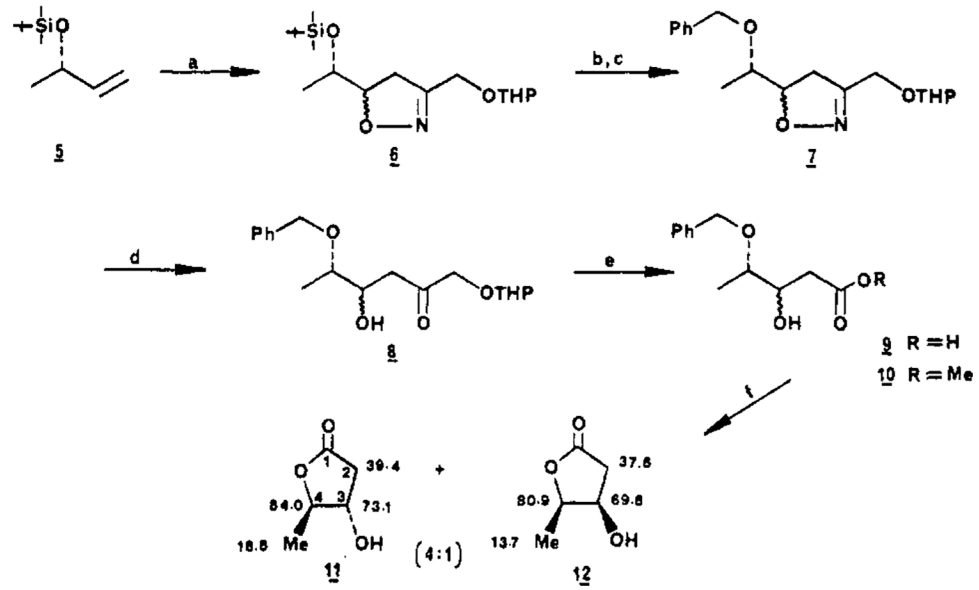



**Figure 1.**




**Scheme I.**

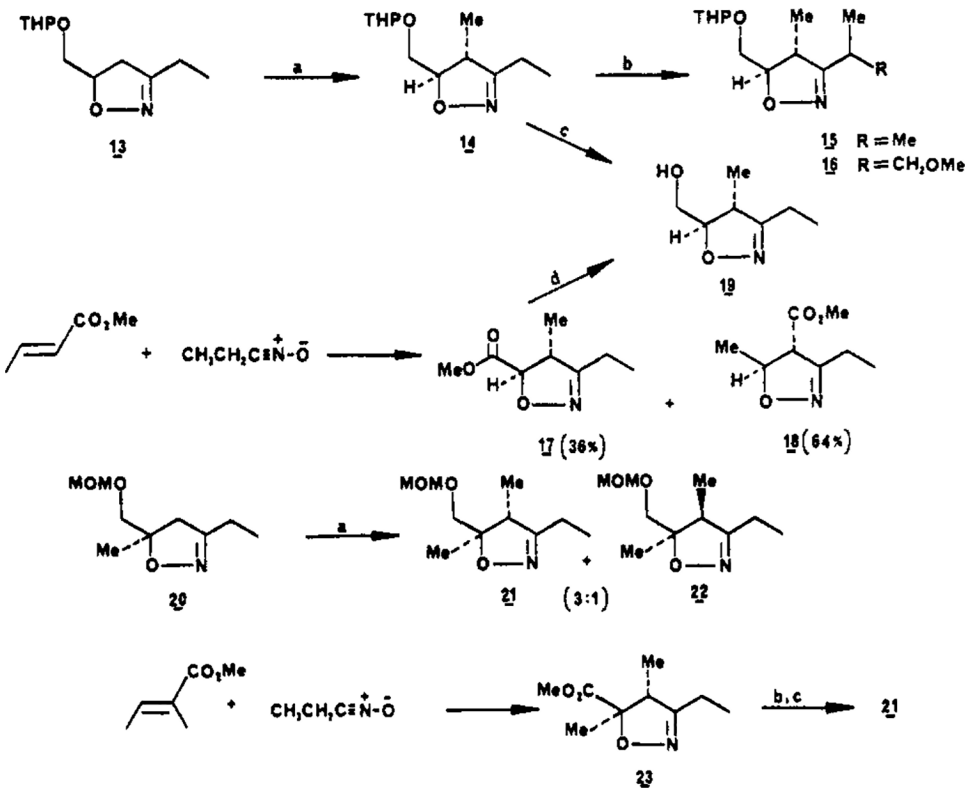
[a] a, CEFNO, $Et_2O$, room temp; b, 10% NaOH, EtOH; $H_3O^+$; $CH_2N_2$; c, $THPOCH_2CH_2NO_2$, PhNCO, $Et_3N$, $C_6H_6$, d, $H_2$, Raney Ni, $AlCl_3$, MeOH, $H_2O$; e, $NaIO_4$, $NaHCO_3$, MeOH; $CH_2N_2$; f, $CH_3CH_2NO_2$, PhNCO, $Et_3N$, $C_6H_6$; g, $H_2$, Raney Ni, HOAc, MeOH, $H_2O$; h, 10% NaOH, MeOH; $H_3O^+$; i, MeLi, $Et_2O$.




