of 0.08 M potassium hydride/THF, 0.30 mmol of **12**, and 0.30 mmol of 18-crown-6 ether was degassed and sealed in a glass tube. The tube was heated at 80 °C for 48 h. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried, and concentrated, leaving 85 mg (98% recovery including 10% unreacted **12**) of a white solid, mp 80-95 °C.

Spectral Characterizations of Elimination Products. The ^{1}H NMR spectra of elimination product mixtures (**23** + **24**) show pairs of partially resolved doublets for the bridgehead protons (H_a in **23** and **24**) in the region δ 4.9-5.2. The vinyl protons lie within the aromatic regions (approximate δ 7-8). The methylene protons absorb as varying types of multiplets for products from **12** (δ 2.8-3.9), four sets of triplets for products from **20** (δ 2.9, 3.1, 4.2, 4.4), and two singlets for products from **22** (δ 4.8). In the case of vinyl chlorides from **22** the area integrations for the two singlets could be used to confirm the product isomeric distribution from analyses of the bridgehead proton absorptions.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

A Nitrone-Based Cycloaddition Approach to the Synthesis of the Glycosyl System of Nogalomycin, Menogaril, and Their Congeners

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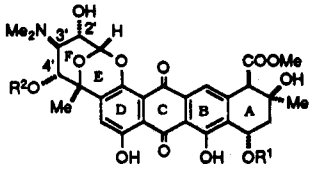
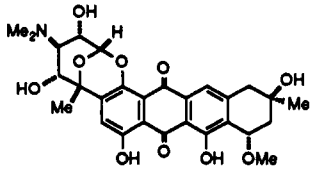
A series of model systems for the benzoxocin portion of nogalomycin was synthesized by cycloaddition of nitrone **8** with assorted dipolarophiles. Cycloaddition between nitrone **8** and vinyltrimethylsilane afforded isoxazolidines which were fragmented to produce either benzoxocins **21** and **23** or tricyclic isomer **27**. Tricyclic systems **23** and **27** were produced also from the adduct of nitrone **8** and allyltrimethylsilane following fragmentation and oxidative cleavage of the resulting homoallylic amine derivative. Dipolar cycloaddition between nitrone **8** and vinylene carbonate yielded two diastereomeric isoxazolidines **40** and **41**, both of which had the intact carbon skeleton of the glycosyl region of nogalomycin but which bore the incorrect relative configuration for transformation to menogaril analogue **5**.

Introduction

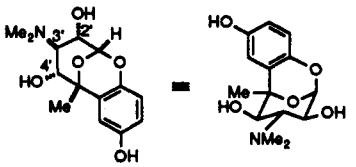
The carbon-linked glycosidic anthracyclines comprise a family of antibiotics with unique biological properties.[2] Nogalomycin (**1**), its degradation product menogaril (**4**), and decilorubicin (**2**) display potent antitumor activity, especially menogaril, which has entered phase II clinical trials. Arugomycin and viriplanin A are two additional members of this family of C-glycosidic anthracyclines whose aglycon differs from nogarol (**3**) only in the relative configuration of the hydroxyl at C-4′. Arugomycin displays antitumor activity similar to nogalomycin. Interestingly, viriplanin A does not have antitumor activity, but is highly active against Herpes simplex virus.[2]





1: Nogalomycin: R^1 = nogalose; R^2 = H
2: Decilorubicin: R^1 = rhodosamine; R^2 = L-decilonitrose-L-diginose
3: Nogarol: $R^1 = R^2$ = H

4: Menogaril



5

Several synthetic strategies for the synthesis of the benzoxocin (DEF ring) system of nogalomycin have been reported,[3] and Terashima has published a total synthesis of menogaril and several F-ring congeners.[4] As an integral portion of our studies concerning the total synthesis of amino sugars, the preparation of the carbon-linked glycosidic portion (the DEF ring) of menogaril employing a nitrone-based strategy has been developed, and a report of this preliminary study has appeared.[1,5] The original approach focused on construction of the acyclic precursor of benzoxocin **5** by a stereoselective, nitrone [3 + 2] cycloaddition as outlined in Scheme I. Cycloaddition of nitrone **8** and vinylene carbonate was anticipated to afford isoxazolidinecarbonate **7**. The stereoselectivity of this cycloaddition was anticipated to occur as indicated based upon previous studies from our laboratory (vide infra).[1,6,7]

Preparation of nitrone **8** was accomplished as outlined in Scheme II. Benzylation of 2,5-dihydroxyacetophenone (**9**) and Horner-Emmons-Wadsworth condensation of the resulting dibenzyl ether gave predominantly the *E* ester (*E*:*Z* = 8:1). The geometry of the major isomer was verified

(1) Taken in part from the Ph.D. Thesis of Joseph M. Leginus, The Pennsylvania State University, 1985.

(2) For a review of this topic see: Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1988; Vol. 2, pp 186-228.

(3) Bates, M. A.; Sammes, P. G. *J. Chem. Soc. Chem. Commun.* **1983**, 896. Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 1169. Joyce, R. P.; Parvez, M.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 4885. Bates, M. A.; Sammes, P. G.; Thomson, G. A. *J. Chem. Soc., Perkins Trans. 1* **1988**, 3037. Semmelhack, M. F.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 605.

(4) Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1988**, *29*, 791 and references cited therein. Matsuda, F.; Kawasaki, M.; Terashima, S. *Pure Appl. Chem.* **1989**, *61*, 385.

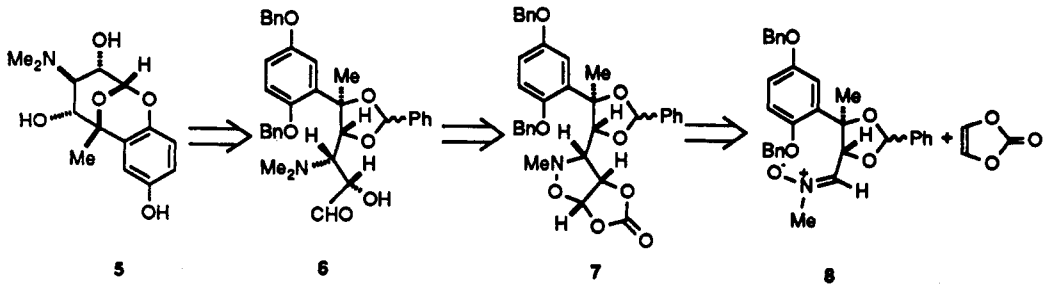
(5) DeShong, P.; Leginus, J. M. *Tetrahedron Lett.* **1984**, *25*, 5355. For additional examples of nitrone cycloadditions involving chiral nitrone derivatives, see: Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730 and references cited therein.

(6) Dicken, C. M. Ph.D. Thesis, The Pennsylvania State University, 1984.

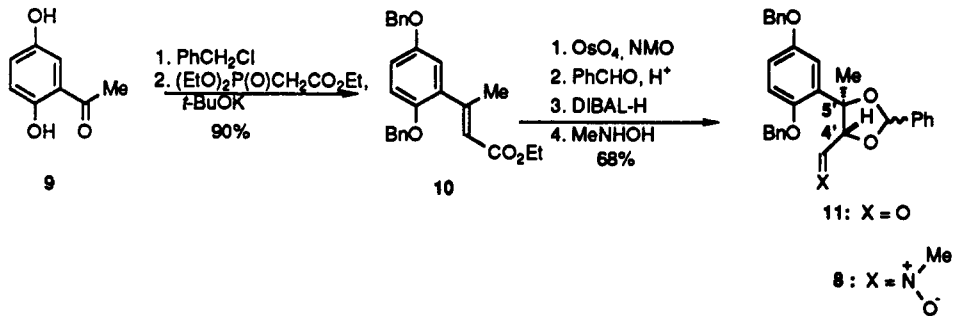
(7) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.

0022-3263/91/1956-1364$02.50/0

Scheme I



Scheme II

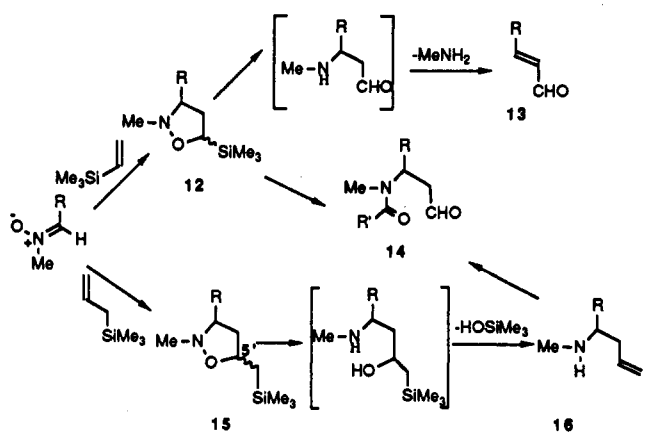


initially by an NOE experiment which showed an enhancement of the methylene signal of the ester function upon irradiation of the alkene methyl substituent and later by X-ray analysis of an intermediate. Catalytic osmylation of alkene **10** with OsO_4/*N*-methylmorpholine *N*-oxide[8] (NMO) was sluggish but produced the corresponding *cis*-diol. This process established the relative configurations at C-4′ and C-5′ (nogalomycin numbering).[9]

Protection of the diol as a benzylidene acetal provided two diastereomeric esters in a 55:45 ratio. Dibal reduction of the ester afforded aldehyde **11**, which was immediately converted to the *Z* nitrone **8** by treatment with *N*-methylhydroxylamine. The two nitrone diastereomers, epimeric at the benzylidene center, could be separated by chromatography, and the structure of the minor (more polar) isomer was determined by single-crystal X-ray analysis.[10] Subsequent studies indicated that both diastereomers behaved similarly in the cycloaddition reactions (vide infra).

We had previously demonstrated that nitrones react with trialkylsilane derivatives to produce isoxazolidine adducts which serve as precursors for various functional groups.[11-13] For example, vinyltrimethylsilane undergoes [3 + 2] dipolar cycloaddition in a completely regioselective manner to produce 5-(trimethylsilyl)isoxazolidines (**12**; Scheme III).[11] 5-Silylisoxazolidines are susceptible to fragmentation to give aldehyde derivatives.[11,12] Depending upon the reagents utilized to induce fragmentation, selective retention or loss of the amino substituent may occur. For example, fluoride-promoted (HF or Bu_4NF) fragmentation of isoxazolidine **12** results in formation of

Scheme III



α,β-unsaturated aldehyde **13**, presumably by β-elimination of methylamine from the initial fragmentation product.[11,12] Alternatively, if isoxazolidine **12** is allowed to react with an acid chloride, the elimination is suppressed, and β-amido aldehyde **14** is the major fragmentation product (Scheme III).[12b]

When allyltrimethylsilane is employed as the dipolarophilic partner, cycloaddition results in regiospecific formation of isoxazolidine **15** as a mixture of diastereomers at C-5 as indicated in Scheme III. Reductive cleavage of the isoxazolidine N,O-bond and elimination of trimethylsilanol yields homoallylic amine **16**.[12b,13] Acylation of the amine and oxidative cleavage of the terminal vinyl group produces β-amido aldehyde **14** (Scheme III).[12b]

It was anticipated that application of the vinyl- and allylsilane methodology could be employed for the preparation of deoxymenogaril congeners.

