via syringe to an Et_2O (25 mL) solution of *t*-BuLi (9 mL of a 1.7 M solution, 1.9 equiv) at −78 °C. After 15 min, 4,4-dimethoxycyclohexadienone (1.3 g, 8.1 mmol) was added, the resulting mixture was stirred for 1 h at −78 °C and then warmed to 0 °C with an ice bath, and the reaction was quenched with saturated NH_4Cl (5 mL). Workup as usual afforded a yellow oil whose NMR spectrum showed the formation of the expected quinol ketal. Without further purification, the crude product was dissolved in cold acetone (50 mL), 8% HOAc (10 mL) was added, and the mixture was stored overnight in the refrigerator. After 24 h, saturated $NaHCO_3$ (25 mL) was added, the acetone was removed in vacuo, and the product was extracted with Et_2O. Workup and concentration gave an orange oil, the ^1H NMR spectrum and TLC of which indicated the major product to be *p*-methoxyphenol.

Formation and Hydrolysis of 3.[3] *n*-BuLi (11.7 mL of a 1.6 M solution) was added over 5 min to a THF (30 mL) solution of 2-bromo-α-methylstyrene (3.4 g, 17 mmol) at −78 °C, and the resulting solution was stirred for 1 h. A solution of 4,4-dimethoxy-2,5-cyclohexadienone (2.6 g, 2.4 mL) in THF (5 mL) was added dropwise via syringe over 10 min, and the resulting brown solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl (10 mL), and the mixture was diluted with Et_2O (150 mL). The layers were separated, and the organic phase was washed with brine (50 mL), dried through $CaSO_4$, and concentrated in vacuo. The crude *p*-quinol ketal was dissolved in THF (30 mL), Zn/Cu couple (3.0 g, 46 mmol) was added, and the mixture was brought to reflux with stirring while 5% HOAc (30 mL) was added dropwise. After being heated and stirred for 30 min, the reaction mixture was cooled to room temperature and was diluted with Et_2O (75 mL). The layers were separated, and the organic phase was washed with brine (2 × 50 mL), dried through $CaSO_4$, and concentrated in vacuo to afford a thick, oily semisolid (2.9 g), which was recrystallized from EtOAc/hexane to afford 4 (1.61 g, 42% overall from the styrene) as tan crystals: mp 115–117 °C; IR (KBr) 1241 (s) cm^{-1}; ^1H NMR δ 8.7–8.5 (structured m, 2 H), 8.1–8.0 (structured m, 1 H), 7.7–7.5 (structured m, 3 H), 7.3–7.2 (structured m, 2 H), 3.9 (s, 3 H), 2.7 (br s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{14}O$ *m/e* 222.1044, obsd *m/e* 222.1044.

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Asymmetric 1,3-Dipolar Cycloadditions of Nitrile Oxides Using Simple Chiral Auxiliaries[1]

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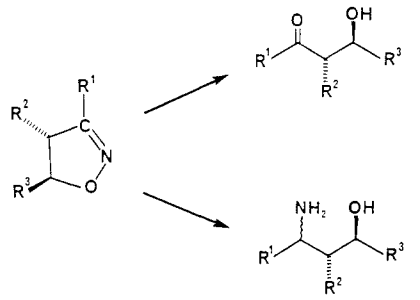
Dipolar cycloadditions of nitrile oxides to substituted bornyl crotonates give substituted isoxazolines with up to 80% diastereoselectivity. Both regioisomers of the adducts are produced in a ratio of approximately 3:1, independent of the substituent on the borneol and the nature of the nitrile oxide. The regioisomers, and sometimes the diastereomers, can be separated by flash chromatography. Reduction of the pure diastereomers with sodium borohydride yields enantiomerically pure 3-substituted 4-(hydroxymethyl)-5-methyl-2-isoxazolines.

A recent paper on the asymmetric induction in nitrile oxide cycloadditions[2] prompts us to report our results in this field. Substituted isoxazolines, resulting from 1,3-dipolar cycloadditions[3] of nitrile oxides[4] to 1,2-disubstituted olefins, are versatile intermediates for the synthesis of a wide variety of natural products.[5-7] Access to optically active isoxazolines would provide alternatives to the well-known asymmetric aldol reactions and, also, supply a new method for synthesizing enantiomerically pure primary amines (Scheme I).

Kozikowski et al. have examined the extent of diastereofacial selection in nitrile oxide additions due to an allylic asymmetric center in the dipolarophile[8] and the effects of chiral nitrile oxides.[9] Kametani and co-workers[10] have used menthyl esters and Curran et al.[2] have used menthyl and camphor sulfonamide derivatives to perform the cycloaddition reactions with chiral induction. Neither of these attempts provides a general method for diastereoselective 1,3-dipolar cycloadditions.