**Scheme II.**

A Proof of Stereochemistry for the Dipolar Cycloaddition Reaction of the *tert*-Butyldimethylsilyl Ether Derivative of 3-Buten-2-ol[a]

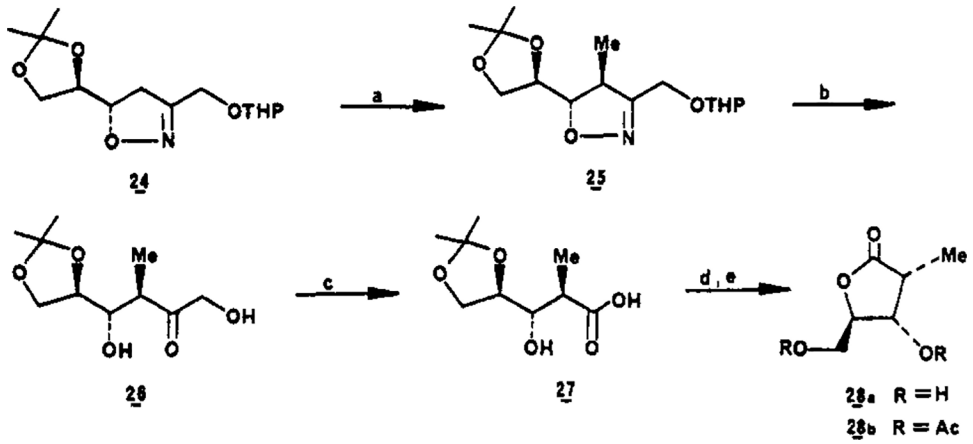
[a] a, PhNCO, $Et_3$ N, $CCl_4$ ; b, $(n\text{-Bu})_4N^+F^-$, THF; c, NaH, THF; $PhCH_2Br$, $(n\text{-Bu})_4$ $N^+$ $I^-$ (catalyst); d, $H_2$, Raney Ni, $BC1_3$, MeOH, $H_2O$; e, $H_5IO_6$, MeOH; $H_2O$; f, $H_2$, 10% Pd/C, MeOH, HCl.




**Scheme III.**

Metalation-Alkylation of 5-Alkoxymethyl Substituted Isoxazolines[a,b]

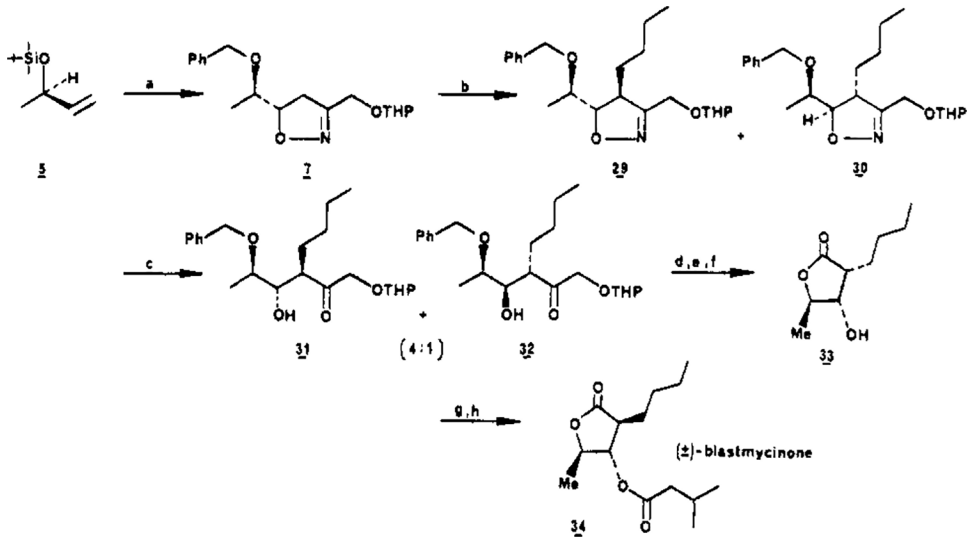
[a] a, LDA, HMPA; MeI; b, LDA, HMPA; MeI (or $MeOCH_2I$); c, PPTS, EtOH; d, $LiBH_4$, diglyme. [b] a, LDA, HMPA; MeI; b, $NaBH_4$, *t*-BuOH, MeOH; c, $(MeO)_2CH_2$, $P_2O_5$, $CH_2Cl_2$.




