Diastereofacial Selectivity Studies on 3-Alkenyl-4,5-diphenyl-4,5-dihydroisoxazoles

Peter A. Wade,*,† James F. Bereznak,† Bruce A. Palfey,† Patrick J. Carroll,‡ William P. Dailey,‡ and S. Sivasubramanian†

Departments of Chemistry, Drexel University and the University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received September 22, 1989

Epoxidation of 3-(1-phenylethenyl)-4,5-diphenyl-4,5-dihydroisoxazole and 3-ethenyl-4,5-diphenyl-4,5-dihydroisoxazole occurred with 74% diastereomer excess (de) and 66% de, respectively. Catalytic cis-hydroxylation of the 3-(1-phenylethenyl)dihydroisoxazole afforded a diol with 80% de. Cycloaddition reactions of the same alkenyl dihydroisoxazoles with bromonitrile oxide and phenylsulfonylcarbonitrile oxide occurred with 10–46% de; opposite diastereomers were preferred in the reactions of 3-ethenyl- and 3-(1-phenylethenyl)dihydroisoxazoles. These results are rationalized based on a combination of two factors: a preference for the s-trans heterodiene conformer and a preference for attack anti to the C-4 phenyl group in all but one case. The s-trans conformer of 3-ethenyl-4,5-dihydroisoxazole was determined by the ab initio method to be 2.8 kcal/mol more stable than the s-cis conformer.

4,5-Dihydroisoxazoles (isoxazolines) are useful for synthesizing a wide variety of open-chain compounds including γ-amino alcohols,[1] aldols,[2] β-cyanohydrins,[3] β-hydroxy esters,[4] and enones.[5] The moderate rigidity of the five-membered ring and the heteroatom lone pairs make dihydroisoxazoles attractive candidates for stereoselective transformations. Diastereomer ratios have been determined for dihydroisoxazole ring-opening and for functionalization of side chains located at the 3- and 5-atoms of the ring.[6,7] The present study is concerned with the diastereoselective functionalization of 3-alkenyl-4,5-dihydroisoxazoles, easily preparable synthetic intermediates.

All of the present studies have been carried out on 4,5-diphenyl-4,5-dihydroisoxazoles. These compounds are readily accessible via cycloaddition reactions to (*E*)-stilbene followed by an appropriate transformation. The 4-phenyl substituent is moderately bulky (*A* value[8] = 3) and influences stereoselectivity predominantly through steric repulsion.

Results

3-(1-Phenylethenyl)-4,5-diphenyl-4,5-dihydroisoxazole (**2a**) was prepared by dehydration of alcohol **1a**[6a] (Scheme I; dehydration of **1b** also gave **2a**). The 3-(ethenyl)dihydroisoxazole **2b** was best prepared by reaction of sulfonyldihydroisoxazole **3** with vinyllithium, although **2b** could be obtained in low yield by reaction of **3** with vinylmagnesium bromide or by alcohol dehydration.

Epoxidation of **2a** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the separable oxiranes **4a** and **5a** in 69% and 10% yield, respectively (87:13 **4a**/**5a** ratio, Table I). ^{1}H NMR analysis of the crude products agreed qualitatively with the isolation experiment (90:10 **4a**/**5a** ratio). Epoxidation using *N*-phenylsulfonyl-3-(4-nitrophenyl)oxaziridine[9] gave the same stereoselectivity but only a 36% total yield of **4a** and **5a**. The configurational assignment for oxirane **4a** was based on its conversion to alcohol **1b** in 92% yield using lithium triethylborohydride. The structure of alcohol **1a** has been determined by X-ray analysis.[6b] The observed stereoselectivity is explicable if attack occurred with a moderate preference anti to the 4-phenyl group on the s-trans conformation of the N=C—C=C system.

Epoxidation of **2b** with *m*-CPBA gave **4b** and **5b** in 43% and 9% yields, respectively, after separation (83:17 ratio, confirmed by NMR of the crude products). The configurational assignment was made by correlation of **4b** to

Scheme I

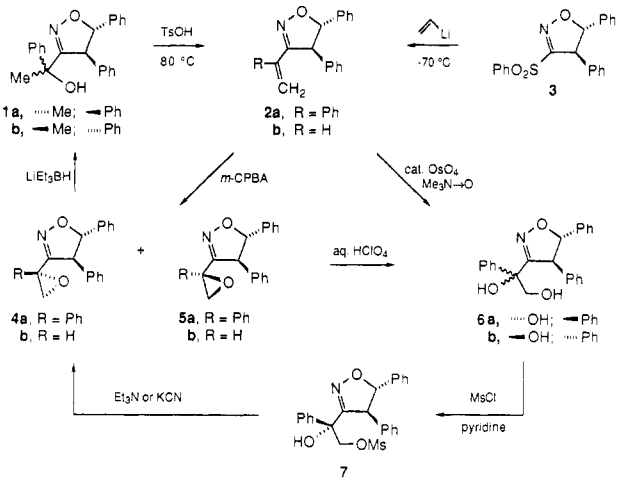


Table I. Reaction Products Derived from Dihydroisoxazoles 2a and 2b

substr	addend	products	ratio	temp, °C	yield, %
2a	*m*-CPBA	**4a**/**5a**	87:13	75–80	79
2a	oxaziridine[a]	**4a**/**5a**	87:13	58–60	36
2b	*m*-CPBA	**4b**/**5b**	83:17	75–80	52
2a	cat. OsO_4[b]	**6a**/**6b**	90:10	0–5	67
2a	BrC≡N→O[c]	**8b**/**9b**	73:27	50–55	70[e]
2b	BrC≡N→O[c]	**9c**/**8c**	65:35	50–55	81[e]
2a	PhO_2SC≡N→O[d]	**8a**/**9a**	65:35	50–55	88[f]
2a	PhO_2SC≡N→O[d]	**8a**/**9a**	68:32	50–55	72[e]
2b	PhO_2SC≡N→O[d]	**9d**/**8d**	55:45	50–55	78[e]

[a] *N*-Phenylsulfonyl-3-(4-nitrophenyl)oxaziridine. [b] Excess Me_3N→O and 0.1 equiv of OsO_4. [c] From Br_2C=NOH. [d] From $PhO_2SC(Br)$=NOH. [e] Based on nitrile oxide precursor as limiting reagent. [f] Based on **2a** as limiting reagent.

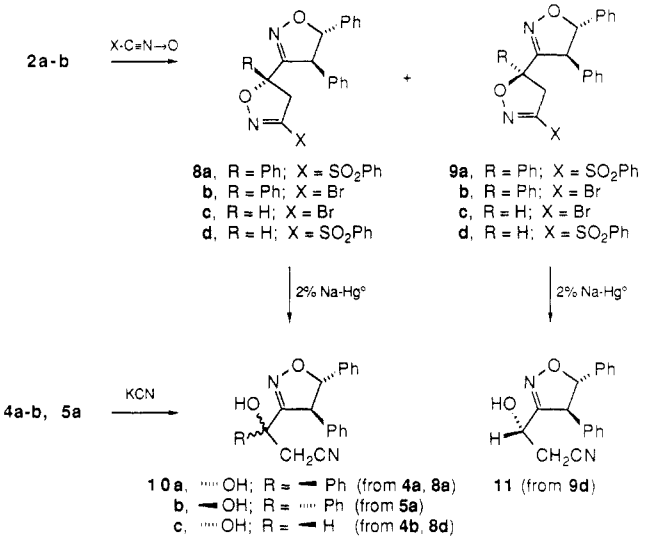
† Drexel University.
‡ University of Pennsylvania.

(1) (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79 and references cited therein. (b) Wade, P. A.; Rao, J. A.; Bereznak, J. F.; Yuan, C.-K. *Tetrahedron Lett.* **1989**, *30*, 5969. (c) Wade, P. A.; Price, D. T. *Tetrahedron Lett.* **1989**, *30*, 1185. (d) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. (e) Müller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777.