Scheme I. Alternative Routes from Chiral Isoxazolines



We have previously reported the use of substituted bornyl crotonates as chiral auxiliaries for conjugate additions of organocuprates[11] and now wish to report the successful use of these auxiliaries in diastereoselective cycloadditions of benzonitrile oxide and acetonitrile oxide.

Results and Discussion

The nitrile oxide additions to the bornyl crotonates 1 give four different cycloadducts; one pair of diastereomers for each regioisomer (Scheme II). The yields, regioselectivities, and diastereoselectivites of the reactions are presented in Table I.

(1) This work has been presented in part at BOSS-1 Namur, Belgium, 1986.
(2) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.
(3) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *2*, 565.
(4) Grundmann, C. *Synthesis* **1970**, 344.
(5) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
(6) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
(7) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519.
(8) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788.
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(10) Kametani, T.; Nagahara, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, *12*, 3048.
(11) Somfai, P.; Tanner, D.; Olsson, T. *Tetrahedron* **1985**, *24*, 5973.

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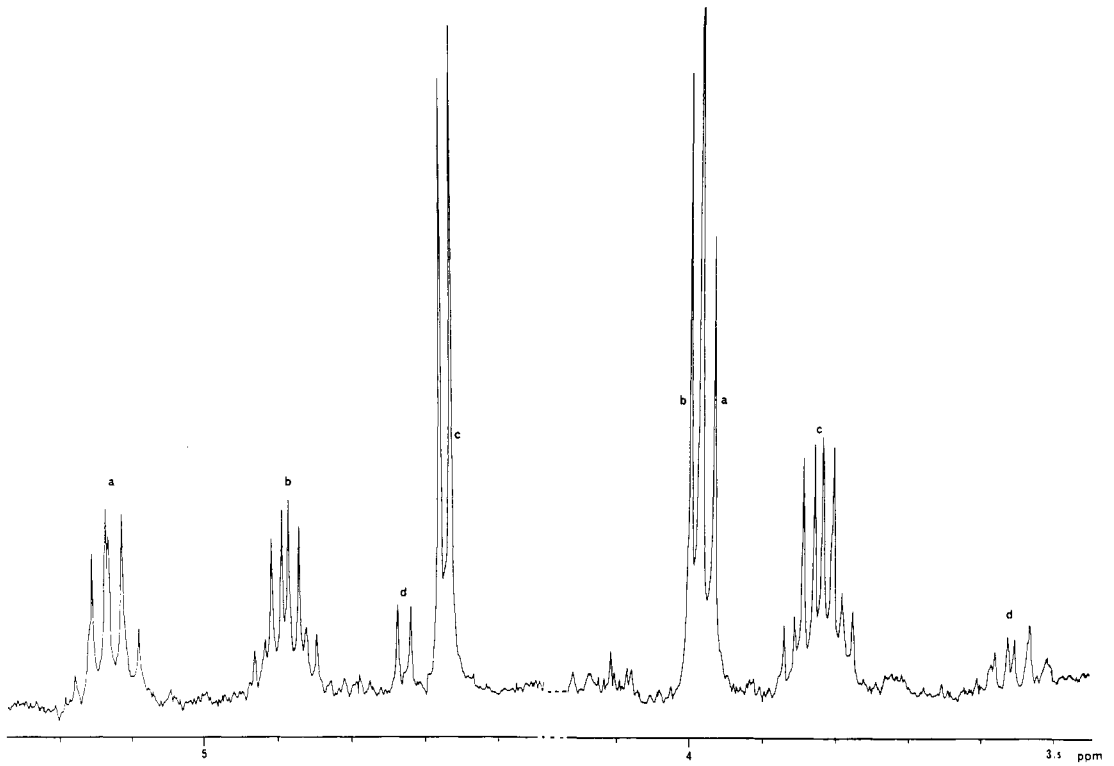
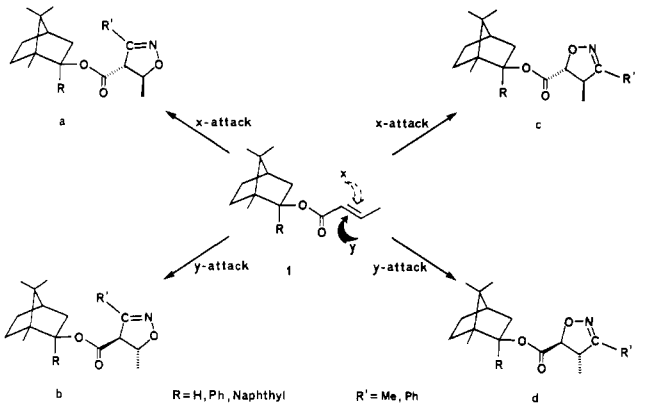


Figure 1. Portion of the isoxazoline region of the 270-MHz ^1H NMR spectrum of **4a–d**.