Dipolar Cycloadditions with Vinyltrimethylsilane. Nitrone **8a** (α-diastereomer at benzylidene) was allowed to react with excess vinyltrimethylsilane to give three of the four possible isoxazolidine cycloadducts **17–19** in a ratio of 60:20:20 (Scheme IV). The relative configurations of **17–19** were assigned by fragmentation of the isoxazolidine ring to yield β-amido aldehyde derivatives (vide infra). As

(8) VanRheenen, V.; Killy, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(9) Nogalomycin numbering is employed throughout.
(10) ORTEP representations of compounds **8β**, **28**, **40**, and **41** appear in the Supplementary Material.
(11) DeShong, P.; Leginus, J. M. *J. Org. Chem.* **1984**, *49*, 3421.
(12) (a) Lander, S. W., Jr. Ph.D. Thesis, The Pennsylvania State University, 1986. (b) Unpublished results. Lander, S. W., Jr.; Lamb, G. W.; McSwine, D. J., manuscript in preparation.
(13) DeShong, P.; Leginus, J. M.; Lander, S. W., Jr. *J. Org. Chem.* **1986**, *51*, 574.

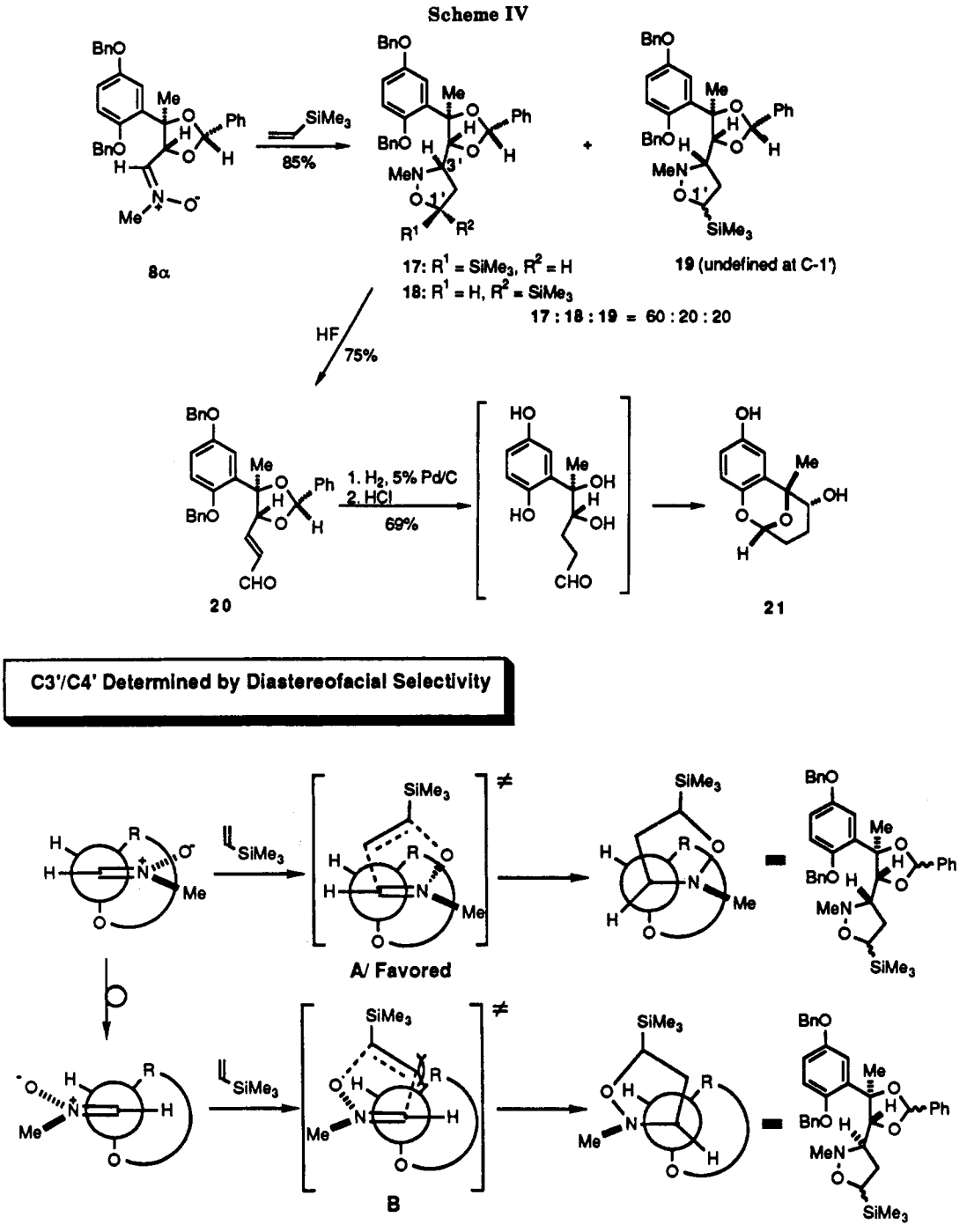


Figure 1.

anticipated from earlier studies,[7] the anti C-3′, C-4′ cycloadducts **17** and **18** were produced stereoselectively. Dipolar cycloaddition of α-alkoxy substituted nitrones had been shown to occur preferentially via Felkin–Anh[14] transition state A in which the developing carbon–carbon bond avoided steric interaction with the bulky R group.[1,7,13,15] This analysis is supported by calculations from Houk which suggest that nitrone cycloaddition proceed via a transition state with unsymmetrical bond formation. The carbon–carbon bond of the isoxazolidine ring is more developed in the transition state than the carbon–oxygen bond.[16] Accordingly, transition state A was preferred. However, this process would afford products having the syn C-3′, C-4′ relative configuration, while the cycloaddition furnished the anti adduct selectively. For the cycloaddition of nitrone **8α** with vinyltrimethylsilane, transition state B must have been favored. Some of the factors which control the facial differentiation between transition states A and B by various dipolarophiles are discussed below.

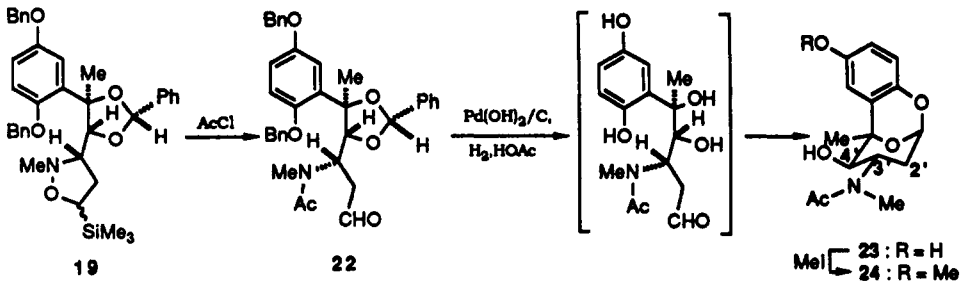
Fluoride-induced fragmentation of isoxazolidines **17**/**18** produced α,β-unsaturated aldehyde **20** in 75% yield. Catalytic reduction of the alkene and concomitant removal of the benzylidene acetal and benzyl ethers produced a

(14) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

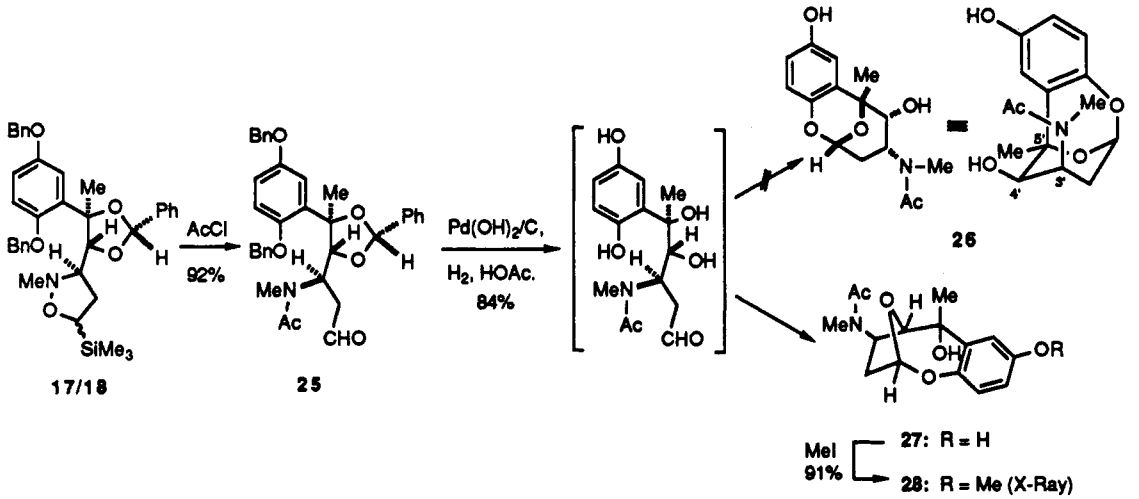
(15) A thorough discussion of the diastereofacial selectivity of α-alkoxynitrone derivatives will appear in a manuscript in preparation.[18]

(16) Professor Ken Houk, personal communication. For a related system, see: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

Scheme V



Scheme VI



transient diol–aldehyde which cyclized in 10% HCl to produce benzoxocin **21**, the C-2′ deoxy, C-3′ deamino analogue of **5** (Scheme IV).

Fragmentation of isoxazolidine **19**, the minor diastereomer bearing the syn C-3′, C-4′ relative configuration, with acetyl chloride afforded β-amido aldehyde **22** (Scheme V). Catalytic reduction with Pearlman's catalyst in acetic acid gave benzoxocin **23**, the 2-deoxy analogue of the nogalomycin/menogaril system. The relative configuration between C-3′, C-4′ was assigned from analysis of the ^{1}H NMR spectrum of methyl ether **24** which displayed the signal of the C-3′ proton at δ 4.57 as a multiplet with coupling constants of 11.8, 11.0, and 6.0 Hz. This coupling pattern is consistent with relative configuration **23** with the C-3′ an C-4′ substituents equatorially disposed.