**Scheme IV.**

Metalation-Alkylation of an (*S*)-Isopropylidene-3-butene-1,2-diol Derived Isoxazoline[a]

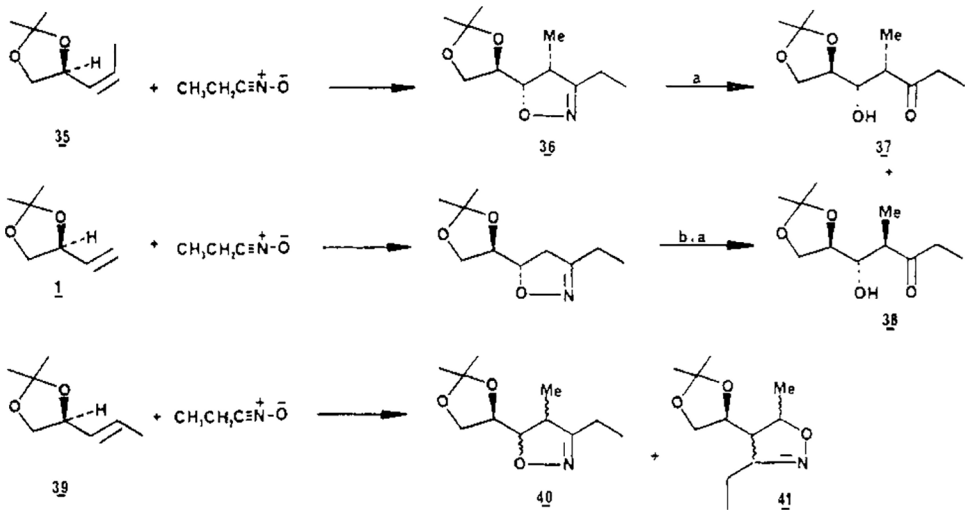
[a] a, LDA, HMPA; MeI; b, $H_2$, Raney Ni, $AlCl_3$, MeOH, $H_2O$; c, $NaIO_4$, $NaHCO_3$, MeOH; $H_3O^+$; d, TFA, $H_2O$; e, $Ac_2O$, Pyr.




**Scheme V.**

A Synthesis of (±)-Blastmycinone[a]

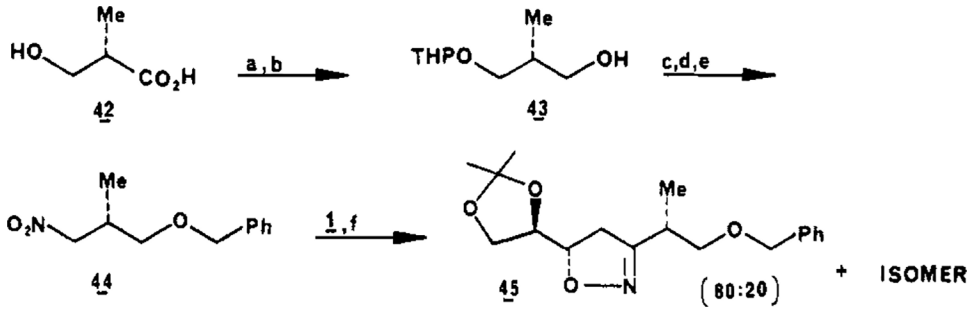
[a] a, See Scheme II; b, LDA, HMPA; *n*-BuI; c, $H_2$, Raney Ni, $BCl_3$, MeOH, $H_2O$; d, separate diastereomers; e, $H_5IO_6$, MeOH, $H_2O$; f, $H_2$, 10% Pd/C, MeOH, HCl; g, NaOMe, MeOH; h, $(Me_2CHCH_2CO)_2O$, Pyr.




**Scheme VI.**

Reactions of 1,2-Disubstituted Alkenes[a]

[a] a, $H_2$, Raney Ni, HOAc, MeOH, $H_2O$; b, LDA, HMPA; MeI.