Scheme II. Addition of Nitrile Oxides to Substituted Bornyl Crotonates



The absolute configurations indicated in Scheme II were determined from the X-ray structure of the pure diastereomer **7a**.

The borneol derivatives **1** were prepared from camphor by a Grignard reaction[12] followed by esterification with crotonoyl chloride.[13] The cycloaddition reactions were performed at the lowest possible temperature to obtain maximum diastereoselectivity within reasonable time. The nitrile oxides were generated in situ from benzaldoxime chloride[14] and nitroethane, respectively.[15]

The yields of the cycloaddition reactions were generally high although the regioselectivities were moderate. This is expected with *trans*-1,2-disubstituted alkenes as dipolarophiles, while acrylates react almost regiospecifically.[16] All of the cycloadducts were *trans*-4,5-disubstituted, reflecting the configurations of the initial double bonds. In all cases the regioisomers could be separated by flash chromatography on silica gel, and several of the diastereomeric mixtures could be partly or fully separated. The best isolated yield of one pure diastereomer was obtained with R = naphthyl and R′ = methyl, where **7a** was isolated in a total yield of 50% by recrystallization of the crude reaction mixture from a 1:1 mixture of ether and pentane.

Table I. Yields, Regioselectivities, and Diastereoselectivities of 1,3-Dipolar Cycloadditions to Chiral Enoates

entry	R	R′	total yield, %	adducts[a]	yield,[b] %	de,[c] %
1	H	Ph	87	**2a + 2b**	65	6
				2c + 2d	22	12
2	Ph	Ph	82	**3a + 3b**	56	10
				3c + 3d	26	28
3	naphthyl	Ph	91	**4a + 4b**	63	5
				4c + 4d	28	80
4	H	Me	100	**5a + 5b**	75	6
				5c + 5d	25	13
5	Ph	Me	71	**6a + 6b**	46	54
				6c + 6d	25	30
6	naphthyl	Me	100	**7a + 7b**	76	47
				7c + 7d	24	75

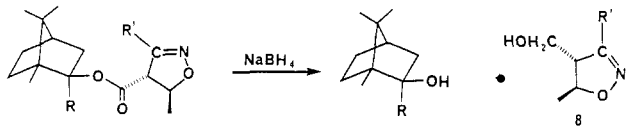
[a] Pairs of diastereomers (see Scheme II). [b] Isolated yields after chromatographic purification. [c] Determined from the ^1H NMR spectra of the crude reaction mixtures.

The structures of the different regioisomers were derived from the ^1H NMR values of the isoxazoline protons (Figure 1). A multiplet arising from the proton *gem* to the methyl substituent is found between δ 4.8 and δ 5.1 for the major regioisomers, where the proton is closest to the electron-withdrawing oxygen of the ring, and between δ 3.2 and δ 4.0 for the minor regioisomers. For the other isoxazoline proton, a doublet is found between δ 3.4 and δ 4.1 for the major regioisomers and between δ 4.4 and δ 4.7 for the minor regioisomers.

The diastereomeric excess in each case was determined by integration of ^1H NMR spectra of the isoxazoline pro-

(12) Coxon, J. M.; Steel, P. J.; Coddington, J. M.; Rae, I. D.; Jones, A. J. *Aust. J. Chem.* **1978**, *31*, 1223.
(13) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.
(14) Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345.
(15) Mukaiama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(16) Grundmann, C.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: Heidelberg, 1971.

Scheme III. Reduction of Esters



tons and, when applicable, the methyl groups of the isoxazoline parts of the molecules. When the signals of the diastereomeric protons were poorly separated, decoupling of the methyl or isoxazoline protons in most cases afforded two separate signals.

Treatment of the cycloadducts with $NaBH_4$ in ethanol cleaved the ester bonds selectively, leaving the isoxazoline functionality unaffected and permitting the recovery of the chiral auxiliary (Scheme III).