Analogously, treatment of the mixture of isoxazolidines **17/18** with acetyl chloride led to efficient fragmentation of the heterocyclic ring to yield β-amido aldehyde **25**. Reductive debenzylation of aldehyde **25**, however, failed to afford the anticipated benzoxocin **26** and resulted instead in formation of the novel tricyclic acetal **27** in which the secondary hydroxyl at C-4′ had participated in acetal formation in preference to the tertiary hydroxyl (Scheme VI).

Presumably, closure of the diol–aldehyde derived from **25** to benzoxocin **26** was precluded by the configuration of the amido stereogenic center at C-3′. The anti C-3′, C-4′ relationship of isoxazolidines **17/18** would result in benzoxocin **26** bearing an axial amino function at C-3′. This axial orientation would be disfavored due to steric interactions imposed by the [3.3.1] system. Therefore, intramolecular acetal formation employing the secondary hydroxyl occurred in preference to closure to the desired [3.3.1] system.

The relative configuration of tricycle **27** was confirmed by single-crystal X-ray analysis of anisole derivative **28** prepared by alkylation of the phenolic hydroxyl with methyl iodide.[10]

The configuration of the benzylidene center of nitrone **8** was shown to have a minimal effect upon the stereoselectivity of the nitrone cycloaddition. Reaction of nitrone **8β** with vinyltrimethylsilane afforded a mixture of the four possible diastereomeric adducts in a ratio of ca. 55:23:17:2 (Scheme VII). This isomer distribution was similar to the ratio of isoxazolidines obtained using nitrone **8α**. The relative configuration at C-3′, C-4′ of adducts **29–32** was established by fragmentation–cyclization of the respective isoxazolidines as outlined for the adducts in Schemes V and VI to produce benzoxocin **23** and tricyclic acetal **27**.

Dipolar Cycloaddition with Allyltrimethylsilane. In an effort to improve the syn C-3′, C-4′ stereoselectivity in the cycloaddition reaction, nitrone **8β** was allowed to react with allyltrimethylsilane to afford four diastereomeric isoxazolidines **33–36** in a ratio of 55:18:18:9, respectively (Scheme VIII). As shown by subsequent cleavage reactions, the anti C-3′, C-4′ adducts **33** and **34** predominated. This stereochemical result parallels the situation in the cycloaddition between nitrone **8** and vinyltrimethylsilane (Schemes IV and VII). The major cycloadduct was tentatively assigned the β-configuration at C-1′ based upon precedents in related systems[5,6] which demonstrated that dipolar cycloadditions with allyltrimethylsilane proceeded preferentially via an exo transition state yielding the syn C-1′, C-3′ configuration.

As in model systems,[12] reduction of the N,O-bond of the major isoxazolidine **33** followed by acetylation and silanol elimination of the resulting α-silyl acetate derivative **37** produced homoallylic amine **38**. Oxidative cleavage of the terminal alkene with $OsO_4/NaIO_4$ gave aldehyde **39**, epimeric at the benzylidene center with aldehyde **25** (Scheme VI). Reductive cyclization of **39** afforded tricyclic acetal **27** and established the relative C-3′, C-4′ configuration of

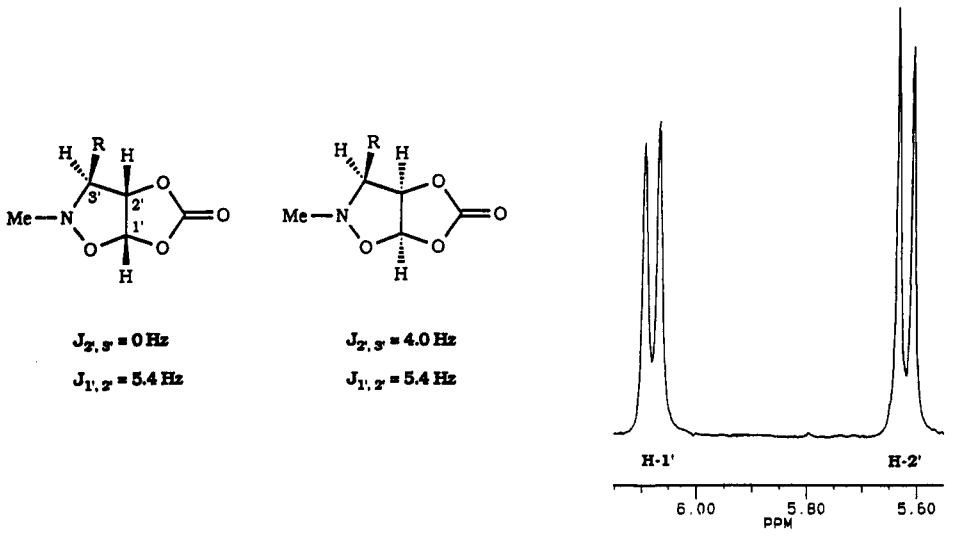
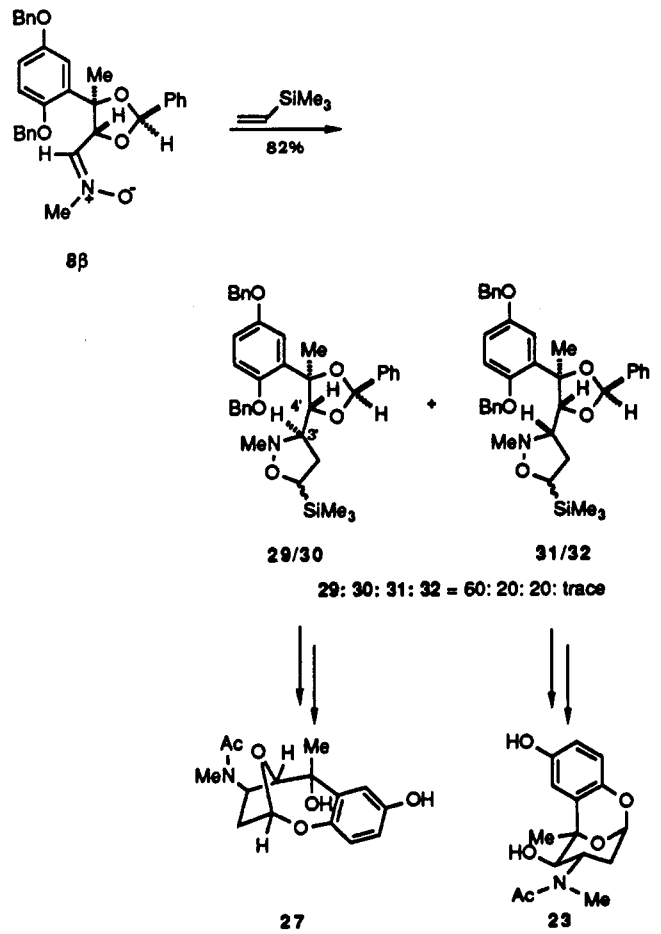


Figure 2.

Scheme VII



major cycloadduct **33** as anti.

Dipolar Cycloadditions with Vinylene Carbonate. The original retrosynthetic strategy outlined in Scheme I had supposed that the C-2′ hydroxyl of the benzoxocin system could be introduced by a stereoselective cycloaddition of nitrone **8** with vinylene carbonate. The experience garnered from cycloadditions of nitrones **8** and silyl dipolarophiles led us to anticipate that the cycloaddition would proceed to afford predominantly (the undesired) anti relative configuration at C-3′, C-4′ in cycloadducts with vinylene carbonate. Accordingly, we were not surprised when cycloaddition of nitrone **8β** with vinylene carbonate produced adducts **40** and **41** in a 67:33 ratio. As in the previous reactions of nitrone **8**, cycloaddition with vinylene carbonate displayed moderate selectivity for the diastereomer having C-3′, C-4′ anti relationship. The stereoselectivity of the cycloaddition could be improved to 80:20 by employing high-pressure conditions (Scheme IX). We had previously demonstrated that application of high-pressure reaction conditions often resulted in improved stereoselectivity in nitrone cycloadditions.[17]

Assignment of the C-3′, C-4′ anti configuration to major adduct **40** was confirmed by single-crystal X-ray analysis.[10]

Proton NMR analysis of isoxazolidines **40** and **41** revealed that each diastereomer bore the C-2′, C-3′ anti relationship. In **41**, for example, the signal for the C-2′ proton appears as a doublet at δ 5.57 with a coupling constant of 5.2 Hz from coupling solely to the C-1′ proton (see Figure 2). In the C-2′, C-3′ anti adducts, the protons at C-2′ and C-3′ fail to display coupling since $\theta \approx 90°$. This feature of the NMR spectrum is uniquely diagnostic for the C-2′, C-3′ anti relationship.[6,7]

Isoxazolidines **40** and **41** arise from cycloaddition of nitrone **8** through the endo transition state (see Scheme X). Preference for the endo transition state in cycloaddition reactions with vinylene carbonate was not anticipated since silyl dipolarophiles had shown a preference for exo transition state derived adducts. We propose that energy of the endo transition state is lowered relative to the exo analogue by a developing anomeric stabilization (Scheme X).[18,19]

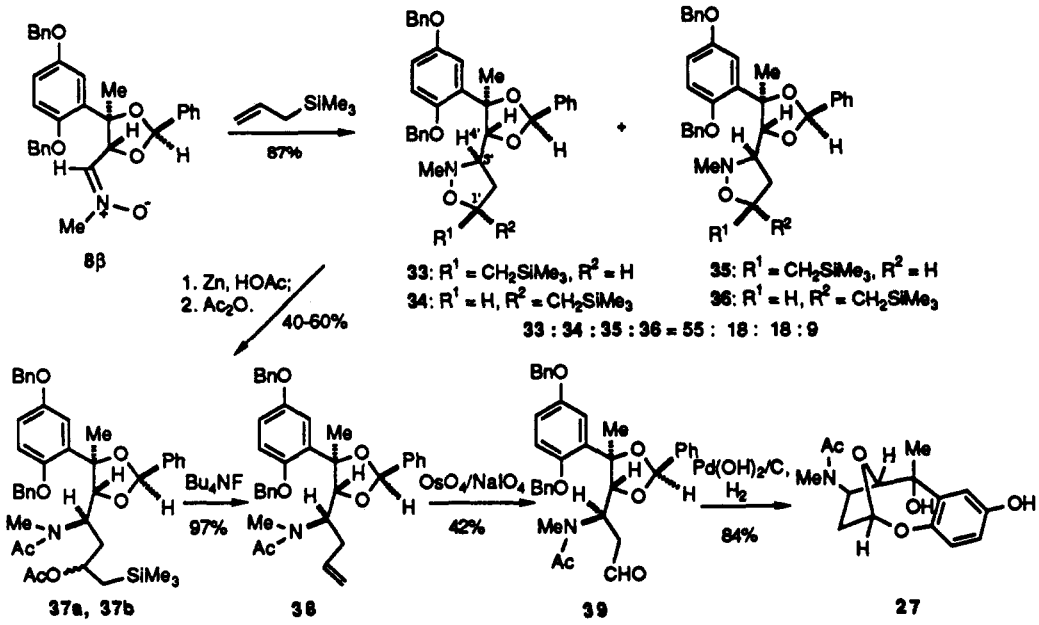
Conversion of isoxazolidines **40** and **41** into menogaril model system **5** was not investigated since the requisite relative configuration at C-2′, C-3′ had not been established

(17) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047.