(2) (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (c) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

0022-3263/90/1955-3045$02.50/0

Scheme II



bis(dihydroisoxazole) **8d** (see Scheme II for the correlation). The configurational assignment for bis(dihydroisoxazole) **8d** was made based on X-ray analysis of the related bis(dihydroisoxazole) **9c**.

The reaction of **2a** with trimethylamine *N*-oxide and catalytic osmium tetroxide[10] led to a 90:10 mixture of diols **6a** and **6b** (Scheme I). Again, attack appears to have occurred preferentially anti to the 4-phenyl group on the s-trans conformer.

Configurational assignment for diols **6a** and **6b** proved somewhat difficult. Attempts to selectively convert oxirane **4a** to diol **6a** and **5a** to **6b** were unsuccessful: under acidic conditions either **4a** or **5a** gave a mixture of **6a** and **6b** with **6a** predominating (85:15 and 80:20 diastereomer ratios, respectively);[11] presumably a common carbocation intermediate was involved. Under basic conditions[12] oxirane **4a** was destroyed without formation of diol. Diol **6a** could be converted to the monomesylate **7** in 72% conversion. That mesylation of **6a** occurred on the primary hydroxyl group is most apparent from mass spectral data; a fragment ion corresponding to loss of CH_2OMs was observed. Also, the NMR signal attributed to the tertiary hydroxyl proton remained a singlet in d_6-DMSO solution. Ring-closure of **7** to give specifically oxirane **4a** was observed for triethylamine. An attempt to prepare β-cyanohydrin **10a** from mesylate **7** using potassium cyanide in DMSO also rapidly gave **4a**. We cannot rigorously exclude the possibility of a transmesylation reaction affording the tertiary mesylate as an intermediate, but the rapid, highly stereoselective ring-closure to give oxirane **4a** is much more consistent with direct closure of **7** as a primary mesylate. Thus, the configuration of **6a** could be assigned with reasonable certainty as the same relative to **4a**.

Nitrile oxide cycloaddition reactions have been examined for dihydroisoxazoles **2a** and **2b** (Scheme II). Diastereomer excesses ranged from 10 to 46%: thus, only poor-to-moderate selectivity was observed, a typical outcome in nitrile oxide cycloadditions (Table I).[1a,13]

Reaction of excess bromo(phenylsulfonyl)formaldoxime and potassium carbonate at 50 °C with dihydroisoxazole **2a** gave a mixture of diastereomeric phenylsulfonylcarbonitrile oxide cycloadducts **8a** and **9a** (65:35 500-MHz ^{1}H NMR diastereomer ratio; 88% yield, based on **2a**). Separation of **8a** and **9a** by repetitive preparative TLC was accomplished, and the isolated quantities qualitatively agreed with the NMR results of the crude product. A similar run using excess alkene and silver nitrate to generate the nitrile oxide gave experimentally indistinguishable stereochemical results (65:35 diastereomer ratio, 72% yield based on bromo oxime). Isomer assignments are based on reductive cleavage of **8a** to the β-cyanohydrin **10a**, the same β-cyanohydrin obtained in 60% yield by nucleophilic ring-opening of oxirane **4a** with potassium cyanide. That β-cyanohydrin **10a** was distinguishable from its diastereomer **10b** was determined by preparation of **10b** from oxirane **5a**.

Reaction of dibromoformaldoxime and potassium carbonate in the presence of dihydroisoxazole **2a** gave a separable mixture of the diastereomeric bromonitrile oxide adducts **8b** and **9b** in 51% and 19% yield, respectively (73:27 **8b**/**9b** ratio). Isomer assignments were made by comparison to NMR spectra of the corresponding (phenylsulfonyl)carbonitrile oxide adducts **8a** and **9a**. The major isomers **8a** and **8b** had similar chemical shift patterns compared to the minor isomers **9a** and **9b**. For example, the 4-proton of the original ring resonated upfield in both major isomers: **8a** δ 3.89 and **9a** δ 4.37 vs **8b** δ 3.94 and **9b** δ 4.50. Again, it seems that attack occurred preferentially anti to the 4-phenyl group on the s-trans conformer.

Cycloaddition of excess bromonitrile oxide to dihydroisoxazole **2b** gave the diastereomeric adducts **9c** and **8c** in 53% and 28% yield, respectively (65:35 ratio, confirmed by ^{1}H NMR of the crude product: Scheme II). The configurational assignments are based on an X-ray study for **9c**. Here, the preferred attack was either anti to the 4-phenyl group on the s-cis conformer or syn to the 4-phenyl group on the s-trans conformer.

Cycloaddition of phenylsulfonylcarbonitrile oxide to dihydroisoxazole **2b** was stereochemically similar. Generation of the nitrile oxide from bromo(phenylsulfonyl)-formaldoxime in the presence of excess **2b** gave a mixture of the diastereomeric cycloadducts **9d** and **8d** (55:45 500-MHz NMR ratio, 78% yield based on nitrile oxide precursor). The products could be separated by repetitive TLC and were isolated in 34% and 29% yield, respectively. Structure assignment was based on the chemical shift patterns compared to those of **9c** and **8c**. The 5-H proton of the newly formed ring resonated upfield in both major isomers: **9c** δ 4.98 and **8c** δ 5.60 vs **9d** δ 5.25 and **8d** δ 5.67. Conversion of bis(dihydroisoxazole) **8d** to β-cyanohydrin

(3) (a) Wade, P. A.; Bereznak, J. F. *J. Org. Chem.* **1987**, *52*, 2973. (b) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366. (c) Wade, P. A.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319.

(4) Curran, D. P.; Scanga, S.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474.

(5) (a) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1987**, *52*, 3541. (b) Jäger, V.; Grund, H.; Schwab, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 78. (c) Curran, D. P.; Kim, B. H. *Synthesis* **1986**, 312.

(6) At the 3-position: (a) Wade, P. A.; Price, D. T.; Carroll, P. J.; Dailey, W. P. *J. Am. Chem. Soc.*, following paper in this issue. (b) Wade, P. A.; Price, D. T.; McCauley, J. P.; Carroll, P. J. *J. Org. Chem.* **1985**, *50*, 2805. (c) Curran, D. P.; Chao, J.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3036.

(7) At the 5-position: (a) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Chem. Soc., Chem. Commun.* **1985**, 403. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217. (d) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569.

(8) Hirsch, J. A. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Interscience: New York, 1967; Vol 1, p 199.

(9) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1775. We thank Dr. Davis for providing us with this compound.

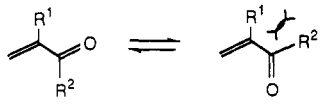
(10) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(11) Acid-catalyzed oxirane opening adjacent to aryl groups is stereochemically unreliable. See, for example: Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, *30*, 4091.

(12) Berti, G.; Macchia, B.; Machia, F. *Tetrahedron Lett.* **1965**, 3421.

(13) Wade, P. A.; Singh, S. M.; Pillay, M. K. *Tetrahedron* **1984**, *40*, 601.

Table II. Selected s-Trans/s-Cis Preferences for Acrylates and Enones from the Literature[14-16]



R^1	R^2	s-trans/s-cis	ΔE, kcal/mol
H	OH	26:74	−0.6
H	OMe	23:77	−0.7
Me	OH	63:27	0.3
H	H	96:4	1.9
Me	H	>98:2	3.0
i-Pr	*n*-Hex	>95:5	
Ph	*n*-Hex	>95:5	
n-Hex	*i*-Pr	>95:5	

10c allowed correlation of its configuration to oxirane **4b**, also converted to **10c**; bis(dihydroisoxazole) **9d** was converted to β-cyanohydrin **11**.