The reductions proceeded quantitatively, although requiring several hours for the more hindered esters. A minor degree of epimerization on C4 occurred due to the basic reaction conditions. The epimers were separated by flash chromatography, and pure isoxazoline **8** was isolated. Both of the regioisomers produced in each case were successfully reduced. The facile reductions of the ester bonds with $NaBH_4$ were somewhat surprising, since esters generally are inert to this reagent. The presence of a coordinating functional group in the structure can, though, effect the reduction of ester bonds,[17] and the oxygen or the C–N double bond of the isoxazoline offers the required coordinating ability. When the mixture of isomers from entry 2 was treated with $NaBH_4$ for a short period of time, the minor regioisomers **3c** + **3d** were completely reduced while the major regioisomers **3a** + **3b** were reduced only to a small extent.

Reduction of the pure diastereomer **7a** yielded enantiomerically pure (–)-3-methyl-4-(hydroxymethyl)-5-methyl-2-isoxazoline, $[\alpha]^{25}_D$ –224.1° (2.1 mg/mL EtOH). The enantiomeric excess (ee) of the reduction products of diastereomeric mixtures **4a** + **4b** and **5a** + **5b** could then be established to 8% and 62%, respectively, by recording optical rotation and comparing with the pure **8** (R = Me). These values correspond quite well with the results from the ^1H NMR measurements on the diastereomers.

The borneol derivatives were selected as chiral auxiliaries to provide a reasonably rigid system with one face of the double bond more available for attack than the other. Borneol derivatives are excellent chiral auxiliaries as they are easily prepared from naturally occurring camphor and can be recovered after cleavage of the cycloaddition products. The enoate functionality serves to increase the dipolarophilic activity of the olefinic compound,[4] and the esters are readily reduced without disturbing other functional groups within the molecules.

The substituent R makes the ester a less flexible structure. The phenyl-substituted ester **1** (R = Ph) shows broad peaks in the aromatic region of the ^1H NMR spectrum at room temperature, consistent with a hindered rotation of the bornyl–phenyl bond. Naphthylborneol shows the same type of behavior, and we have estimated the rotational barrier of the bornyl–naphthyl bond of naphthylborneol to approximately 50 kJ/mol at 25 °C using dynamic ^1H NMR and the DNMR5 line shape analysis program.[18] The corresponding ester **1** (R = naphthyl) shows one set of sharp peaks, and no exchange processes over a temperature range of –60 to +50 °C can be seen on the NMR time scale. This indicates the sole presence of one rotamer of the naphthyl ester.

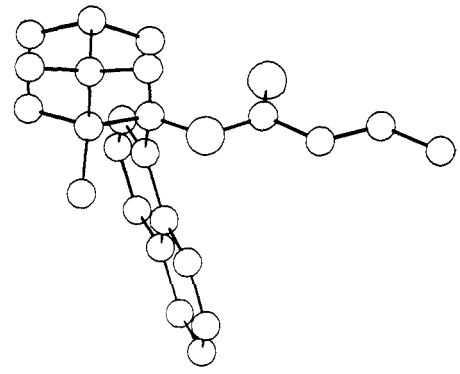


Figure 2. Lowest energy s-cis conformation of ester **1** (R = naphthyl) according to molecular mechanics.

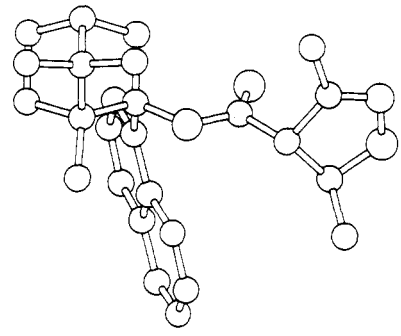


Figure 3. X-ray structure of **7a**.

We consequently assumed that a larger R group would yield a higher diastereomeric excess (de) in the product. This assumption proved to be valid for the minor regioisomer produced, giving 12% de for benzonitrile oxide and 13% for acetonitrile oxide addition to the bornyl ester, 28% and 30% de when added to the phenylbornyl ester, and 80% and 75% de with the naphthylbornyl ester. For the major regioisomer, however, the diastereoselectivity did not follow the size of the borneol substituent. Benzonitrile oxide additions to all the esters gave <10% de, while addition of acetonitrile oxide afforded 6% de for addition to the bornyl ester and 54% and 47% de respectively for addition to the phenyl and naphthyl esters.

Molecular mechanics calculations[19] on the naphthylbornyl ester give four low-energy conformations. Two of these have the ester in the s-cis conformation and two in the s-trans conformation. The s-cis conformer in Figure 2 would explain the obtained stereoselectivity, and it also resembles the X-ray structure of the cycloaddition product **7a** (Figure 3). This conformer would also give a lower diastereoselectivity for the major regioisomer when a nitrile oxide with a larger R′ group is added, since a large group would interact with the methyl substituents of the bridge in the borneol. This is indeed observed when benzonitrile oxide is added, giving a substantially higher de value for the minor regioisomer as compared to the major, more crowded, regioisomer.