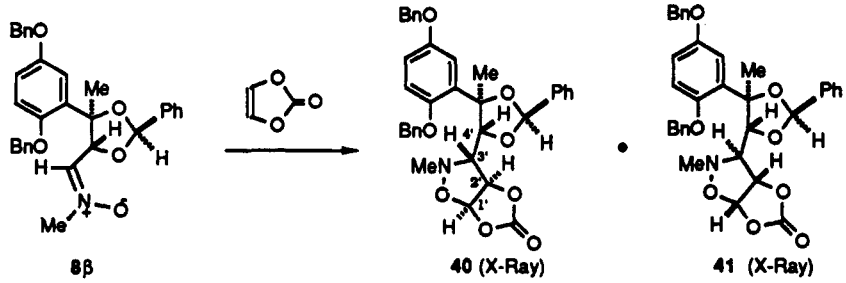
(18) A thorough discussion of the stereoselectivity of these nitrone cycloadditions will appear in DeShong, P.; Dicken, C. M.; Leginus, J. M.; Lander, S. W., Jr.; Kennington, J. W., Jr.; Li, W., manuscript in preparation.

(19) A referee has suggested that the exo selectivity observed in the nitrone cycloaddition may result from steric factors analogous to those observed by Vasella (see ref 5). We discount this possibility because in our system, the nitrone bears only a structurally undemanding methyl group, whereas the Vasella nitrones have bulky glycosyl moieties attached to nitrogen.

Scheme VIII



Scheme IX



Reaction Conditions	40 : 41	Yield (%)
1 atm, 120 °C, toluene	1 : 2	55
12 kbar, r.t., ether	1 : 4	60

in the cycloaddition (compare 41 with 7, Scheme I).[20]

Subsequent investigations will focus upon altering the stereoselectivity of the dipolar cycloaddition of nitrone 8 with selected dipolarophiles in order to produce isoxazolidines bearing appropriate stereochemical relationships for transformation into menogaril and congeners.

Experimental Section

General Procedures. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. Solvents were dried according to established protocols by distillation under nitrogen from an appropriate drying agent. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium or potassium benzophenone ketyl immediately prior to use. Toluene and xylenes were distilled from sodium benzophenone ketyl, while triethylamine, diisopropylamine, diisopropylethylamine, and acetonitrile were distilled from calcium hydride and stored under nitrogen. Immediately prior to use, dichloromethane and all alkyl halides were distilled from calcium hydride. Methanol was distilled from magnesium methoxide and stored under nitrogen. Reactions involving air- and/or moisture-sensitive reagents were conducted under an atmosphere of nitrogen or argon and the glassware was flame-dried under a stream of anhydrous nitrogen prior to use. Reported yields are for compounds determined to be >95% homogeneous by ^1H and ^{13}C NMR.

The high-pressure apparatus consisted of a hydraulically pressurized autoclave containing castor oil. Pressures were determined directly from a gauge attached to the autoclave. High-pressure reactions were conducted in a disposable plastic tuberculin syringe sealed with a luer lock cap. Details of the reaction apparatus have been previously reported.[21]

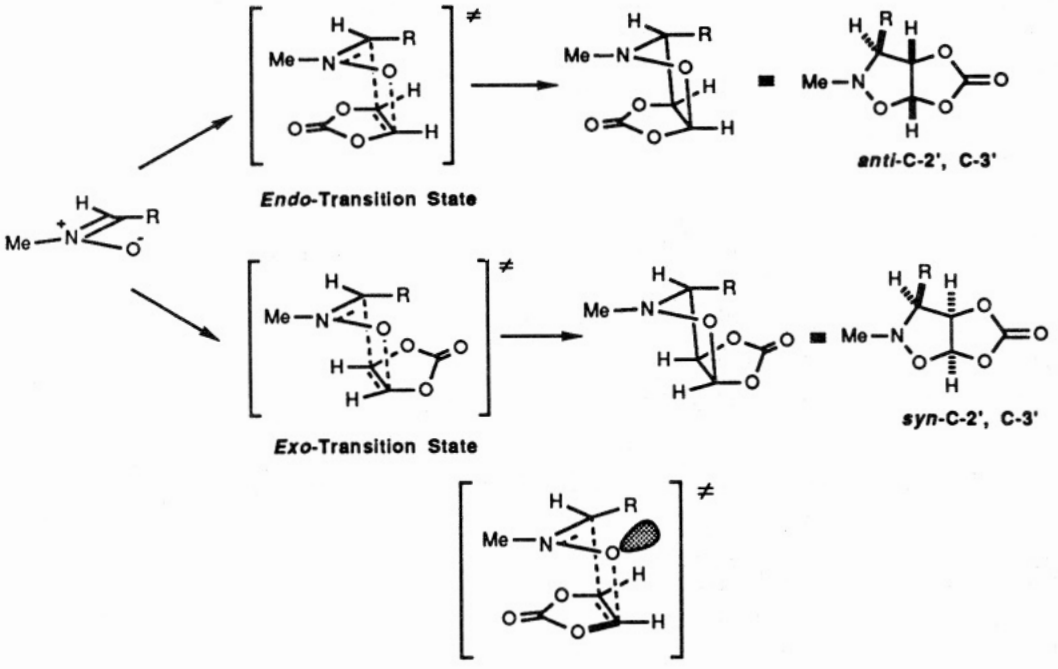
2′,5′-Bis(benzyloxy)acetophenone. A solution of 2′,5′-dihydroxyacetophenone (9) (2.0 g, 13.1 mmol), benzyl chloride (3.5 g, 27.6 mmol), and K_2CO_3 (4.3 g, 31.1 mmol) in 40 mL of absolute EtOH was refluxed for 18 h. The green suspension was filtered while hot, and the filter cake was washed thoroughly with ethanol. Upon cooling the solution, brown crystals precipitated, which were filtered, washed with cold ethanol, and recrystallized from ethanol to give 3.2 g (75%) of the ketone as beige crystals: mp 77–78 °C; IR (Nujol) 3040 (m), 1735 (m), 1670 (s), 1490 (s); ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 4.9 (s, 2 H), 5.1 (s, 2 H), 6.9 (m, 2 H), 7.3 (m, 11 H); mass spectrum, m/z (relative intensity) 332 (M^+, 6), 290 (1), 243 (3), 91 (100).

α,β-Unsaturated Ester 10. A flame-dried flask was charged with potassium *tert*-butoxide (1.28 g, 11.80 mmol) and anhydrous THF (40 mL). To this mixture, triethyl phosphonoacetate (2.64 g, 11.06 mmol) was added dropwise while the temperature of the solution was maintained at 30–35 °C. After addition was complete, the solution was stirred for 1 h at room temperature, and 2′,5′-

(20) Attempts to coax nitrone 8 to undergo cycloaddition with vinylene carbonate via an exo transition state are underway.

(21) DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. N. *Org. Prep. Proced. Int.* 1983, *14*, 369.

Scheme X



bis(benzyloxy)acetophenone (3.40 g, 10.02 mmol) in 50 mL of benzene was then added dropwise. Stirring was continued for 10 h at reflux. The reaction mixture was quenched with cold water (10 mL), and the resulting mixture was extracted with ether (3 × 50 mL), washed with water (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The ^1H NMR of the crude product indicated that the E/Z ratio of the resulting alkenes was 8:1 in favor of the E isomer. Column chromatographic separation of the E/Z mixture (30:1 hexane/EtOAc) gave 3.55 g of E alkene **10** and 0.43 g of Z alkene (combined yield 98%). ***E* Alkene** (recrystallized from 9:1 hexanes/ethyl acetate): mp 78–79 °C; IR (CH_2Cl_2) 2900 (w), 1710 (s), 1630 (m), 1105 (s); ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3 H), 2.51 (d, J = 1.5 Hz, 3 H), 4.19 (q, J = 7.0 Hz, 2 H), 5.00 (s, 2 H), 5.01 (s, 2 H), 5.93 (q, J = 1.5 Hz, 1 H), 6.8–7.4 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.9, 59.7, 70.6, 71.2, 114.2, 114.9, 116.0, 119.5, 127.2, 127.5, 127.8, 128.5, 134.5, 137.0, 149.7, 152.9, 156.1, 166.7; mass spectrum, m/z (relative intensity) 402 (M^+, 4), 357 (1), 311 (1), 91 (100). ***Z* Alkene** (recrystallized from 9:1 hexane/ethyl acetate): mp 77–78 °C; IR (CH_2Cl_2) 2900 (s), 1715 (s), 1645 (w), 1020 (s); ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.0 Hz, 3 H), 2.15 (d, J = 1.5 Hz, 3 H), 3.95 (q, J = 7.0 Hz, 2 H), 4.99 (s, 2 H), 5.00 (s, 2 H), 5.96 (q, J = 1.5 Hz, 1 H), 6.7–7.4 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 26.1, 59.4, 70.5, 71.2, 114.1, 115.3, 119.1, 126.9, 127.4, 127.5, 127.7, 128.3, 128.4, 132.2, 137.2, 137.5, 148.9, 152.6, 152.9, 165.4; mass spectrum m/z (relative intensity) 402 (M^+, 6), 311 (1), 91 (100). Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.45; H, 6.76.