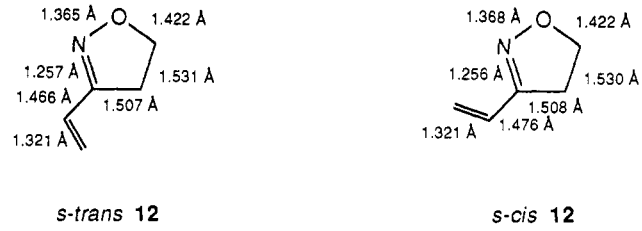
Discussion

Preferential attack of the oxidants on the s-trans conformation of alkenyl dihydroisoxazoles **2a** and **2b** anti to the 4-phenyl group provides a rationale for both the epoxidation results and hydroxylation results. The results of the nitrile oxide cycloadditions were less clear-cut. Presumably attack occurred preferentially on the s-trans conformation of **2a** anti to the 4-phenyl group. Preferential attack on **2b**, however, occurred on the opposite face with low selectivity.

Nitrile oxide cycloadditions, epoxidations, and hydroxylations all have early transition states, although the degree of earliness may differ. Therefore, the ground-state heterodiene conformational preferences should be important in deciding face selectivity. The differences in selectivity would then be attributable to different transition state stereochemical requirements.

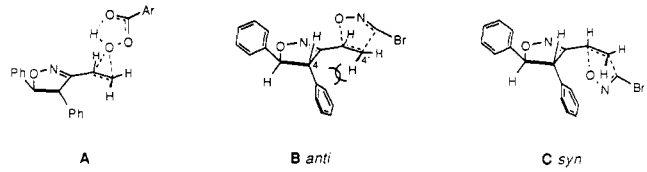
No direct information is available for the conformational preferences of **2a** and **2b**. However, conformational preferences for acrolein,[14] acrylate esters,[15] and eneones[16] have been studied and are likely to be similar: the carbonyl group and imino group are both polar with a lone pair of electrons positioned to interact similarly with the rest of the heterodiene system. For acrolein, the s-trans conformer is preferred by 1.7–2.1 kcal/mol. For acrylic acid and methyl acrylate, however, ab initio calculations indicate that the s-cis conformer is preferred by 0.6 and 0.7 kcal/mol, respectively. For methacrylic acid, ab initio calculations indicate that the s-trans conformer is slightly preferred (by 0.3 kcal/mol). Apparently, substitution at the internal carbon sites (R^1–R^2, Table II) disfavors the s-cis conformer. Enones show a similar trend. Consequently, the s-trans conformer should be more prevalent for **2a** than **2b**, although the absolute preference for **2b** is unclear.

We initially attempted to model conformational preferences of **2a** and **2b** by molecular mechanics (Gajewski's MMX program[17] using Allinger's parameters). However, this approach was terminated after calculations on methyl acrylate and methyl methacrylate indicated a common preference for the s-trans conformer (by 0.85 and 0.86 kcal/mol, respectively, at strong variance with the above ab initio calculations).[17b] Literature reports for acrolein, glyoxal, and 1,3-butadiene suggest that the MNDO approximation method is also unsuitable for accurate modelling of **2a** and **2b**.[18]



s-trans **12** *s-cis* **12**

Figure 1. Calculated 6-31G* bond lengths for the s-trans and s-cis conformers of **12**.



A B *anti* C *syn*

Figure 2. Transition states for epoxidation and nitrile oxide cycloaddition to **2b**.

For these reasons, the structures and energies for the s-trans and s-cis conformers of 3-ethenyl-4,5-dihydroisoxazole (**12**) were determined using ab initio theory.[19] At the HF/3-21G level, both conformers were calculated to be nonplanar, but the differences in energies between planar and nonplanar forms were miniscule (0.01 kcal/mol). Therefore, in order to take advantage of molecular symmetry and do more sophisticated calculations, both conformers were constrained to C_s symmetry and their geometries were optimized at the HF/6-31G* level of theory (bond lengths, Figure 1). The total energies were calculated to be −322.637 47 au for the s-trans conformer and −322.633 01 au for the s-cis conformer. The difference is 2.8 kcal/mol in favor of the s-trans conformer, similar but somewhat larger than the experimental values determined for acrolein (1.9–2.1 kcal/mol) for which ab initio calculations predicted a difference of 1.7 kcal/mol.[14]

Phenyl groups on the dihydroisoxazole ring, particularly at C-4, would modify the conformational energies determined for **12**. Although of somewhat dubious value for this system, MMX calculations indicate a slight increase in preference for the s-trans conformer (0.31 kcal/mol) of **2b** compared to **12**. Thus, it seems likely that the s-trans conformer is heavily preferred (>90:10 ratio) for both **2b**

(14) (a) Experimentally determined values: Carreira, L. A. *J. Phys. Chem.* **1976**, *80*, 1149 [Raman]. Blom, C. E.; Müller, R. P.; Gunthard, Hs. H. *Chem. Phys. Lett.* **1980**, *73*, 483 [ultraviolet]. DeGroot, M. S.; Lamb, J. *Proc. R. Soc. London, Ser. A* **1957**, *242*, 36. (b) Calculationally determined values: Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(15) (a) Loncharich, R. J.; Schwatz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. (b) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.

(16) (a) Oelichmann, H.-J.; Bougeard, D.; Schrader, B. *Angew. Chem. Suppl.* **1982**, 1404. (b) Durig, J. R.; Qui, J.; Dehoff, B.; Little, T. S. *Spectrochim. Acta* **1986**, *42A*, 89.

(17) (a) MMX program: Gajewski, J.; Gilbert, K. (Indiana University). Input data for the MMX program was generated using Model KS 2.94: Steliou, K. (University of Montreal). (b) Subsequent molecular mechanics calculations (Macintosh II version of PCMODEL; Gilbert, K. E., Gajewski, J. J.; Serenea Software, Bloomington, IN) have proven much more accurate. Thus, for methyl acrylate the s-cis conformer was calculated to be 0.35 kcal/mol more stable than the s-trans conformer and for methyl methacrylate the s-trans conformer was calculated to be 0.05 kcal/mol more stable than the s-cis conformer.

(18) Apparently, the σ–π^* and π–π^* bond–antibond matrix elements are seriously overestimated with the result that gauche conformations are artificially stabilized; the s-cis conformers are also calculationally more stable than appears to be warranted: Tyrrel, J.; Weinstock, R. B.; Weinhold, F. *Int. J. Quantum Chem.* **1981**, *19*, 781.

(19) The calculations employed GAUSSIAN 88: Frisch, M. J.; Head-Goron, M.; Schlegel, H. B.; Ragavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA.

and **2a** at room temperature.

The stereochemical results for the epoxidation and hydroxylation reactions appear to be in line with the ground-state heterodiene conformational preferences. Preferential attack via transition state A is observed for both **2a** and **2b**, although it is more heavily favored for **2a** (Figure 2).

Epoxidations with *m*-CPBA and *N*-phenylsulfonyl-3-(4-nitrophenyl)oxaziridine have been postulated to proceed with a similar planar transition state.[20] The fact that attack on **2a** is equally stereoselective for *N*-phenylsulfonyl-3-(4-nitrophenyl)oxaziridine, a sterically demanding reagent, and for *m*-CPBA, a nondemanding reagent, suggests a common stereodiscrimination. The relative percentages of attack on the s-trans and s-cis conformers should be very similar for the two reactions. Since the oxaziridine should be more sensitive than *m*-CPBA to steric interaction with the 4-phenyl group, this suggests that both reagents strongly avoid the 4-phenyl group; i.e., anti attack is heavily favored. The minor products, then, presumably arise from attack on the s-cis conformer anti to the 4-phenyl group and are formed to the same extent. While this analysis is suggestive, it certainly does not exclude the possibility of attack syn to the 4-phenyl group as a second route to minor products, particularly with other reagents.