Molecular mechanics calculations give that the two s-trans conformers have a slightly lower energy (approximately 10 kJ) than the s-cis conformers. However, Curran's group and Houk[2] have shown that the major cycloadducts of their investigated acrylate substrates derive from the s-cis conformations of the esters. Our earlier reported cuprate additions to the borneol esters **1** and the nitrile oxide additions give seemingly contradictory results,

(17) Hajos, A. *Komplexe Hydride*; Vrb. Deutscher Verlag der Wissenschaften: Berlin, 1966; p 258.
(18) Stephenson, D. S.; Binsch, G. *QCPE* **1978**, *12*, 365.
(19) Allinger, N. L.; Yuh, Y. *QCPE* **1976**, *12*, 318.

with the cuprates and nitrile oxides adding to opposite sides. This suggests that the cuprates add to the s-trans conformers of the esters.

Experimental Section

General Methods. All of the reactions were performed with dry equipment in an argon atmosphere. Solvents were dried by distillation from sodium/benzophenone. ^1H NMR spectra were recorded on a Bruker WH-270 instrument in $CDCl_3$ using TMS as internal reference. GC/MS were recorded on a Finnigan 1020 instrument. A Perkin-Elmer 197 spectrophotometer was used for obtaining IR spectra. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Merck silica gel (230–400 mesh ASTM) was used for flash chromatography.

Phenylhydroximoyl chloride was prepared according to the literature.[20] Procedures for the preparations of substituted borneols and bornyl crotonates have been published along with spectral data in a preceding paper.[11]

We found that slow generation of the nitrile oxides by adding the base over a period of time suppressed the formation of dimers from the nitrile oxides and allowed a ratio more close to 1:1 of nitrile oxide precursor and dipolarophile.

Cycloaddition of Benzonitrile Oxide. General Procedure. Ester 1 (5 mmol) is dissolved in 20 mL of ether. Phenylhydroximoyl chloride (7.5 mmol) in 10 mL of ether is added at −78 °C. Triethylamine (15 mmol) is added dropwise over a period of 3 h. Stirring is continued at −78 °C until the reaction is complete according to TLC (2–5 h). The reaction is then quenched by adding 30 mL of saturated ammonium chloride. Ether extraction, drying with $MgSO_4$, and evaporation of the solvent yield a mixture of regioisomers and diastereomers. Flash chromatography with a 20% ether/pentane mixture gives the isolated regioisomers, the major regioisomer always being eluated ahead of the minor isomer.

For the diastereomeric mixtures **2a + 2b** and **3a + 3b**, repeated chromatography with the same eluent afforded separation of the diastereomers. The diastereomers **3a + 3b** were almost completely separated, while the mixture **2a + 2b** only was separated to a small extent by flash chromatography but was separable by GC on a capillary column (OV-101).

Characteristic spectral data and physical properties of the cycloadducts:[21]

2a + 2b: pale yellow syrup. Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 3.45. Found: C, 73.9; H, 8.0; N, 4.1. **2a**: ^1H NMR 1.45 (d, 3 H, J = 6 Hz), 4.05 (d, 1 H, J = 6 Hz), 5.05 (quint, 1 H, J = 6 Hz); MS m/e 161 ($C_6H_5C_3H_6CNO^+$), 137 ($C_{10}H_{17}^+$), 81 ($C_6H_9^+$). **2b**: ^1H NMR 1.45 (d, 3 H, J = 6 Hz), 4.05 (d, 1 H, J = 6 Hz), 5.05 (quint, 1 H, J = 6 Hz).

2c + 2d: pale yellow syrup. **2c**: ^1H NMR 1.40 (d, 3 H, J = 7 Hz), 3.95 (dq, 1 H, J = 7, 4.5 Hz), 4.70 (d, 1 H, J = 4.5 Hz); MS m/e 160 ($C_6H_5C_3H_5CNO^+$), 137 ($C_{10}H_{17}^+$), 81 ($C_6H_9^+$). **2d**: ^1H NMR 1.40 (d, 3 H, J = 7 Hz), 3.95 (dq, 1 H, J = 7, 4.5 Hz), 4.70 (d, 1 H, J = 4.5 Hz).