Aldehyde 11. Preparation of the Ethoxycarbonyl Diol. To a stirred solution of 6 mL of H_2O, 32 mL of acetone, *N*-methylmorpholine *N*-oxide (2.0 g, 22.2 mmol), and 50 mg of OsO_4 (in 5 mL of *t*-BuOH) was added E alkene **10** (8.5 g, 21.1 mmol) in 100 mL of acetone. The solution was heated at 75 °C for 36 h, diluted with 25 mL of saturated $NaHSO_3$, and extracted with EtOAc (3 × 75 mL). Drying (Na_2SO_4) of the combined organic layers followed by concentration in vacuo left a yellow residue which was chromatographed on silica (2:1 hexane/EtOAc) to give 4.0 g (44%, 92% based on recovered starting material) of diol (recrystallized from ethyl ether) and 4.2 g (49%) of recovered alkene **10**. Ethoxycarbonyl diol: mp 105–106 °C; IR (CH_2Cl_2) 3520 (m), 2870 (w), 1725 (s), 1000 (s); ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.64 (s, 3 H), 3.16 (d, J = 7.3 Hz, 1 H), 3.97 (s, 1 H), 4.11 (m, 2 H), 4.78 (d, J = 7.3 Hz, 1 H), 5.02 (s, 2 H), 5.10 (s, 2 H), 6.8 (s, 2 H), 7.4 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 23.7, 61.3, 70.5, 71.0, 75.7, 76.5, 113.3, 113.8, 115.2, 127.4, 127.5, 127.9, 128.1, 128.5, 128.7, 133.3, 136.4, 137.1, 149.6, 153.1, 172.9; mass spectrum, m/z (relative intensity) 332 (4), 91 (100). Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.50; H, 6.54.

Preparation of the Benzylidene Esters. The diol (3.25 g, 7.45 mmol), TsOH (100 mg), $MgSO_4$ (2 g), and freshly distilled benzaldehyde (1.1 g, 10.4 mmol) in 25 mL of CH_2Cl_2 were stirred at room temperature for 48 h. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated to a thick oil. Flash chromatography of the crude mixture (19:1 hexane/EtOAc) afforded 3.8 g (98%) of the diastereomeric benzylidenes. The mixture was separated by radial chromatography (4 mm, 200:1 hexane/EtOAc) to give 1.71 g (44%) of the β-isomer and 2.09 g (54%) of the α-isomer. ***β*-Isomer**: ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3 H), 1.72 (s, 3 H), 4.07 (dq, J = 1.3, 7.1 Hz, 2 H), 4.45 (A of AB q, J = 11.5 Hz, 1 H), 4.46 (B of AB q, J = 11.5 Hz, 1 H), 5.09 (s, 2 H), 5.29 (s, 1 H), 6.68 (s, 1 H), 6.81 (m, 2 H), 7.30 (d, J = 2.4 Hz, 1 H), 7.31–7.55 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.9, 60.5, 69.9, 70.4, 82.9, 84.0, 104.4, 112.8, 113.6, 115.1, 126.8, 127.3, 127.6, 127.8, 128.0, 128.3, 128.4, 129.0, 134.3, 136.9, 137.1, 137.8, 148.2, 152.4, 170.4. ***α*-Isomer**: IR (CCl_4) 3069 (w), 3036 (w), 2983 (w), 2940 (w), 2874 (w), 1755 (s), 1738 (m), 1496 (s), 1489 (s), 1454 (m), 1276 (s), 1199 (s), 1100 (s), 1027 (s); ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3 H), 1.71 (s, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.03 (s, 2 H), 5.13 (s, 2 H), 5.25 (s, 1 H), 5.92 (s, 1 H), 6.89 (m, 2 H), 7.28–7.73 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.3, 60.7, 70.5, 70.6, 81.7, 85.2, 103.6, 112.6, 113.6, 114.5, 127.3, 127.7, 127.87, 127.92, 128.2, 128.5, 128.6, 129.6, 132.3, 136.7, 136.9, 137.1, 149.4, 153.0, 170.6; mass spectrum, m/z (relative intensity) 524 (M^+, 6), 418 (2), 91 (100).

Preparation of Aldehyde 11. Diisobutylaluminum hydride (3.6 mL, 1.0 M in CH_2Cl_2, 3.6 mmol) was added over 15 min to a solution of the diastereomeric ethoxycarbonyl esters (1.7 g, 3.2 mmol) in 100 mL of CH_2Cl_2 at −78 °C. The mixture was stirred for 1 h at −78 °C, quenched with H_2O (10 mL), and allowed to stir for 2 h at room temperature (additional ether was added if stirring became difficult). The salts were filtered and thoroughly washed with ether. The filtrate was dried ($MgSO_4$) and concentrated. Flash chromatography (10:1 hexane/EtOAc) of the oil obtained provided 1.5 g (89%) of aldehyde **11** as an inseparable mixture of acetal epimers: IR (neat) 3030 (m), 2970 (s), 2860 (m), 1735 (s), 1210 (s); ^1H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 5.1 (m, 4 H), 5.82 (s, 1 H), 6.8 (m, 2 H), 6.88 (d, J = 2.1 Hz, 1 H), 7.3 (m, 16

H), 9.48 (d, J = 2.1 Hz, 1 H); mass spectrum, m/z (relative intensity) 480 (M^+, 5), 91 (100).

***N*-Methylnitrone 8.** To a mixture of *N*-methylhydroxylamine hydrochloride (320 mg, 3.8 mmol), 340 mg of $NaHCO_3$, and 600 mg of $MgSO_4$ in 25 mL of CH_2Cl_2 was added aldehyde **11** (1.73 g, 3.6 mmol) dissolved in 15 mL of CH_2Cl_2. The reaction mixture was stired at room temperature for 3 h and then filtered and concentrated. Purification of the residue by flash chromatography (2:1 EtOAc/hexane) provided 1.55 g (85%) of a mixture (by ^1H NMR) of *Z* nitrones epimeric at the benzylidene center. High R_f nitrone isomer 8α: IR (CCl_4) 3035 (w), 2985 (m), 1585 (m), 1180 (s); ^1H NMR ($CDCl_3$) δ 1.76 (s, 3 H), 3.12 (s, 3 H), 4.96 (A of AB q, J = 11.5 Hz, 1 H), 5.03 (s, 1 H), 5.07 (B of AB q, J = 11.5 Hz, 1 H), 5.43 (d, J = 7.4 Hz, 1 H), 5.79 (s, 1 H), 6.71 (dd, J = 0.6, 7.4 Hz, 1 H), 6.86 (m, 2 H), 7.23–7.55 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 23.6, 52.8, 70.5, 70.6, 77.5, 82.6, 102.0, 112.8, 114.0, 126.9, 127.4, 127.7, 127.8, 128.0, 128.3, 128.5, 128.7, 129.5, 133.8, 134.5, 136.3, 137.1, 149.3, 152.9; mass spectrum, m/z (relative intensity) 280 (10), 91 (100). Low R_f nitrone isomer 8β: mp 168–169 °C (recrystallized from 1:1:1 toluene/hexane/ethyl acetate); IR (CCl_4) 3035 (w), 2985 (m), 1585 (m), 1180 (s); ^1H NMR ($CDCl_3$) δ 1.77 (s, 3 H), 3.19 (s, 3 H), 4.85 (A of AB q, J = 11.4 Hz, 1 H), 4.90 (B of AB q, J = 11.7 Hz, 1 H), 4.96 (A of AB q, J = 11.7 Hz, 1 H), 5.02 (B of AB q, J = 11.4 Hz, 1 H), 5.45 (d, J = 7.4 Hz, 1 H), 6.18 (s, 1 H), 6.74 (d, J = 7.4 Hz, 1 H), 6.8 (m, 2 H), 7.24–7.54 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 52.9, 70.4, 70.6, 83.2, 102.2, 112.4, 113.3, 114.4, 126.9, 127.4, 127.8, 128.0, 128.2, 128.4, 128.7, 128.8, 129.2, 133.5, 134.8, 137.0, 137.5, 148.8, 152.7; mass spectrum, m/z (relative intensity) 280 (8), 91 (100). Anal. Calcd for $C_{32}H_{31}NO_5$: C, 75.46; H, 6.43; N, 2.75. Found: C, 75.15; H, 6.13; N, 2.71.

5-(Trimethylsilyl)isoxazolidines 17, 18, and 19. Freshly distilled vinyltrimethylsilane (5.00 mL, 3.25 g, 32.37 mmol) was added to a toluene (20 mL) solution containing nitrone isomer 8α (736 mg, 1.44 mmol). The reaction mixture was stirred at reflux for 10 h and then concentrated in vacuo. Undesired side products were removed by flash chromatography (18:1 CH_2Cl_2/Et_2O), and the ^1H NMR of the products showed that the isoxazolidine isomers **17**, **18**, and **19** were distributed in a ratio of 60:20:20. Separation of the cycloadducts by radial chromatography (4 mm, 19:1 hexane/EtOAc) afforded pure **17** (444 mg, 51%), **18** (150 mg, 17%), and a mixture of isoxazolidines **18**/**19**. **Isoxazolidine 17**: mp 151–152 °C (10:1 hexane/EtOAc); IR (CCl_4) 3036 (m), 2984 (s), 2956 (vs), 2871 (vs), 1559 (vs), 1491 (vs), 1250 (s), 1215 (vs), 1019 (vs); ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 1.69 (s, 3 H), 1.96 (m, 1 H), 2.29 (s, 3 H), 2.45 (m, 1 H), 2.72 (m, 1 H), 3.42 (dd, J = 6.8, 11.5 Hz, 1 H), 4.4 (s, 1 H), 5.96 (s, 2 H), 5.11 (s, 2 H), 5.80 (s, 1 H), 6.9 (m, 2 H), 7.4 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ −3.9, 23.4, 34.3, 43.6, 68.6, 70.5, 70.8, 83.0, 100.4, 112.3, 113.4, 113.7, 126.6, 127.4, 127.9, 128.1, 128.4, 128.5, 128.7, 129.0, 135.4, 136.4, 136.9, 137.1, 149.4, 153.1; mass spectrum, m/z (relative intensity) 610.2986 (M^+ + 1, calcd for $C_{37}H_{43}NO_5Si$ 610.2989), 494 (13), 388 (32), 106 (100), 91 (86), 78 (23). Anal. Calcd for $C_{37}H_{43}NO_5Si$: C, 72.87; H, 7.11. Found: C, 72.57; H, 7.09. **Isoxazolidine 18**: IR (CCl_4) 3025 (w), 2960 (w), 1480 (m), 1450 (m), 1080 (vs); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 1.76 (s, 2 H), 5.14 (s, 2 H), 5.80 (s, 1 H), 6.90 (m, 2 H), 7.40 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ −3.6, 23.3, 68.2, 69.1, 69.5, 70.8, 71.0, 84.8, 85.5, 101.8, 113.6, 113.9, 114.9, 126.8, 127.4, 128.0, 128.2, 128.4, 128.6, 128.8, 129.0, 133.5, 136.7, 137.2, 138.2, 153.1; mass spectrum, m/z (relative intensity) 609 (M^+, 0.5), 280 (11), 91 (100).