The preferred transition state for nitrile oxide cycloaddition to **2a** also appears to involve anti attack on the s-trans conformation, although the preference is less than observed for the epoxidation and hydroxylation reactions. This is consistent with the low steric demand of a linear species such as a nitrile oxide; some syn attack would be likely. Cycloaddition to **2b** occurs preferentially from the opposite face. Since **2b** apparently prefers a ground-state s-trans conformer, either the transition state preference is reversed or the attack is syn to the 4-phenyl group of the s-trans conformer. It is felt that the latter may be the correct explanation.

Why would nitrile oxides prefer to attack syn to the 4-phenyl group of dihydroisoxazole **2b**? The C–O bond is thought to be less developed than the C–C bond.[21] Perhaps phenyl repulsion of the C_4, methylene of the incipient dihydroisoxazole ring is more severe than repulsion with the developing C–O bond (cf. transition states B and C); this would disfavor anti attack through transition state B. In agreement with this hypothesis, MMX calculations suggest a nonbonded aryl C, 4'H distance of 2.56 Å in transition state B.[22]

The syn cycloaddition of diazomethane to cyclobutene-3,4-diol diacetate has been reported by Gandolfi et al.[23] They have suggested that syn attack is sterically favorable based on ab initio calculations at the STO-3G level. These calculations suggest a deformation of the alkene hydrogen atoms making the syn face more open than the anti face. Such considerations might also apply to nitrile oxide cycloaddition on **2b**.

In summary, epoxidation and hydroxylation reactions of dihydroisoxazoles **2a** and **2b** occur preferentially anti to the 4-phenyl group on the s-trans conformer, the more stable ground-state conformer. Nitrile oxides cycloadd similarly to **2a** but with reduced diastereoselectivity. Nitrile oxide cycloaddition to **2b** is anomalous, favoring the opposite face to epoxidation.

Experimental Section

General. Thin-layer chromatography (TLC) was carried out on 0.25-mm analytical, 0.25-mm preparative, and 1.00-mm preparative silica gel GF plates (Analtech). ^1H NMR spectra were taken in $CDCl_3$ (TMS internal standard) on Bruker WP-250 and JEOL FX-90Q instruments, unless otherwise stated. Infrared (IR) spectra were recorded on a Perkin-Elmer 467 spectrometer. Mass spectra (MS) were recorded on a Finnegan 4023 GC–MS instrument. Procedures for the preparation of sulfonyl dihydroisoxazole **3**[24] and dihydroisoxazoles **1a**,**b**[6a] have been described elsewhere. Reactions were worked up, unless otherwise stated, by washing the organic layer with water, drying the organic layer over anhydrous Na_2SO_4, and concentrating at reduced pressure. THF was distilled from sodium–benzophenone ketyl under nitrogen. Flash chromatography was conducted using Kieselgel 60, 230–400 mesh (Merck). Commercial *m*-CPBA (Aldrich, 85% technical grade) was washed with pH 7.5 phosphate buffer to remove residual 3-chlorobenzoic acid.

Preparation of Alkene 2a. A solution of alcohol **1a** (5.02 g, 14.6 mmol), benzene (60 mL), and *p*-TsOH·H_2O (4.06 g, 22.6 mmol) was refluxed for 2 h. The solution was cooled to room temperature and washed with 5% NaOH (two 50-mL portions) followed by the standard workup. Recrystallization of the residue from benzene–hexanes gave large, cubic crystals of **2a** (3.72 g). Preparative TLC (CH_2Cl_2) of the mother liquor gave an additional 0.2416 g of **2a** (83% total yield): mp 87–88 °C; NMR δ 7.29 (m, 15 H), 5.52 (d, 1 H, J = 5.7 Hz), 5.45 (s, 1 H), 5.33 (s, 1 H), 4.55 (d, 1 H, J = 5.7 Hz); MS m/e 325 (M^+).

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.94; H, 5.84. Found: C, 85.33; H, 5.74.

Preparation of Alkene 2b. A solution of tetravinyltin (0.9139 g, 4 mmol) in anhydrous ether (10 mL) under N_2 was treated with PhLi (7.2 mL of a 1.8M solution in cyclohexane–Et_2O, 13 mmol) added all at once. The mixture was stirred at room temperature for 30 min and was then filtered through a fritted glass funnel under N_2 to provide a clear yellow solution of vinyllithium. This solution was added dropwise over 5 min to a cold (−78 °C) solution of sulfonyldihydroisoxazole **3** (0.9862 g, 2.7 mmol) in Et_2O–toluene (90:10, 100 mL) (reaction temperature <−70 °C). The reaction mixture was stirred at <−70 °C for 25 min, and then wet THF (5 mL) was carefully added to the cold solution followed by 5% HCl (2 mL). Further workup gave the crude product which was subjected to flash chromatography (95:5 hexanes–EtOAc). Subsequent to the elution of the less polar tin derivatives, alkene **2b** (0.6089 g, 89% yield) was obtained as an oil contaminated with *trans*-4,5-dihydro-3,4,5-triphenylisoxazole (3 mol %, by NMR). Removal of the contaminant could be effected by preparative TLC (CH_2Cl_2) to give 0.3721 g (55% yield) of pure **2b** as the lower two-thirds of the main chromatography band. Recrystallization from CCl_4–hexanes gave fine white needles: mp 68–69 °C; NMR δ 7.24–7.41 (m, 10 H), 6.63 (dd, 1 H, J = 11.0 Hz, 17.6 Hz), 5.13–5.47 (m, 3 H), 4.44 (d, 1 H, J = 5.7 Hz); MS m/e 249 (M^+).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.93; H, 6.02. Found: C, 81.87; H, 5.89.

Alkene **2b** could also be prepared from **3** using commercial vinymagnesium bromide, but only in 19% yield. Dehydration of alcohol 1-[(4,5-dihydro-4,5-diphenyl)-3-isoxazolyl]ethanol gave **2b**, but only in 12% yield.

Epoxidation of Alkene 2a Using *m*-CPBA. A mixture of **2a** (0.5042 g, 1.6 mmol), *m*-CPBA (0.8486 g, 4.7 mmol), $NaHCO_3$ (0.8012 g, 9.5 mmol), $CHCl_3$ (40 mL), and water (40 mL) was heated at 75–80 °C for 90 min. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and treated

(20) Bach, R. D.; Wolber, G. V. *J. Am. Chem. Soc.* **1984**, *106*, 1410 and references cited therein.

(21) For leading references on the nitrile oxide cycloaddition transition state, see: (a) Komornicki, A.; Goddard, J.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1980**, *102*, 1763. (b) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. (c) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (d) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(22) The syn s-trans transition state was calculated to have an 0.34-kcal/mol energy advantage over the anti transition state: this energy value is, however, questionable due to the noted difficulties in treating heterodiene systems.

(23) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Poppi, A. L.; Rastelli, A. *Tetrahedron Lett.* **1985**, *26*, 4653.

(24) Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595.

with saturated aqueous Na_2SO_3. Further workup gave 0.6318 g of a mixture of **4a** and **5a** (90:10 ratio, NMR). Preparative TLC (60:40 CH_2Cl_2–CCl_4) provided **4a** (0.3660 g higher R_f isomer, 69% yield). A second preparative TLC (90:10, hexanes–EtOAc) provided the analytical sample as an oil: IR ($CHCl_3$) 1235 and 900 cm^{-1} (oxirane C–O stretch); NMR δ 7.19–7.36 (m, 15 H), 5.53 (d, 1 H, J = 6.2 Hz), 4.23 (d, 1 H, J = 6.2 Hz), 3.24 (d, 1 H, J = 5.6 Hz), 2.77 (d, 1 H, J = 5.6 Hz); MS m/e 341 (M^+); Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.94; H, 5.57. Found: C, 80.60; H, 5.62.

Also isolated from the first preparative TLC was **5a** (0.0529 g lower R_f isomer, 10% yield) as an oil: IR ($CHCl_3$) 1215 and 900 cm^{-1} (oxirane C–O stretch); NMR δ 7.20–7.33 (m, 15 H), 5.55 (d, 1 H, J = 5.9 Hz), 4.23 (d, 1 H, J = 5.9 Hz), 3.27 (d, 1 H, J = 5.6 Hz), 2.97 (d, 1 H, J = 5.6 Hz); MS m/e 341 (M^+).