3a–d: colorless syrups. **3a**: ^1H NMR 1.40 (d, 3 H, J = 7 Hz), 3.90 (d, 1 H, J = 6 Hz), 5.10 (dq, 1 H, J = 6, 7 Hz); MS m/e 212 ($C_6H_5C_{10}H_{15}^+$). **3b**: ^1H NMR 1.37 (d, 3 H, J = 7 Hz), 3.95 (d, 1 H, J = 6 Hz), 5.10 (dq, 1 H, J = 6, 7 Hz). **3c**: ^1H NMR 1.37 (d, 3 H, J = 7 Hz), 3.80 (dq, 1 H, J = 7, 4 Hz), 4.60 (d, 1 H, J = 4 Hz); MS m/e 212 ($C_6H_5C_{10}H_{15}^+$). **3d**: ^1H NMR 1.35 (d, 3 H, J = 7 Hz), 3.95 (dq, 1 H, J = 7, 4 Hz), 4.65 (d, 1 H, J = 4 Hz).

4a–d: colorless glasses. **4a**: ^1H NMR 1.30 (d, 3 H, J = 6 Hz), 3.98 (d, 1 H, J = 5 Hz), 5.05 (dq, 1 H, J = 6, 5 Hz). **4b**: ^1H NMR 1.30 (d, 3 H, J = 6 Hz), 4.00 (d, 1 H, J = 4 Hz), 4.95 (dq, 1 H, J = 6, 4 Hz). **4c**: ^1H NMR 1.37 (d, 3 H, J = 7 Hz), 3.92 (dq, 1 H, J = 7, 4 Hz), 4.65 (d, 1 H, J = 4 Hz). **4d**: ^1H NMR 1.40 (d, 3 H, J = 7 Hz), 3.50 (dq, 1 H, J = 7, 5 Hz), 4.70 (d, 1 H, J = 5 Hz).

Cycloaddition of Acetonitrile Oxide. General Procedure. The ester 1 (5 mmol) is dissolved in 10 mL of benzene. Phenyl isocyanate (16 mmol) is added. Nitroethane (8 mmol) and 1 drop of triethylamine dissolved in 5 mL of bezene are added during a period of 3 h. Stirring is continued until the reaction is complete according to TLC (2–6 h). The precipitated diphenylurea is filtered off and washed thoroughly with benzene. The combined benzene layers are washed with water and dried with $MgSO_4$. The solvent is evaporated and the residue subjected to flash chromatography with 20% ether/pentane as eluent to achieve separation of the regioisomers (minor isomer more polar).

The cycloadduct of the naphthyl-substituted bornyl ester was purified by recrystallization from 15 mL of a 1:1 ether/pentane mixture. A 50% yield of the pure diastereomer **7a** was isolated.

Characteristic spectral data and physical properties of the cycloadducts:[21]

5a + 5b: pale yellow syrup. **5a**: ^1H NMR 1.35 (d, 3 H, J = 6 Hz), 2.05 (d, 3 H, J = 1 Hz), 3.55 (dd, 1 H, J = 1, 8.5 Hz), 4.85 (dq, 1 H, J = 6, 8.5 Hz). **5b**: ^1H NMR 1.35 (d, 3 H, J = 6 Hz), 2.05 (d, 3 H, J = 1 Hz), 3.55 (dd, 1 H, J = 1, 8.5 Hz), 4.85 (dq, 1 H, J = 6, 8.5 Hz).

5c + 5d: yellow syrup. **5c**: ^1H NMR 1.35 (d, 3 H, J = 7 Hz), 1.97 (s, 3 H), 3.35 (quint, 1 H, J = 7 Hz), 4.50 (d, 1 H, J = 7 Hz). **5d**: ^1H NMR 1.35 (d, 3 H, J = 7 Hz), 1.97 (s, 3 H), 3.35 (quint, 1 H, J = 7 Hz), 4.50 (d, 1 H, J = 7 Hz).

6a + 6b: pale yellow syrup. **6a**: ^1H NMR 1.40 (d, 3 H, J = 6 Hz), 1.95 (d, 3 H, J = 1 Hz), 3.47 (dd, 1 H, J = 1, 8 Hz), 4.92 (dq, 1 H, J = 6, 8 Hz). **6b**: ^1H NMR 1.40 (d, 3 H, J = 6 Hz, 2.03 (d, 3 H, J = 1 Hz), 3.47 (dd, 1 H, J = 1, 8 Hz), 4.92 (dq, 1 H, J = 6, 8 Hz).