Aldehyde 20. In a polyethylene reaction tube, the respective 5-(trimethylsilyl)isoxazolidine (609 mg, 1 mmol) was dissolved in acetonitrile (10 mL) to which 5 drops of a 50% HF(aq) solution was added. The solution was stirred for 0.5 h and then diluted with water (5 mL). Solid K_2CO_3 was added until evidence of two layers was apparent. The aqueous layer was extracted with diethyl ether (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue provided 372 mg (75%) of the homologated α,β-unsaturated aldehyde **20**: IR (CCl_4) 3050 (w), 2880 (w), 2730 (w), 1695 (vs); ^1H NMR δ 1.46 (s, 3 H), 4.99 (dd, J = 1.1, 2.5 Hz, 1 H), 5.07 (s, 4 H), 5.74 (s, 1 H), 6.3 (m, 2 H), 6.9 (m, 2 H), 7.4 (m, 16 H), 8.86 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 70.6, 71.1, 83.2, 84.1, 86.5, 101.2, 112.6, 114.2, 127.0, 127.3, 127.9, 128.4, 128.5, 129.0, 129.1, 129.7, 131.8, 134.5, 136.1, 137.1, 153.2, 153.7, 193.6; mass spectrum, m/z (relative intensity) 506 (M^+, 0.1), 332 (7), 91 (100). Anal. Calcd for $C_{33}H_{30}O_5$: C, 78.22; H, 5.97. Found: C, 78.03; H, 6.12.

Benzoxocin 21. Aldehyde **20** (99 mg, 0.19 mmol) was hydrogenated for 24 h under 1 atm of H_2 using 100 mg 5% Pd/C as the catalyst and 95% EtOH (10 mL) as the solvent. The catalyst was removed by filtering the reaction mixture through Celite. The filtrate was concentrated, passed through a plug of silica (EtOAc), concentrated, and immediately dissolved in a mixture of 30 mL of acetone, 1 mL of H_2O, and 1 mL of 10% HCl(aq). The reaction mixture was heated at 60 °C for 24 h, neutralized with saturated $NaHCO_3$, and evaporated to dryness. Flash chromatography of the residue (1:1 hexane/EtOAc) provided 29 mg (67%) of benzoxocin **21** as white crystals: mp 151–154 °C (crystallized from 7:1 hexane/ethyl acetate); IR (CCl_4) 3620 (m), 2960 (s), 1480 (s), 1080 (vs); ^1H NMR (acetone-d_6) δ 1.52 (s, 3 H), 1.7–2.1 (m, 4 H), 3.64 (dd, J = 4.2, 11.5 Hz, 1 H), 5.41 (dd, J = 1.9, 2.3 Hz, 1 H), 6.5–6.7 (m, 3 H); mass spectrum, m/z (relative intensity) 222 (M^+, 64), 204 (11), 178 (36), 137 (100). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.44; H, 6.53.

Methyl Benzoxocin 24. Benzoxocin **24** was isolated in 76% yield as a colorless oil from the reaction mixture when cycloadducts **17**/**18**/**19** were used for the fragmentation following the same procedure as that described for the preparation and methylation of benzoxocin **23**. Benzoxocin **24** crystallized from 4:1:1 hexane/ethyl acetate/chloroform: mp 166–167.5 °C; ^1H NMR (400 MHz) δ 1.68 (s, 3 H), 2.07 (s, 3 H), 2.11 (m, 2 H), 2.52 (br, 1 H), 2.91 (s, 3 H), 3.61 (d, J = 11.0 Hz, 1 H), 3.76 (s, 3 H), 4.57 (m, J = 6.0, 11.0, 11.8 Hz, 1 H), 5.66 (m, J = 1.6, 1.7 Hz, 1 H), 6.69–6.80 (m, 3 H); ^{13}C NMR δ 22.4, 23.6, 30.5, 35.5, 50.7, 55.7, 74.7, 75.9, 93.5, 112.1, 112.4, 114.8, 115.8, 116.1, 123.1, 173.8; mass spectrum, m/z (relative intensity) 307.1418 (M^+, calcd for $C_{16}H_{21}NO_5$ 307.1420), 216 (30), 193 (23), 166 (35), 151 (57), 115 (38), 98 (25), 86 (100).

Aldehyde 25. Acetyl chloride (0.46 mL, 0.65 mmol) was added to a suspension of $NaHCO_3$ (120 mg, 1.43 mmol) and isoxazolidines **17**/**18** (262 mg, 0.43 mmol) in 5 mL of THF at 0 °C with stirring. After 15 min, saturated $NaHCO_3$ was slowly added until the pH of the resulting mixture was 7, and the aqueous layer was extracted with ether (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue (2:1 hexane/EtOAc) provided 229 mg (92%) of amido aldehyde **25** as a colorless oil which solidified slowly upon standing: mp 151–152 °C; IR (CCl_4) 3025 (m), 2920 (m), 2720 (w), 1727 (vs), 1651 (vs), 1488 (vs), 1454 (vs), 1214 (vs), 1057 (vs), 1025 (vs); ^1H NMR ($CDCl_3$) δ 1.73 (s, 3 H), 1.77 (s, 3 H), 2.6–2.8 (m, 2 H), 2.75 (s, 3 H), 4.56 (d, J = 3.4 Hz, 1 H), 4.98 (s, 2 H), 5.12 (A of AB q, J = 13.6 Hz, 1 H), 5.27 (B of AB q, J = 13.6 Hz, 1 H), 5.74 (s, 1 H), 5.88 (m, 1 H), 6.70 (m, 2 H), 7.3 (m, 16 H), 9.64 (dd, J = 1.7, 4.0 Hz, 1 H); ^{13}C NMR δ 21.0, 21.8, 30.3, 43.0, 47.9, 69.2, 69.8, 83.6, 83.7, 100.5, 112.0, 113.0, 113.3, 125.5, 125.9, 126.1, 126.6, 127.0, 127.2, 127.6, 127.7, 127.9, 128.9, 133.5, 135.9, 136.4, 136.9, 148.5, 152.2, 170.2, 200.7; mass spectrum, m/z (relative intensity) 580 (M^+ + 1, 1), 332 (9), 91 (100).

Benzoxocin 27. Aldehyde **25** (24.0 mg, 0.042 mmol) in 3 mL of glacial acetic acid was hydrogenated under 1 atm of H_2 for 10 h using 20% $Pd(OH)_2/C$ as catalyst. The catalyst was removed by filtration through a pad of Celite, and the acid was removed in vacuo. The benzoxocin **27** (10.2 mg, 84%) was obtained as a colorless oil after column chromatography (silica gel, 12:1 CH_2Cl_2/MeOH): IR (CCl_4) 3500–3100 (b), 2950 (w), 1620 (m), 1120 (s); 880 (vs); ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 2.05 (m, 3 H), 2.10 (s, 3 H), 2.94 (s, 3 H), 4.02 (d, J = 0.8 Hz, 1 H), 4.82 (dd, J = 5.8, 6.2 Hz, 1 H), 5.96 (dd, J = 2.5, 4.1 Hz, 1 H), 6.67 (m, 2 H), 7.25 (d, J = 2.7 Hz, 1 H), 7.92 (br s, 1 H); ^{13}C NMR δ 22.1, 26.2, 31.4, 33.7, 55.2, 77.2, 90.8, 103.1, 114.1, 115.4, 123.3, 137.4, 143.3, 152.9, 172.6; mass spectrum, m/z (relative intensity) 293.1254 (M^+, calcd for $C_{15}H_{19}NO_5$ 293.1263), 202 (48), 152 (100).

Benzoxocin 28. To a suspension of the tricyclic compound **27** (20 mg, 0.068 mmol) and potassium carbonate (40 mg, 0.29 mmol) in 2 mL of acetone was added methyl iodide (1.14 g, 0.50 mL, 8.03 mmol). The reaction mixture was then heated at reflux for 7 h. After filtration, the solvent and excess methyl iodide were removed under reduced pressure. Flash chromatography of the resulting oil (1:1 hexane/EtOAc) provided the methyl ether (19 mg, 91%) as a colorless oil. Crystallization of the product from

hexane/ethyl acetate/chloroform (6:1:1) afforded single crystals suitable for X-ray analysis: mp 152.5–154 °C; IR (CCl_4) 3369 (s), 2977 (s), 2955 (s), 2937 (s), 1652 (s), 1632 (s), 1486 (s), 1409 (m), 1202 (m), 1043 (m), 1019 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3 H), 1.63 (br, 1 H), 2.00 (dd, J = 9.6, 15.1 Hz, 1 H), 2.11 (s, 3 H), 2.22 (m, J = 5.3, 6.1, 15.1 Hz, 1 H), 2.95 (s, 3 H), 3.81 (s, 3 H), 3.97 (d, J = 1.5 Hz, 1 H), 4.69 (m, J = 1.5, 5.3, 9.6 Hz, 1 H), 5.99 (d, J = 6.1 Hz, 1 H), 6.71 (dd, J = 3.1, 8.7 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.39 (d, J = 3.1 Hz, 1 H); ^{13}C NMR δ 22.2, 26.0, 31.4, 32.7, 55.5, 55.6, 77.0, 92.1, 103.3, 112.4, 114.5, 123.1, 138.1, 144.2, 156.0, 172.2; mass spectrum, m/z (relative intensity) 307.1414 (M^+, calcd for $C_{16}H_{21}NO_5$ 307.1419), 216 (29), 166 (100), 151 (34), 98 (14), 86 (21).