Epoxidation of Alkene 2a Using *N*-Phenylsulfonyl-3-(4-nitrophenyl)oxaziridine. A solution of **2a** (0.3258 g, 1.0 mmol) and the oxidant (0.3666 g, 1.2 mmol) in $CHCl_3$ (15 mL) was heated at 58–60 °C under N_2 for 22 h. After cooling to room temperature, hexanes (2 mL) were added and the mixture was refrigerated. The crystals of imine byproduct were removed by filtration and the filtrate was concentrated to give 0.5340 g of crude product which consisted of oxiranes (ca. 50%), *N*-phenylsulfonyl-3-(4-nitrophenyl)oxaziridine, imine byproduct, and unreacted **2a** (ca 50%). The diastereomer ratio of **4a** and **5a** determined by NMR was similar to that seen in the *m*-CPBA reaction. The crude product was dissolved in CH_2Cl_2 (10 mL) and was treated with solid $NH_4^+I^-$ followed by saturated aqueous Na_2SO_3 (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated to 5 mL; this was refrigerated overnight and the imine precipitate was then filtered. The filtrate was concentrated at reduced pressure and the residue purified by repetitive preparative TLC (90:1 hexanes–ethyl acetate followed by 80:20 CH_2Cl_2–CCl_4). Alkene **2a** (0.1173 g, 36%), oxirane **4a** (0.1188 g, 35%), and oxirane **5a** (0.0174 g, 5%) were obtained (87:13, **4a**/**5a** ratio).

Epoxidation of Alkene 2b Using *m*-CPBA. A solution of **2b** (0.3426 g, 1.4 mmol) and *m*-CPBA (0.6390 g, 3.6 mmol) in $CHCl_3$ (30 mL) was heated at 75–80 °C under N_2 for 3 h. The reaction solution was cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and treated with saturated aqueous Na_2SO_3. Further workup gave 0.4782 g of a mixture of **4b** and **5b** (83:17 ratio, NMR). This mixture was subjected to preparative TLC (90:10 hexanes–EtOAc) to provide pure **4b** (0.1566 g, 43% yield, higher R_f isomer) as an oil: IR (neat) 910 cm^{-1} (oxirane C–O stretch); NMR δ 7.16–7.42 (m, 10 H), 5.46 (d, 1 H, J = 5.3 Hz), 4.21 (d, 1 H, J = 5.3 Hz), 3.84 (dd, 1 H, J = 2.8, 4.2 Hz), 2.74 (t, 1 H, $J \approx$ 4.7 Hz), 2.24 (dd, 1 H, J = 2.8, 4.9 Hz); MS m/e 265 (M^+); Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.69. Found: C, 76.55, H, 5.76.

Also obtained from preparative TLC was **5b** (0.0324 g, 9% yield, lower R_f isomer) as an oil: IR (neat) 905 cm^{-1} (oxirane C–O stretch); NMR δ 7.15–7.26 (m, 10 H), 5.3 (d, 1 H, J = 6.6 Hz), 4.10 (d, 1 H, J = 6.6 Hz), 3.61 (t, 1 H, J = 3.4 Hz), 2.85 (d, 2 H, J = 3.4 Hz); MS m/e 265 (M^+).

Cis-Hydroxylation of Alkene 2a. A cold (0–5 °C) solution of **2a** (75 mg, 0.23 mmol) and trimethylamine *N*-oxide dihydrate (51.4 mg, 0.45 mmol) in water–THF (9:1, 1.2 mL) was treated with OsO_4 (0.3 mL of a 2.5% *t*-BuOH solution, 0.03 mmol of oxidant), and the reaction was stirred at ambient temperature for 5 h. After $NaHSO_3$ (0.09 g) was added, the reaction mixture was stirred for 30 min. Workup gave 95 mg of crude product containing diols **6a** and **6b** (90:10 ratio) and a trace of (4,5-dihydro-4,5-diphenyl-3-isoxazolyl)phenylmethanone. Preparative TLC (Et_2O–CCl_4 67:33) gave 55.1 mg (67% yield) of a mixture of **6a** and **6b**. A second preparative TLC (99:1 CH_2Cl_2–MeOH) gave 40.8 mg (50% yield) of **6a** as the top two-thirds of the main band. Recrystallization from CCl_4 gave **6a** as a crystalline solid: mp 118–119 °C; NMR δ 7–7.3 (m, 15 H), 5.38 (d, 1 H, J = 4.4 Hz), 4.31 [dd, 1 H, J = 11.5, 3.7 Hz (collapses to d, J = 11.5 Hz when OH exchange rate increases)], 3.87 (d, 1 H, J = 4.4 Hz), 3.41 [br t, 1 H, $J \approx$ 11 Hz (collapses to d, J = 11.5 Hz when OH exchange rate increases)], 2.84 (s, 1 H, O*H*), 2.6–2.7 (br m, 1 H, O*H*); MS m/e 327 ($M^+ - CH_2OH$); Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.88; H, 5.85. Found: C, 76.30; H, 6.19.

Also isolated as the bottom one-third of the TLC band was 2.3 mg (3% yield) of diol **6b** which was recrystallized from CCl_4: mp 178–182 °C dec; NMR δ 6.9–7.4 (m, 15 H), 5.52 (d, 1 H, J = 6.4 Hz), 4.41 (d, 1 H, J = 6.4 Hz), 4.34 (d, 1 H, J = 11.7 Hz), 3.53 (d, 1 H, J = 11.7 Hz), 1.7 (br s, 2 H, O*H* [the 1°-OH was coupled to the δ 3.53 and 4.34 signals in some of the spectra]).

Preparation of Mesylate 7. Mesyl chloride (17.6 μL, 0.23 mmol) was added to a solution of diol **6a** (40.8 mg, 0.11 mmol) and pyridine (18.3 μL) in CH_2Cl_2 (3.7 mL) under argon, and the resulting solution was stirred for 30 min. Workup was according to the general procedure except that brine rather than water was employed. The crude product was subjected to preparative TLC (CH_2Cl_2–MeOH 99:1) to give 11.4 mg of recovered **6a** and 25.8 mg (72% conversion) of **7**. The analytical sample of **7** was recrystallized from CH_2Cl_2–hexanes: mp 101–103 °C; IR (KBr) 3300 (OH), 1350 and 1175 cm^{-1} (SO_2); NMR δ 7.1–7.5 (m, 15 H), 5.46 (d, 1 H, J = 4.4 Hz), 4.88 (d, 1 H, J = 10.4 Hz), 4.38 (d, 1 H, J = 10.4 Hz), 4.01 (d, 1 H, J = 4.4 Hz), 3.03 (s, 3 H), 2.52 (s, 1 H, O*H*); MS m/e 437 (M^+), 328 ($M^+ - CH_2OMs$).

Conversion of 7 to Oxirane 4a. Triethylamine (0.42 mL) was added to a solution of mesylate **7** (3.3 mg, 7.5μmol) in CH_2Cl_2 (0.6 mL) and the solution stirred for 18 h. Volatiles were removed at reduced pressure and the crude product purified by preparative TLC (CH_2Cl_2) to give 2.3 mg (89% yield) of pure oxirane **4a**.

A solution of **7** (9 mg, 21 μmol) and NaCN (1.9 mg, 38 μmol) in DMSO (1 mL) was stirred for 1 h and added to ice water (20 mL). The organic products were extracted with CH_2Cl_2. Further workup followed by preparative TLC (CH_2Cl_2–MeOH, 99:1) gave 1.3 mg (19% yield) of pure oxirane **4a**.