6c + 6d: yellow syrup. **6c**: ^1H NMR 1.25 (d, 3 H, J = 7 Hz), 1.97 (d, 3 H, J = 1 Hz), 3.30 (dq, 1 H, J = 7, 6 Hz), 4.4 (dd, 1 H, J = 6, 1 Hz). **6d**: ^1H NMR 1.25 (d, 3 H, J = 7 Hz), 2.00 (d, 3 H, J = 1 Hz), 3.30 (dq, 1 H, J = 7, 6 Hz), 4.43 (d, 1 H, J = 6 Hz).

7a: colorless needles: mp 120 °C; ^1H NMR 1.30 (d, 3 H, J = 6 Hz), 1.70 (d, 3 H, J = 1 Hz), 3.55 (dd, 1 H, J = 1, 8 Hz), 4.80 (dq, 1 H, J = 6, 8 Hz); IR (KBr, cm^{-1}, 3030, 2950, 1720, 1440 (2-isoxazoline), 770, 800 (α-substituted naphthalene). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.71; N, 3.45. Found: C, 77.1; H, 7.8; N, 3.5.

7b–d: colorless glasses. **7b**: ^1H NMR 1.50 (d, 3 H, J = 6 Hz), 1.67 (d, 3 H, J = 1 Hz), 3.60 (dd, 1 H, J = 1, 8 Hz), 4.80 (dq, 1 H, J = 6, 8 Hz). **7c**: ^1H NMR 1.20 (d, 3 H, J = 7 Hz), 1.95 (s, 3 H), 3.20 (dq, 1 H, J = 7, 6 Hz), 4.45 (d, 1 H, J = 6 Hz). **7d**: ^1H NMR 1.20 (d, 3 H, J = 7 Hz), 1.97 (s, 3 H), 3.20 (dq, 1 H, J = 7, 6.5 Hz), 4.50 (d, 1 H, J = 6.5 Hz).

Reduction of Cycloadducts. General Procedure. The cycloadduct (1 mmol) is dissolved in 2 mL of ethanol. $NaBH_4$ (1.5 mmol) is added, and stirring is continued until the reduction is complete according to TLC. The reaction is quenched with a little saturated ammonium chloride, and the solvent is evaporated. The residue is subjected to flash chromatography without further workup, since extraction with water proved to reduce the yields. With ether as the eluent, pure (hydroxymethyl)isoxazoline is isolated in >95% yield. For the successful reduction of cycloadduct **7a** it was necessary to add 2 mL of THF as a cosolvent.

Characteristic data:

3-Phenyl-4-(hydroxymethyl)-5-methyl-2-isoxazoline (8, R = Ph): pale yellow oil; ^1H NMR 3.45 (ddd, 1 H, J = 4.5, 3, and 6.5 Hz), 3.72 (dd, 1 H, J = 6.5 12 Hz), 3.85 (dd, 1 H, J = 3, 12 Hz), 4.82 (dq, 1 H, J = 6, 4.5 Hz), 7.36 (m, 2 H), 7.70 (m, 3 H); MS m/e 191 (M^+), 146 ($M^+ - 45$), 77 ($C_6H_5^+$).

3-Phenyl-4-methyl-5-(hydroxymethyl)-2-isoxazoline: pale yellow oil; ^1H NMR 1.30 (d, 3 H, J = 6 Hz), 3.6–3.8 (m, 2 H), 4.48 (m, 1 H), 7.35 (m, 2 H), 7.65 (m, 3 H); MS m/e 191 (M^+), 160 ($M^+ - CH_2OH$), 132 ($M^+ - 59$), 117 ($M^+ - 74$), 77 ($C_6H_5^+$).

3-Methyl-4-(hydroxymethyl)-5-methyl-2-isoxazoline (8, R = Me): colorless oil; ^1H NMR 2.00 (d, 3 H, J = 1 Hz), 2.90 (dq, 1 H, J = 1, 6 Hz), 3.82 (dd, 2 H, J = 5, 6 Hz), 4.50 (quint, 1 H, J = 6 Hz); MS m/e 129 (M^+), 84 ($M^+ - 45$). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.8; H, 8.7; N, 10.8 (corrected for a small amount of water).

3-Methyl-4(*S*)-(hydroxymethyl)-5(*S*)-methyl-2-isoxazoline: $[\alpha]^{25}_D$ (2.1 mg/mL EtOH) −224.1°.

3-Methyl-4-methyl-5-(hydroxymethyl)-2-isoxazoline: pale yellow oil; ^1H NMR 1.95 (s, 3 H), 3.08 (quint, 1 H, J = 7 Hz), 3.60 (dd, 1 H, J = 12, 4 Hz), 3.80 (dd, 1 H, J = 12, 3 Hz), 4.18 (ddd, 1 H, J = 7, 4, 3 Hz).