5-(Trimethylsilyl)isoxazolidines 29, 30, 31, and 32. 5-(Trimethylsilyl)isoxazolidines **29**, **30**, **31**, and **32** were obtained in 82% yield as a 58:23:17:trace ratio of products by the reaction of the 8β nitrone with vinyltrimethylsilane following the same procedure as that described for the preparation of isoxazolidines **17** and **18**. **Isoxazolidine 29**: IR (CCl_4) 3035 (m), 2956 (vs), 2872 (vs), 1496 (vs), 1454 (s), 1251 (s), 1214 (vs), 1027 (vs), 840 (vs); ^1H NMR (200 MHz) δ 0.06 (s, 9 H), 1.74 (s, 3 H), 2.08 (m, 1 H), 2.37 (s, 3 H), 2.50 (m, 1 H), 2.92 (br, 1 H), 3.56 (dd, J = 7.2, 11.0 Hz, 1 H), 4.41 (A of AB q, J = 11.5 Hz, 1 H), 4.62 (s, 1 H), 4.64 (B of AB q, J = 11.5 Hz, 1 H), 5.05 (s, 2 H), 6.35 (s, 1 H), 6.73 (dd, J = 3.0, 8.9 Hz, 1 H), 6.84 (d, J = 8.9 Hz, 1 H), 7.01 (d, J = 3.0 Hz, 1 H), 7.24–7.55 (m, 15 H); ^{13}C NMR (50 MHz) δ −3.8, 22.8, 33.7, 44.1, 68.4, 70.0, 70.9, 83.8, 84.2, 103.4, 113.0, 113.4, 114.8, 115.0, 126.7, 127.5, 127.7, 127.9, 128.1, 128.2, 128.4, 128.7, 135.2, 136.7, 137.2, 139.5, 148.7, 152.5; mass spectrum, m/z (relative intensity) 609.2908 (M^+, calcd for $C_{37}H_{43}NO_5Si$ 609.2911), 332 (8), 280 (31), 158 (100), 105 (61). **Isoxazolidine 30**: IR (CCl_4) 3035 (m), 2956 (s), 2859 (s), 1490 (vs), 1453 (s), 1250 (s), 1222 (vs), 1194 (s), 1027 (s), 842 (vs); ^1H NMR (200 MHz) δ 0.04 (s, 9 H), 1.77 (s, 3 H), 2.34 (m, 2 H), 2.49 (s, 3 H), 3.44 (m, 1 H), 3.71 (dd, J = 8.0, 10.0 Hz, 1 H), 4.34 (A of AB q, J = 11.5 Hz, 1 H), 4.60 (m, J = 7.2, 11.5 Hz, 2 H), 5.04 (A of AB q, J = 11.2 Hz, 1 H), 5.10 (B of AB, q, J = 11.2 Hz, 1 H), 6.16 (s, 1 H), 6.70 (dd, J = 3.0, 8.9 Hz, 1 H), 6.78 (d, J = 8.9 Hz, 1 H), 7.00 (d, J = 3.0 Hz, 1 H), 7.26–7.51 (m, 15 H); ^{13}C NMR (50 MHz) δ −3.5, 22.2, 32.7, 43.0, 66.2, 67.0, 69.9, 70.9, 84.4, 84.8, 101.8, 113.6, 113.8, 115.0, 126.7, 127.5, 127.6, 128.1, 128.4, 128.5, 128.7, 135.6, 137.4, 137.5, 139.1, 149.1, 152.4; mass spectrum, m/z (relative intensity) 609.2900 (M^+, calcd for $C_{37}H_{43}NO_5Si$ 609.2911), 332 (3), 280 (31), 158 (100), 105 (67). **Isoxazolidine 31**: IR (CCl_4) 3038 (m), 2985 (s), 2953 (vs), 2873 (vs), 1559 (vs), 1493 (vs), 1249 (s), 1216 (vs), 1020 (vs); ^1H NMR ($CDCl_3$) δ −0.04 (s, 9 H), 1.70 (s, 3 H), 1.99 (m, 1 H), 2.51 (s, 3 H), 3.29 (m, 1 H), 4.72 (d, J = 8.7 Hz, 1 H), 5.02 (s, 2 H), 5.07 (s, 2 H), 5.96 (s, 1 H), 6.87 (m, 3 H), 7.24–7.48 (m, 15 H); ^{13}C NMR δ −3.8, 23.2, 68.8, 69.1, 69.5, 70.7, 71.0, 84.1, 85.5, 101.8, 113.9, 114.1, 114.3 126.9, 127.4, 127.9, 128.1, 128.2, 128.4, 128.6, 128.8, 129.0, 133.5, 136.7, 137.2, 138.2, 153.1.

Isoxazolidines 33, 34, 35, and 36. A mixture of the nitrone 8β (1.03 g, 2.02 mmol) and allyltrimethylsilane (3.60 g, 5.00 mL, 0.03 mmol) in 25 mL of toluene was heated to reflux for 24 h. The toluene and excess allyltrimethylsilane were removed in vacuo. After passage of the reaction mixture through a plug of silica to remove polar impurities, the residue, 1.09 g (87%), was examined by ^1H NMR spectroscopy which indicated that four products, **33**, **34**, **35**, and **36**, were formed in a ratio of 55:18:18:9, respectively. Purification of the cycloadducts by radial chromatography (4 mm, 20:1 hexane/EtOAc) provided two pure isomers, **33** and **34**, and a mixture of the other two isomers, **35** and **36**. **Isoxazolidine 33**: IR (CCl_4) 3050 (m), 2970 (m), 1490 (s), 1200 (s); ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.68 (dd, J = 9.0, 13.9 Hz, 1 H), 4.37 (A of AB q, J = 11.5 Hz, 1 H), 4.56 (d, J = 1.5 Hz, 1 H), 4.60 (B of AB q, J = 11.5 Hz, 1 H), 5.00 (s, 2 H), 6.32 (s, 1 H), 6.6–7.4 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ −0.9, 22.7, 22.8, 38.9, 43.5, 69.1, 70.1, 70.9, 75.4, 83.6, 84.2, 103.7, 113.0, 113.3, 114.8, 126.7, 127.5, 127.8, 128.0, 128.1, 128.4, 128.7, 135.0, 136.6, 137.2, 139.5, 148.7, 152.6; mass spectrum, m/z (relative intensity) 624.3152 (M^+ + 1, calcd for $C_{38}H_{45}NO_5Si$ 624.3145), 172 (26), 105 (81), 91 (100), 77 (50). **Isoxazolidine 34**: IR (CCl_4) 3050 (m), 2970 (m), 1490 (s), 1200 (s); ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.91 (dd, J = 8.6, 14.0 Hz, 1 H), 0.94 (dd, J = 5.8, 14.0 Hz, 1 H), 1.71 (s, 3 H), 2.03 (m, 1 H), 2.45 (m, 1 H), 2.46 (s, 3 H), 3.34 (m, 1 H), 4.2 (m, 2 H), 4.52 (A of AB q, J = 16.5 Hz, 1 H), 4.67 (B of AB q, J = 16.5 Hz, 1 H), 5.03 (A of AB, q, J = 11.2 Hz, 1 H), 5.06 (B of AB q, J = 11.2 Hz, 1 H), 6.16 (s, 1 H), 6.6–7.4 (m, 18 H); mass spectrum, m/z (CI) 624 (M^+ + 1, 88).

β-Amido Acetates 37a and 37b. General Procedure for Zinc–Acetic Acid Reduction of Isoxazolidines 33/34 and 35/36. Activated zinc (1 g) was added in small portions to a solution of the isoxazolidines **33**/**34** (1.7 g, 2.7 mmol) dissolved in 15 mL of HOAc–H_2O (2:1). The reaction mixture was heated to 80 °C. The solid was removed by filtration, and the solution was concentrated in vacuo. The residue was taken up in EtOAc and washed with H_2O (2 × 10 mL), brine (1 × 10 mL), and saturated $NaHCO_3$ (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated.

From isoxazolidine **33**, the diastereomeric amino alcohol (62 mg, 72%) was obtained following radial chromatography (4 mm, 10:1 CH_2Cl_2/MeOH) as an orange oil: IR (CH_2Cl_2) 3030 (w), 2960 (vs), 1070 (vs), 1000 (vs); ^1H NMR ($CDCl_3$) δ 0.1 (s, 9 H), 0.8 (m, 2 H), 1.6 (s, 3 H), 1.8 (m, 2 H), 1.9 (s, 3 H), 3.3 (m, 1 H), 3.9 (m, 1 H), 4.5 (AB q, J = 12.0 Hz, 2 H), 5.0 (s, 2 H), 6.2 (s, 1 H), 6.8 (m, 2 H), 7.2 (m, 16 H).

From isoxazolidine **34**, the product was obtained following radial chromatography (4 mm, 3:2 hexane/EtOAc) as 516 mg (79%) of a yellow oil: IR (CCl_4) 3350–3100 (b), 3050 (m), 2940 (s), 2895 (s), 1125 (vs); ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 0.8 (m, 2 H), 1.6 (s, 3 H), 1.8 (s, 3 H), 1.9 (m, 2 H), 3.0 (m, 1 H), 3.4 (br s, 2 H, disappears + D_2O), 4.3 (AB q, J = 12 Hz, 2 H), 4.6 (m, 1 H), 4.9 (s, 2 H), 5.9 (s, 1 H), 6.8 (m, 2 H), 7.2 (m, 16 H).

General Method for Acetylation of Amino Alcohols. The respective amino alcohol (1.0 mmol) was dissolved in 2 mL of pyridine to which 1 mL of acetic anhydride and 10 mg of (dimethylamino)pyridine were added. The reaction mixture was stirred at room temperature for 6 h and then concentrated, and the residue was taken up in 25 mL of EtOAc, washed with saturated $CuSO_4$ (2 × 25 mL), dried (Na_2SO_4), and concentrated. Radial chromatography (4 mm, 2:1 hexane/EtOAc) provided the respective acetate–amides as yellow oils. **37a**: 471 mg (54%); IR (CCl_4) 3020 (s), 2940 (m), 1728 (vs), 1640 (s); ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.88 (dd, J = 10.7, 14.5 Hz, 1 H), 1.37 (dd, J = 3.1, 14.5 Hz, 1 H), 1.75 (s, 3 H), 1.81 (s, 3 H), 1.9 (m, 2 H), 2.01 (s, 3 H), 2.58 (s, 3 H), 4.37 (d, J = 11.6 Hz, 1 H), 4.7 (m, 3 H), 5.05 (A of AB q, J = 12.8 Hz, 1 H), 5.09 (B of AB q, J = 12.8 Hz, 1 H), 5.28 (ddd, J = 3.4, 7.0, 11.6 Hz, 1 H), 6.21 (s, 1 H), 6.7–7.5 (m, 18 H). **37b**: 445 mg (76%); IR (CCl_4) 3020 (w), 2940 (m), 1730 (s), 1650 (s), 880 (vs); ^1H NMR ($CDCl_3$) δ 0.08 (s, 9 H), 0.7 (m, 2 H), 1.69 (s, 3 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 1.9–2.1 (m, 2 H), 2.80 (s, 3 H), 4.30 (d, J = 11.8 Hz, 1 H), 4.57 (A of AB q, J = 12.0 Hz, 1 H), 4.60 (B of AB q, J = 12.0 Hz, 1 H), 4.7 (m, 1 H), 5.35 (m, 1 H), 6.12 (s, 1 H), 6.7–7.4 (m, 18 H).