Preparation of Dibromoformaldoxime. A cold (0–5 °C) solution of oximinoacetic acid[25] (6 g, 67 mmol) in water (200 mL) was treated with Br_2 (5 mL, 67 mmol) added in 1-mL portions every 10–15 min. Upon addition of the final 1-mL portion of Br_2, the resulting solution maintained a faint amber coloration. The solution was then extracted with Et_2O (three 100-mL portions) and the combined organic layers were washed with saturated $NaHSO_3$ followed by the standard workup to give a white solid. This solid was recrystallized from Et_2O–hexanes to give fine, cream-colored crystals of the oxime (6.5 g, 47% yield): mp 70–71 °C (lit. mp[26] 65–66 °C).

Cycloaddition of Bromonitrile Oxide to Excess Alkene 2a. A solution of bromoformaldoxime (0.35 g, 1.8 mmol) in THF (4 mL) was added dropwise over 1 h (syringe pump) to a warm (50–55 °C) stirred mixture of **2a** (0.1091 g, 0.3 mmol), pulverized K_2CO_3 (0.4354 g, 3.2 mmol), and THF (5 mL). The mixture was stirred for 3 h at 50–55 °C, cooled to room temperature, diluted with CH_2Cl_2 (30 mL), and filtered. The K_2CO_3 residue was washed with CH_2Cl_2 (three 10-mL portions) and the combined organic layers were further worked up to give crude product. Preparative TLC (70:30, $CHCl_3$–hexanes) gave **9b** (0.0271 g, 19% yield) as the higher R_f stereoisomer and **8b** (0.0770 g, 51% yield) as the lower R_f isomer (73:27 isolated ratio).

Major isomer **8b** was crystallized from benzene–hexanes to yield fine white needles: mp 118–119 °C; NMR δ 7.09–7.34 (m, 15 H), 5.52 (d, 1 H, J = 5.9 Hz), 4.37 (d, 1 H, J = 17.3 Hz), 3.94 (d, 1 H, J = 5.9 Hz), 3.30 (d, 1 H, J = 17.3 Hz); MS m/e 448 (M^+ ^{81}Br), 446 (M^+ ^{79}Br); Anal. Calcd for $C_{24}H_{19}N_2O_2Br$: C, 64.43; H, 4.25. Found: C, 64.36; H, 4.28.

The minor isomer **9b** was an oil: NMR δ 6.87–7.35 (m, 15 h), 5.55 (d, 1 H, J = 6.5 Hz), 4.50 (d, J = 6.5 Hz) on 4.42 (d, J = 17.3 Hz), 2 H total, 3.30 (d, 1 H, J = 17.3 Hz); MS m/e 448 (M^+ ^{81}Br) and 446 (M^+ ^{79}Br).

Cycloaddition of Bromonitrile Oxide to Excess Alkene 2b. To a stirred, warmed (50–55 °C) mixture of alkene **2b** (0.1140 g, 0.46 mmol), K_2CO_3 (0.5895 g, 4.3 mmol), and THF (5 mL) under N_2 was added dropwise over 1 h (syringe pump) a solution of dibromoformaldoxime (0.4625 g, 2.3 mmol) in THF (5 mL). The reaction mixture was stirred for 30 min at 50–55 °C, and H_2O (5 mL) was then introduced over 30 min by syringe pump. The resulting mixture was stirred for 30 min, cooled to room temperature, and worked up. Preparative TLC (80:20 CH_2Cl_2–CCl_4) of the crude product afforded **9c** (0.0899 g, 53% yield) as the higher R_f stereoisomer and **8c** (0.0475 g, 28% yield) as the lower R_f isomer (65:35 ratio).

(25) Jahngen, G. E., Jr.; Rossamondo, E. F. *Synth. Commun.* **1982**, *12*, 601.

(26) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *Tetrahedron Lett.* **1984**, *25*, 487.

The major isomer **9c** was recrystallized from benzene–hexanes to give long white needles: mp 91–92 °C; NMR δ 7.10–7.36 (m, 10 H), 5.51 (d, 1 H, J = 6.8 Hz), 4.98 (dd, 1 H, J = 6.5, 10.7 Hz), 4.42 (d, 1 H, J = 6.8 Hz), 3.73 (dd, 1 H, J = 6.5, 17.3), 3.21 (dd, 1 H, J = 10.7, 17.3 Hz); MS m/e 372 (M^+ ^{81}Br), 370 (M^+ ^{79}Br); Anal. Calcd for $C_{18}H_{15}N_2O_2Br$: C, 58.22; H. 4.07. Found: C, 58.14; H, 4.14.

The minor isomer **8c** gave fine white needles from hexanes: mp 115–116 °C; NMR δ 7.23–7.46 (m, 10 H), 5.60 (m, 2 H), 4.40 (d, 1 H, J = 5.2 Hz), 3.21 (dd, 1 H, J = 11.6, 17.6 Hz), 2.56 (dd, 1 H, J = 6.7, 17.6 Hz); MS m/e 372 (M^+ ^{81}Br), 370 (M^+ ^{79}Br).

Cycloaddition of Phenylsulfonylcarbonitrile Oxide to Alkene 2a (Excess Nitrile Oxide Precursor). To a warm (50–55 °C) mixture of alkene **2a** (0.1064 g, 0.33 mmol), solid K_2CO_3 (0.4554 g, 3.3 mmol), and THF (3 mL) was added dropwise over 1 h (syringe pump) a solution of $PhSO_2C(Br)NOH$ (0.3045 g, 1.2 mmol) in THF (3 mL). The resulting mixture was stirred an additional 3 h at 50–55 °C and was worked up. Preparative TLC (CH_2Cl_2) of the crude product provided 3,4-bis(phenylsulfonyl)furazan N-oxide (0.0764 g) as the more mobile band and an impure (NMR) mixture of **8a** and **9a** (0.1586 g) as the less mobile band. A second preparative TLC (EtOAc–hexanes 20:80) gave pure **9a** (5 mg, 3% yield) as the upper third (higher R_f) of the chromatography band, a mixture of **8a** and **9a** (56 mg, 33% yield, ca. 40:60 ratio by ^1H NMR) as the middle third of the band, and pure **8a** (86 mg, 52% yield) as the low third of the band. The total yield of **8a** and **9a** was 147 mg (88% yield, based on **2a** as the limiting reagent).

Compound **9a** gave white needles on recrystallization from benzene–hexanes: mp 124–125 °C; IR ($CHCl_3$) 1340 and 1170 cm^{-1} (SO_2); NMR δ 7.2–8.1 (m, 20 H), 5.51 (d, 1 H, J = 6.4 Hz), 4.51 (d, $J \approx$ 17.4 Hz), overlapping 4.37 (d, $J \approx$ 6.4 Hz), 2 H total, 3.42 (d, 1 H, J = 17.4 Hz); MS m/e 508 (M^+), 367 ($M^+ - PhSO_2$).

Compound **8a** likewise gave a white solid on recrystallization from benzene–hexanes: mp 108–109 °C; IR (film) 1340 and 1170 cm^{-1} (SO_2); NMR δ 7.0–8.0 (m, 20 H), 5.49 (d, 1 H, J = 5.9 Hz), 4.53 (d, 1 H, J = 17.4 Hz), 3.89 (d, 1 H, J = 5.9 Hz), 3.46 (d, 1 H, J = 17.4 Hz); MS m/e 508 (M^+), 367 ($M^+ - PhSO_2$). Anal. Calcd for $C_{30}H_{24}N_2O_4S$: C, 70.85; H, 4.76. Found: C, 70.81; H, 4.83.