Determination of Stereochemical Purity. The crystallized product in entry 6 consisted of the pure diastereomer **7a** according

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(21) ^1H NMR data for the borneol parts of the molecules are available on request.

to NMR. No trace of the other diastereomer could be detected, so we assumed that the reduction of **7a** would yield enantiomerically pure isoxazoline **8** (R = Me). The reduction product of **7a** (10.71 mg) was dissolved in dry ethanol and diluted to 5 mL (2.14 g/mL ethanol). In a 10-cm cell this solution gave α -0.480°, which gives $[\alpha]^{25}_D$ -224.1°. The cycloadducts produced in entry 5 were separated into two fractions of regioisomers by flash chromatography. The major fraction contained the diasteromeric pair **6a + 6b**, and no trace of the other regioisomer could be detected by NMR. The reduction product of this fraction gave $[\alpha]^{25}_D$ -139.7° (2.46 mg/mL ethanol), corresponding to an ee of 62.3% assuming a linear relationship. The optical purity of the reduction product of **5a + 5b** was established in the same way; $[\alpha]^{25}_D$ -18.6° (1.88 mg/mL ethanol) gave an ee of 8.3%.

X-ray Crystallography of 7a. Crystals were obtained from a 1:1 ether/pentane solution, and a crystal with dimensions 0.36 × 0.16 × 0.13 mm was used for data collection on an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections were measured to calculate the lattice parameters. Intensity data for reflections with $\theta < 60°$ were collected by the $\theta/2\theta$ scan method using monochromated Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated a slight decay (4%) of the crystal. The measured intensities were rescaled to account for this decay. A total of 1682 unique reflections were recorded and, of these, 1503 reflections with $I > 3\sigma(I)$ were considered observed. All intensities were corrected for Lorentz and polarization effects, but not for absorption or extinction. Crystal data: $C_{26}H_{31}NO_3$, M = 405.54, trigonal, space group $P3_2$, $a = b$ = 11.692 (3) Å, c = 14.357 (5) Å, V = 1699.8 Å^3, d_{calcd} = 1.188 g cm^{-3}, Z = 3.

The structure was solved with the program MITHRIL,[22] which provided the non-hydrogen atom positions (Table II, Supplementary Material). Methyl hydrogen positions were determined from Fourier difference synthesis maps, and the remaining hydrogen atoms were included at expected positions. Refinement was carried out by the full-matrix least-squares method using anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atoms were assigned a temperature factor equal to the U_{eq} value of their parent atoms. The hydrogen atom parameters were not refined.

After refinement the R and R_w values were 0.058 and 0.085, respectively. The weighting scheme used in the later part of the refinement was $w = 1/(1 + ((|F_{ob}| - 7)/5)^2)$. The form factors used were those given by Cromer and Mann.[23] All calculations were performed on a DEC system-10 computer mainly using the X-RAY 72 program system.[24]

Supplementary Material Available: Atom-numbering scheme for **7a** (Figure 4), positional and thermal parameters for **7a** (Tables II and III), and bond lengths and bond angles for **7a** (Table IV) (4 pages). Ordering information is given on any current masthead page. The structure factor table is available from the Department of Structural Chemistry.

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Hydroxyversicolorone: Isolation and Characterization of a Potential Intermediate in Aflatoxin Biosynthesis

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Mutagenesis of aflatoxigenic, wild-type *Aspergillus parasiticus* (SU-7) is described to afford a new mutant that accumulates two polar anthraquinone metabolites in a 20:1 ratio. These pigments were isolated and characterized as 1'-hydroxyversicolorone (**2**) and versicolorone (**10**), respectively, by spectroscopic and chemical means. The potential role of hydroxyversicolorone as the product of the first oxidative step of three in the conversion of the side chain of averufin (**1**) to the dihydrobisfuran of versicolorin A (**4**) and aflatoxin B_1 (**5**) is discussed.

Pigmented mutants generated from wild-type aflatoxigenic strains of *Aspergillus parasiticus* have played an essential role in investigations of the aflatoxin biosynthetic pathway.[1-4] In particular, tetrahydroxyanthraquinone derivatives isolated from these mutants in radioactive form have been shown not only to label aflatoxin B_1 (**5**) but also to incorporate radiolabel in a fixed sequence among themselves.[4-7] Central among these is averufin (**1**), which in specifically labeled forms has given intact incorporations of marker into aflatoxin and, in turn, has allowed the complete mapping of the carbon skeleton from this central intermediate into the highly rearranged coumarin nucleus of **5** bearing fused cyclopentenone and dihydrobisfuran rings.[8]

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