Homoallylic Amide 38. Under a nitrogen atmosphere, 1 mL of tetra-*n*-butylammonium fluoride (1 N in THF, 1 mL, 1 mmol) was added to amide **37** (0.5 mmol) in 15 mL of THF. The solution was heated to 70 °C for 12 h, concentrated, and then passed through a plug of silica (EtOAc). Flash chromatography of the residue (1:1 hexane/EtOAc) provided homoallylic amide **38** as a light green oil (354 mg, 97%): IR (CCl_4) 3020 (w), 2920 (w), 1645 (vs), 1170 (s); ^1H NMR ($CDCl_3$) δ 1.75 (s, 3 H), 1.78 (s, 3 H), 2.45 (s, 3 H), 2.5 (m, 2 H), 4.36 (A of AB q, J = 11.5 Hz, 1 H), 5.0 (m, 3 H), 5.4 (m, 1 H), 5.7 (m, 1 H), 6.23 (s, 1 H), 6.7–7.4 (m, 18 H); mass spectrum, m/z (CI) 577 (M^+ + 1, 9).

Aldehyde 39 from Homoallylic Amide 38. Homoallylic amide **38** (300 mg, 0.52 mmol) was dissolved in a mixture of dioxane/H_2O (3:1) to which a catalytic amount of OsO_4 was added. After 5 min, $NaIO_4$ (230 mg, 1.1 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h. Saturated $NaHSO_3$ was added until a black color persisted. Extraction with EtOAc (3 × 15 mL) followed by drying (Na_2SO_4) and concentration in vacuo of the extracts left a brown residue which was chromatographed (1:1 hexane/EtOAc) to give 126 mg (42%) of amido aldehyde **39**: IR (CCl_4) 3020 (w), 2950 (vs), 2720 (w), 1725 (s), 1650 (s); ^1H NMR (400 MHz) δ 1.74 (s, 3 H), 1.75 (s, 3 H), 2.51 (s, 3 H), 2.65 (ddd, J = 4.8, 10.5, 15.3 Hz, 1 H), 2.85 (ddd, J = 0.8, 4.1, 15.3 Hz, 1 H), 4.39 (A of AB q, J = 11.5 Hz, 1 H), 4.63 (B of AB q, J = 11.5 Hz, 1 H), 4.69 (d, J = 7.0 Hz, 1 H), 5.04 (A of AB q, J = 12.4 Hz, 1 H), 5.08 (B of AB q, J = 12.4 Hz, 1 H), 5.86 (ddd, J = 4.1, 7.0, 10.0 Hz, 1 H), 6.21 (s, 1 H), 6.7–7.4 (m, 18 H), 9.57 (dd, J = 0.8, 4.7 Hz, 1 H); ^{13}C NMR (100 MHz)

δ 20.6, 22.0, 30.8, 43.9, 47.5, 70.0, 70.9, 83.1, 85.0, 102.1, 113.6, 114.2, 115.2, 126.5, 127.5, 127.7, 127.8, 128.1, 128.3, 128.4, 128.7, 129.0, 133.5, 137.2, 138.5, 149.1, 152.6, 171.1, 200.6; mass spectrum, m/z (relative intensity) 579.2635 (M^+, calcd for $C_{36}H_{37}NO_6$ 579.2621), 382 (1), 331 (5), 309 (1), 255 (1), 218 (1), 190 (1), 148 (2), 128 (3), 91 (100).

Vinylidene Carbonate Cycloadducts 40 and 41. Freshly distilled vinylene carbonate (2.71 g, 2.00 mL, 0.03 mmol) was transferred to a sealed tube apparatus containing nitrone 8β (692 mg, 1.36 mmol) in 10 mL of anhydrous xylenes. The mixture was heated at 120 °C for 72 h and then concentrated in vacuo. Flash chromatography of the residue (2:1 hexane/ethyl acetate) provided a 2:1 mixture of low R_f isomer 41 to high R_f isomer 40 for a combined yield of 55%. The diastereomers were separated by flash chromatography to afford 160 mg (18%) of high R_f isomer 40 and 325 mg (37%) of lower R_f isomer 41.

High-Pressure Cycloaddition of Nitrone 8β with Vinylene Carbonate. Freshly distilled vinylene carbonate (0.50 mL, 0.678 g, 7.87 mmol) was added to a solution of nitrone 8β in 3 mL of anhydrous THF. The solution was placed into a syringe and then into a high-pressure reactor. The vessel was pressurized to 12 kbar and allowed to react for 72 h. The syringe was removed and washed with EtOAc, and the solvent was removed in vacuo. Flash chromatography of the residue (2:1 hexanes/EtOAc) afforded an 80:20 mixture of diastereomers in 60% yield that were separated as above.

Cycloadduct 40. Crystallization of 40 in hexane/methylene chloride (9:1) afforded single crystals suitable for X-ray analysis: mp 200-201 °C; IR ($CHCl_3$) 1819 (vs), 1497 (m), 991 (m); ^1H NMR ($CDCl_3$) δ 1.73 (s, 3 H), 2.64 (s, 3 H), 3.56 (d, J = 2.5 Hz, 1 H), 4.41 (d, J = 2.5 Hz, 3 H), 4.87 (AB q, J = 11.7 Hz, 2 H), 5.01 (AB q, J = 9.8 Hz, 2 H), 5.23 (d, J = 5.3 Hz, 1 H), 5.92 (d, J = 5.3 Hz, 1 H), 6.21 (s, 1 H), 6.87 (dd, J = 8.8, 3.0 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 7.29 (d, J = 3.0 Hz, 1 H), 7.36 (m, 15 H); ^{13}C NMR (50 MHz) δ 22.6, 47.4, 70.4, 71.0, 71.3, 77.2, 84.7, 90.1, 103.3, 105.2, 112.3, 112.8, 114.4, 127.1, 127.5, 127.9, 128.4, 128.5, 129.1, 129.2, 129.3, 129.5, 135.7, 136.3, 137.2, 148.4, 152.3, 153.0; mass spectrum, m/z (relative intensity) 595.2209 (calcd for $C_{35}H_{33}NO_8$ 595.2206), 580 (12), 504 (8), 254 (15), 234 (24), 160 (79), 144 (32), 105 (100). **Cycloadduct 41.** Crystallization of 41 in hexane/methylene chloride (9:1) afforded single crystals suitable for X-ray analysis: mp 137-138 °C; IR ($CHCl_3$) 1817 (vs), 1491 (vs), 1378 (m); ^1H NMR ($CDCl_3$) δ 1.76 (s, 3 H), 2.65 (s, 3 H), 4.00 (d, J = 4.4 Hz, 1 H), 4.50 (d, A of AB q, J = 11.5 Hz, 1 H), 4.61 (d, J = 4.4 Hz, 1 H), 4.71 (d, B of AB q, J = 11.5 Hz, 1 H), 5.03 (AB q, J = 9.6 Hz, 2 H), 5.63 (d, J = 5.3 Hz, 1 H), 6.10 (d, J = 5.3 Hz, 1 H), 6.76 (dd, J = 8.9, 3.0 Hz, 1 H), 6.85 (d, J = 8.9 Hz, 1 H), 7.03 (d, J = 3.0 Hz, 1 H), 7.33 (m, 15 H); ^{13}C NMR (50 MHz) δ 21.9, 68.8, 70.2, 71.2, 80.8, 84.8, 87.2, 102.8, 103.9, 113.1, 113.6, 115.1, 126.5, 127.1, 127.5, 127.8, 128.0, 128.4, 128.5, 128.6, 128.9, 129.2, 133.9, 136.1, 137.1, 138.2, 148.6, 152.7, 152.9; mass spectrum, m/z 595.2195 (calcd for $C_{35}H_{33}NO_8$ 595.2206), 505 (29), 504 (89), 296 (19), 254 (18), 234 (32), 168 (20), 163 (27), 144 (59), 105 (100). Anal. Calcd for $C_{35}H_{33}NO_8$: C, 70.58; H, 5.58. Found: C, 70.17; H, 5.57.

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Supplementary Material Available: ^1H NMR spectra of compounds 8α, 8β, 11, 17, 18, 24-30, 33, 34, 38, and 39; ORTEP diagrams and X-ray data of compounds 8β, 28, 40, and 41; and tables of fractional coordinates and temperature factors, bond distances in angstroms, and bond angles in degrees (44 pages). Ordering information is given on any current masthead page.

Anthracenediols as Reactive Dienes in Base-Catalyzed Cycloadditions: Reduction-Cycloaddition Reactions of Anthraquinones[1]

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Anthraquinone is readily reduced to the hydroquinone (9,10-anthracenediol), which under basic conditions serves as a reactive diene for cyloaddition purposes. Catalytic hydrogenation in pyridine solvent provides convenient access to this species, and efficient reactions occur with dienophiles in situ, provided that they are sufficiently reactive. Thus *N*-methylmaleimide (NMM) gives the bicyclic bridgehead diol in near quantitative yield when the H_2/Pd reduction of anthraquinone is carried out in pyridine containing 1 equiv of NMM. Fumaronitrile and maleonitrile similarly give high yields in stereospecific reactions, with the dienophile geometry retained in the cycloadduct. Less reactive dienophiles suffer competitive reduction. Dimethyl fumarate in situ gives cycloadduct (stereospecifically) in only 35-60% yield, with the remainder of the dienophile reduced to dimethyl succinate. Stepwise reduction followed by addition of dienophile leads to a higher yield in this and related reactions. The benzologues 5,12-naphthacenedione and 6,13-pentacenedione undergo analogous reactions with NMM, leading to novel bridgehead diols. The monimine of anthraquinone exhibits NMR features attributed to syn/anti isomerism. Under neutral or mildly basic conditions, the aromatic protons on the ring proximal to the NH are clearly distinguished (500 MHz) from those on the distal ring. The addition of acid causes rapid syn/anti NH exchange leading to time averaged symmetry. This imine behaves similarly to anthraquinone in the reduction/cycloaddition sequence. For example, with NMM in situ an essentially quantitative yield of the novel bridgehead amino alcohol adduct is obtained. Related benzologue reactions and attempts to extend the sequence to the oxime and methylene analogues of anthraquinone are described. Base-catalyzed ring opening of the cycloadduct of NMM/anthracenediol leads to a novel retro-bis-aldol reaction, resulting in the formation of anthraquinone and *N*-methylsuccinimide.

Introduction

Novel base-catalyzed Diels-Alder reactions of 9-anthrone have recently been described.[1,2] The oxyanion or an amine hydrogen-bonded variant is believed to be the intermediate responsible for the very rapid cycloadditions which are observed in the presence of base. The possibility that hydroquinones and other substituted anthrone analogues

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(2) Koerner, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 2662.

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