Cycloaddition of Phenylsulfonylcarbonitrile Oxide to Excess Alkene 2a. The preceding procedure was repeated using **2a** (0.2618 g, 0.81 mmol), K_2CO_3 (0.8050 g, 5.83 mmol), THF (8 mL), and a solution of $PhSO_2C(Br)NOH$ (0.1542 g, 0.58 mmol) in THF (6 mL). Preparative TLC (EtOAc–hexanes 20:80) afforded, in order of decreasing R_f: 0.1114 g (43% recovery) of **2a**, pure **9a** (0.0452 g, 15% yield) as the upper third of a chromatography band, a mixture of **8a** and **9a** (0.0698 g, 23% yield, 65:35 ratio by ^1H NMR) as the middle third of the band, and pure **8a** (0.0654 g, 22% yield) as the lower third of the bis(dihydroisoxazole) band. The yield of **8a** and **9a** was 0.1804 g (60%, based on $PhSO_2C(Br)NOH$ as the limiting reagent). Using solid $AgNO_3$ (0.2295 g, 1.35 mmol) instead of K_2CO_3 afforded **8a** and **9a** in 72% yield and a 68:32 ratio (500-MHz[27] ^1H NMR).

Cycloaddition of Phenylsulfonylcarbonitrile Oxide to Alkene 2b. A warm (50–55 °C) mixture of alkene **2b** (0.1769 g, 0.71 mmol), $AgNO_3$ (0.1245 g, 0.74 mmol), and THF under N_2 was treated dropwise over 1 h (syringe pump) with a solution of $PhSO_2C(Br)NOH$ (0.1401 g, 0.53 mmol) in THF (10 mL). The mixture was stirred an additional 2 h at 50–55 °C, cooled, and treated with CH_2Cl_2 (30 mL). The mixture was filtered, and the filtrate was worked up to give crude product. Preparative TLC (CH_2Cl_2–CCl_4 80:20) afforded 0.1784 g (78% yield, based on $PhSO_2C(Br)NOH$) of a 55:45 mixture of **9d** and **8d** (500-MHz[27] ^1H NMR). A second preparative TLC (CH_2Cl_2–CCl_4 80:20) provided pure **9d** (0.0614 g) as the top third (higher R_f) of the chromatography band, 0.0553 g of a mixture as the middle third, and pure **8d** (0.0523 g) as the bottom third. Bis(dihydroisoxazole) **8d** was recrystallized from absolute ethanol to give an analytical sample: mp 161–162 °C; IR ($CHCl_3$) 1335 and 1170 cm^{-1} (SO_2); NMR δ 7.1–8.0 (m, 15 H), 5.67 (dd, 1 H, J = 11.8, 8.9 Hz) on 5.58 (d, 1 H, J = 5.6 Hz), 4.31 (d, 1 H, J = 5.6 Hz), 3.31 (dd, 1 H, J = 11.8 Hz, 17.6 Hz), 2.91 (dd, 1 H, J = 8.9 Hz, 17.6 Hz); MS m/e 432 (M^+), 291 ($M^+ - PhSO_2$), 141 ($PhSO_2^+$). Anal. Calcd for $C_{24}H_{20}N_2O_4S$: C, 66.67; H, 4.63. Found: C, 66.32; H, 4.79.

Bis(dihydroisoxazole) **9d** was obtained as an oil: IR ($CHCl_3$) 1335 and 1170 cm^{-1} (SO_2); NMR δ 7.1–8.0 (m, 15 H), 5.58 (d, 1 H, J = 6.9 Hz), 5.25 (dd, 1 H, J = 7.1 Hz, 11 Hz), 4.39 (d, 1 H, J = 6.9 Hz), 3.88 (dd, 1 H, J = 7.1 Hz, 17.4 Hz), 3.41 (dd, 1 H, J = 11 Hz, 17.4 Hz); MS m/e 432 (M^+), 291 ($M^+ - PhSO_2$), 141 ($PhSO_2^+$).

The reaction was also run using K_2CO_3 (0.5394 g) instead of $AgNO_3$. A 34% yield of **9d** and a 29% yield of **8d** (54:46 ratio) were obtained.

Conversion of 8a to β-Hydroxy Nitrile 10a. A mixture of **8a** (0.1128 g, 0.22 mmol), THF (12 mL), water (0.38 mL), and freshly prepared 2% Na–Hg^0, (5.5 g, 4.8 mmol of Na^0) was stirred at room temperature for 1 h. More water (0.23 mL) and 2% Na–Hg^0, (2.7 g, 2.3 mmol of Na^0) were added and stirring was continued for an additional 1 h. Methylene chloride (13 mL) and anhydrous Na_2SO_4 were added; the resulting mixture was filtered and was concentrated at reduced pressure. Preparative TLC (CH_3OH–CH_2Cl_2 1:99) of the residue gave 0.0407 g (50% yield) of pure product which was identical (NMR) with **10a** obtained from oxirane **4a**.

Conversion of 8d to β-Hydroxy Nitrile 10c. A solution of **8d** (0.1334 g, 0.31 mmol) in CH_2Cl_2 (60 mL) was treated with 2% Na–Hg^0 (11.64 g, 10.1 mmol Na^0) followed by 20 mL of a pH 7.15 buffer solution (prepared by mixing 59 mL of 2 M NaOH and 100 mL of 2 M KH_2PO_4). The mixture was stirred *very gently* so that the layers remained segregated. A second portion of 2% Na–Hg^0 (11.02 g) was added after 30 min. The aqueous layer remained at pH <8 throughout the reaction. Anhydrous Na_2SO_4 was added and the mixture was filtered. The filtrate was concentrated at reduced pressure and the residue was purified by preparative TLC (CH_3OH–CH_2Cl_2 1:99) to give 0.0654 g (73% yield) of **10c**. Recrystallization from CCl_4 gave white needles: mp 118–9 °C; IR ($CHCl_3$) 3450 (OH) and 2250 cm^{-1} (CN); NMR δ 7.19–7.46 (m, 10 H), 5.58 (d, 1 H, J = 6.5 Hz), 4.70 (t, 1 H, J = 5.9 Hz), 4.36 (d, 1 H, J = 6.5 Hz), 2.29–2.57 (m on br singlet, 3 H total); MS m/e 292 (M^+), 252 ($M^+ - CH_2CN$). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52. Found: C, 73.89; H, 5.40.

Conversion of 9d to β-Hydroxy Nitrile 11. In a manner analogous to the formation of **10c**, reaction of **9d** (0.1244 g, 0.28 mmol) produced **11** (0.0669 g, 80% yield) as an oil: IR ($CHCl_3$) 3410 (OH) and 2260 cm^{-1} (CN); NMR δ 7.19–7.45 (m, 10 H), 5.55 (d, 1 H, J = 6.7 Hz), 4.42–4.53 (m) on 4.49 (d, J = 6.7 Hz, 2 H, total) 2.54–2.89 (m on br s, 3 H total); MS m/e 292 (M^+), 252 ($M^+ - CH_2CN$).

Conversion of Oxirane 4a to Alcohol 1b Using $LiEt_3BH$. To a cold (0–5 °C) solution of **4a** (0.0602 g, 0.18 mmol) in THF (5 mL) under N_2 was added $LiEt_3BH$ (0.36 mL of a 1.0 M THF solution). After 5 min, water (0.1 mL) was added and the reaction was worked up to give crude product. Preparative TLC (CH_2Cl_2) afforded pure **1b** (0.0558 g, 92% yield) which was identical with authentic **1b**[6a] obtained by reaction of (4,5-dihydro-4,5-diphenyl-3-isoxazolyl)phenylmethanone with methylmagnesium bromide.

Conversion of Oxirane 4a to β-Hydroxy Nitrile 10a. A solution of **4a** (0.47 mmol), KCN (1.9 mmol), $MgSO_4$ (1.6 mmol), DMSO (3 mL) under N_2 was heated in an oil bath at 48–52 °C for 48 h. The solution was then cooled to room temperature, CH_2Cl_2 (80 mL) was added, and the reaction worked up to give crude product. Preparative TLC (CH_2Cl_2) afforded **10a** in 60% yield. Crystallization from CCl_4 gave white needles of **10a**: mp 155–156 °C; IR ($CHCl_3$) 3580 (OH) and 2260 cm^{-1} (CN); NMR δ 7.09–7.31 (m, 15 H), 5.45 (d, 1 H, J = 5.5 Hz), 3.86 (d, 1 H, J = 5.5 Hz), 3.31 (d, 1 H, J = 16.7 Hz), 2.98 (d, 1 H, J = 16.7 Hz), 2.05 (s, 1 H); MS m/e 368 (M^+), 328 ($M^+ - CH_2CN$). Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47. Found: C, 78.10; H, 5.45.