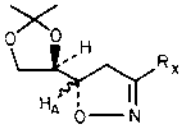

**Scheme VII.**

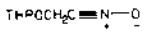
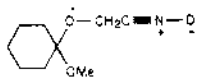
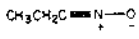
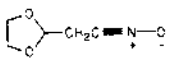
Reaction of an Optically Active Nitrile Oxide with (*S*)-Isopropylidene-3-butene-1,2-diol[a]

[a] a, DHP, PPTS, $CH_2Cl_2$; b, $NaBH_4$, *t*-BuOH, MeOH; c, NaH, THF; $\phi CH_2Br$, $(n\text{-Bu})_4N^+I^-$ (catalyst); d, PPTS, MeOH; e, TsCl, Py; NaI, MeCOMe; $AgNO_2$, $Et_2O$; f, PhNCO, $Et_3N$, PhH.

**Table I.**

Diastereoselection in the Reaction of (+)-(*S*)-Isopropylidene-3-butene-1,2-diol with Various Nitrile Oxides

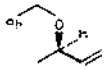
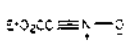
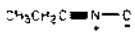
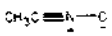
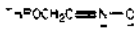
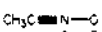


| no. | dipole | isomer ratio | chemical shift and coupling constants for $H_A$[a] |
|---|---|---|---|
| 1 |  | 80:20 | anti: 4.72 (ddd, $J$ = 10.30, 7.88, **6.71** Hz)<br>syn: 4.85 (ddd, $J$ = 11.5, 8.49 **4.24** Hz) |
| 2 |  | 88:12 | anti: 4.45 (ddd, $J$ = 10.10, **7.68**, 6.46 Hz)<br>syn: 4.63 (ddd, $J$ = 10.91, 7.88, **4.75** Hz) |
| 3 |  | >94:<6 | difficult to assign because of overlapping peaks |
| 4 |  | 83:17 | anti: 4.67 (ddd, $J$ = 10.10, **7.61**, 6.67 Hz)<br>syn: 4.83 (ddd, $J$ = 11.11, 8.08, **4.65** Hz) |
| 5 |  | >94:<6 | anti: 4.55 (ddd, 10.10, **7.50**, 6.67 Hz)<br>syn: not assigned |
| 6 |  | 90:10 | anti: 4.47 (ddd, $J$ = 10,30, **7.68**, 6.26 Hz)<br>syn: 4.62 (ddd, $J$ = 10.81, 7.88, **4.85** Hz) |
| 7 |  | 80:20 | anti: 4.49 (ddd, $J$ = 10.3, **7.28**, 6.67 Hz)<br>syn: 4.65 (ddd, 10.91, 7.68, **4.85** Hz) |

[a]The boldfaced coupling constant is $J_{AX}$, and its magnitude is diagnostic of the syn and anti isomers.

**Table II.**

Diastereoselection in the Reactions of Derivatives of 3-Buten-2-ol with Various Nitrile Oxides

| no. | dipolarophile | dipole | isomer ratio[a] | diagnostic NMR data[b] |
|---|---|---|---|---|
| 1 |  |  | 66:34 | anti: 4.42 (ddd, $J$ = 11.21, 7.58, 3.79 Hz)<br>syn: 4.51 (ddd, $J$ = 10.91, 7.88, 4.85 Hz) |
| 2 |  |  | 68:32[c] | anti: 4.76 (ddd, $J$ = 11.52, 8.28, 4.24 Hz)<br>syn: 4.85 (ddd, $J$ = 11.32, 8.69, 5.25 Hz) |
| 3 |  |  | 73:27 | anti: 4.36 (ddd, $J$ = 10.91, 7.48, 3.74 Hz)<br>syn: 4.48 (ddd, $J$ = 10.31, 8.08, 5.05 Hz) |
| 4 |  |  | 73:27 | anti: 4.32 (ddd, $J$ = 11.02, 7.68, 3.84 Hz)<br>syn: 4.43 (ddd, $J$ = 10.25, 8.03, 5.07 Hz) |
| 5 |  |  | 71:29 | anti: 4.63 (ddd, $J$ = 11.12, 7.88, 3.13 Hz)<br>syn: 4.72 (ddd, $J$ = 11.31, 8.08, 4.85 Hz) |
| 6 |  |  | 81:19 | difficult to assign because of overlapping peaks |
| 7 |  |  | 75:25 | anti: 4.51 (ddd, $J$ = 11.12, 7.68, 3.84 Hz)<br>syn: 4.62 (ddd, $J$ = 10.51, 7.88, 5.05 Hz) |
| 8 |  |  | 52:48 | |
| 9 |  |  | 50:50 | |

[a] The isomer ratios were based on $^1$H NMR integrations and HPLC analysis.

[b] The boldfaced coupling constant is $J_{AX}$' and its magnitude is diagnostic of the syn and anti isomers.

[c] These isomers were separated by HPLC (Waters instrument with a $\mu$-porasil column) with 10% ethyl acetate-hexane as the solvent system.