The product obtained from this route was identical (NMR) with **10a** produced from the cleavage of bis(dihydroisoxazole) **8a**.

Conversion of Oxirane 5a to β-Hydroxy Nitrile 10b. The procedure used to convert oxirane **4a** to **10a** was repeated on oxirane **5a**. β-Hydroxy nitrile **10b** was obtained in 56% yield. Recrystallization from CCl_4 gave fine white needles: mp 147–149 °C; IR ($CHCl_3$) 3580 (OH) and 2260 cm^{-1} (CN); NMR δ 7.17–7.33 (m, 15 H), 5.53 (d, 1 H, J = 6.9 Hz), 4.34 (d, 1 H, J = 6.9 Hz),

(27) We thank Dr. J. P. McCauley (University of Pennsylvania) for obtaining the spectra.

3.32 (s, 1 H), 3.16 (d, 1 H, J = 16.5 Hz), 2.99 (d, 1 H, J = 16.5 Hz); MS m/e 368 (M^+), 328 ($M^+ - CH_2CN$).

Conversion of Oxirane 4b to β-Hydroxy Nitrile 10c. The procedure used to convert oxirane **4a** to **10a** was repeated on oxirane **4b**. β-Hydroxy nitrile **10c** was obtained in 48% yield. This sample was identical with **10c** derived from cleavage of the minor bis(dihydroisoxazole) **8d**.

Reaction of Oxirane 4a with Aqueous 30% $HClO_4$. A solution of **4a** (46.6 mg, 0.13 mmol) and 30% $HClO_4$ (90 μL) in THF–water (3:1, 6 mL) was stirred at room temperature for 24 h under N_2. The resulting solution was diluted with CH_2Cl_2 (10 mL) and was washed with saturated $NaHCO_3$. Further workup gave crude product containing **6a,b** (85:15 **a/b** ratio by NMR) some (4,5-dihydro-4,5-diphenyl-3-isoxazolyl)phenylmethanone and several other unidentified products. Preparative TLC (99:1 CH_2Cl_2–MeOH) provided 32.5 mg (66% yield) of **6a** and 10.1 mg (21% yield) of a mixed fraction (40:60 ratio) of **6a** and **6b**.

Reaction of Oxirane 5a with Aqueous 30% $HClO_4$. A solution of **5a** (26 mg, 0.076 mmol) and 30% $HClO_4$ (50 μL) in THF–water (3:1, 4 mL) was stirred at room temperature for 21 h under N_2. Workup and preparative TLC as described in the previous reaction gave 15.8 mg (58% yield) of a mixture (80:20 **a/b** ratio by NMR) of **6a,b**.

Supplementary Material Available: ^1H NMR spectra of **5a,b**, **6b**, **7**, **8c**, **9a,b**, **d**, **10b**, and **11**, ORTEP drawing of **9c**, crystal data for **9c**, tables of refined positional and thermal parameters for **9c**, and tables of bond lengths and bond angles for **9c** (15 pages). Ordering information is given on any current masthead page.

Diastereofacial Selectivity Studies on 4-Substituted 3-Acyl-4,5-dihydroisoxazoles

Peter A. Wade,*,† David T. Price,† Patrick J. Carroll,‡ and William P. Dailey‡

Departments of Chemistry, Drexel University and the University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received September 22, 1989

Carbonyl addition of organolithium reagents to 3-acyl-4,5-diphenylisoxazoles gave tertiary alcohols with ≥98% diastereomer excess (de) in the two cases examined. Similar carbonyl addition of Grignard reagents also occurred with ≥96% de, but with a preference for the *opposite* stereoisomer. Diastereoselectivities for addition to benzoyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazole were lower (≥86% de). Carbonyl addition to 4,5-diphenyl-4,5-dihydro-3-isoxazolecarboxaldehyde also gave much reduced diastereoselectivity (12–80% de). Reduction of 3-acyldihydroisoxazoles with a series of hydride reagents showed diastereoselectivity, but only 9-BBN gave ≥86% de. These changes in stereoselectivity are rationalized based on a combination of heterodiene conformational preference and attack anti to the 4-substituent. The s-trans conformer of 4,5-dihydro-3-isoxazolecarboxaldehyde was determined by the ab initio method to be 6.8 kcal/mol more stable than the s-cis conformer.

3-Acyl-4,5-dihydroisoxazoles, readily prepared by nitrile oxide cycloaddition to alkenes,[1] are attractive intermediates for the synthesis of carbohydrates. The moderate rigidity of the five-membered ring and the availability of coordination sites at ring N and O atoms (perhaps in conjunction with the carbonyl O atom) suggest the possibility for stereoselective transformation of the carbonyl group. In a preliminary publication,[2] it was demonstrated that very high diastereomer excess (de) and virtually complete stereochemical control were possible by judicious choice of organolithium reagents or Grignard reagents. This, coupled with the known procedures[3,4] for reductive cleavage of the dihydroisoxazole ring, should then provide a new approach to the construction of 2-amino 1,4-diols and 1,2,4-triols. Here more extensive stereochemical studies on acyldihydroisoxazoles and complete experimental details will be presented.

α-Nitro ketones, either directly or as the methyl nitronic esters, cycloadd to (*E*)-stilbene and cyclopentene providing easy access to the dihydroisoxazoles **1a**, **3a**, and **3b**.[5] Dihydroisoxazole **1b** was prepared in 31% yield by methylating the dicyclohexylamine salt of nitroacetone with diazomethane and reacting the resulting nitronic ester with stilbene in the presence of *p*-toluenesulfonic acid. 4,5-Diphenyl-4,5-dihydro-3-isoxazolecarboxaldehyde (**1c**) was prepared by published procedures.[6]

Table I. Addition of Organometallic Reagents to 3-Acyl-4,5-dihydroisoxazoles

substr	organometallic	alcohols	ratio	solvent/temp, °C	yield, %
1a	MeLi	**2a/2b**	99.5:0.5	THF/−78	94
1b	PhLi	**2a/2b**	1:99	THF/−78	82
1a	MeMgBr	**2a/2b**	2:98[a]	CH_2Cl_2/−78	72
1a	MeMgBr	**2a/2b**	20:80	THF/0–5	55
1b	PhMgBr	**2a/2b**	>99:1[b]	CH_2Cl_2/−78	82
1c	MeLi	**2c/2d**	70:30	THF/−78	76
1c	MeMgBr	**2c/2d**	34:66	CH_2Cl_2/0–5	95
1c	PhLi	**2e/2f**	90:10	CH_2Cl_2/−78	70
1c	PhMgBr	**2e/2f**	56:44	CH_2Cl_2/−78	86
3a	MeLi	**4a/5a**	95:5	THF/−78	88
3a	MeMgBr	**4a/5a**	7:93	CH_2Cl_2/−78	78
3b	MeLi	**4b/5b**	59:41[c]	THF/−78	93
3b	MeMgBr	**4b/5b**	49:51[d]	CH_2Cl_2/−78	83

[a] 3:97 at 0–5 °C. [b] Using freshly prepared Grignard reagent; 98:2 at 0–5 °C in ether or CH_2Cl_2. [c] Isolated in 55% and 38% yield (62:38 ratio), respectively, in a previously reported[5] run. [d] 46:54 in a duplicate run.

† Drexel University.
‡ University of Pennsylvania.

(1) Grundmann, Ch.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971.
(2) Wade, P. A.; Price, D. T.; McCauley, J. P.; Carroll, P. J. *J. Org. Chem.* **1985**, *50*, 2804.

0022-3263/90/1955-3051$02.50/0